Court File #: CV-22-0069-1880-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

RESPONDING (PLAINTIFFS) MOTION RECORD
(S.137.1 Motion Returnable November 19th, 2024)

December 15th, 2023

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PROFESSIONAL CORPORATION
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Ontario M6H 1A9

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Lawyers for the Defendant, David Fisman

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TAB 1

ONTARIO

SUPERIOR COURT OF JUSTICE

BETWEEN:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

STATEMENT OF CLAIM

TO THE DEFENDANT:

A LEGAL PROCEEDING HAS BEEN COMMENCED AGAINST YOU by the Plaintiff. The claim made against you is set out in the following pages.

IF YOU WISH TO DEFEND THIS PROCEEDING, you or an Ontario lawyer acting for you must prepare a statement of defence in Form 18A prescribed by the Rules of Civil Procedure, serve it on the Plaintiff's lawyer or, where the Plaintiff does not have a lawyer, serve it on the Plaintiff, and file it, with proof of service, in this court office, WITHIN TWENTY DAYS after this statement of claim is served on you, if you are served in Ontario.

If you are served in another province or territory of Canada or in the United States of America, the period for serving and filing your statement of defence is forty days. If you are served outside of Canada and the United States of America, the period is sixty days.

Instead of serving and filing a statement of defence, you may serve and file a notice of intent to defend in Form 18B prescribed by the Rules of Civil Procedure. This will entitle you to ten more days within which to serve and file your statement of defence.

IF YOU FAIL TO DEFEND THIS PROCEEDING, A JUDGMENT MAY BE GIVEN AGAINST YOU IN YOUR ABSENCE AND WITHOUT FURTHER NOTICE TO YOU. IF YOU WISH TO DEFEND THIS PROCEEDING BUT ARE UNABLE TO PAY LEGAL FEES, LEGAL AID MAY BE AVAILABLE TO YOU BY CONTACTING A LOCAL LEGAL AID OFFICE.

IF YOU PAY THE PLAINTIFFS' CLAIM, and $10,000.00 for costs, within the time for serving and filing your statement of defence you may move to have this proceeding dismissed by the court. If you believe the amount claimed for costs is excessive, you may pay the Plaintiffs' claim and $400 for costs and have the costs assessed by the court.

TAKE NOTICE: THIS ACTION WILL AUTOMATICALLY BE DISMISSED if it has not been set down for trial or terminated by any means within five years after the action was commenced unless otherwise ordered by the court.

Date: Issued by:

Address of Local Office: 393 University Ave.
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TO: Harpreet Hansra
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AND TO: David Norman Fisman
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Toronto, Ontario
M5T 3M7
Email: david.fisman@utoronto.ca
Tel: 416 978 6866

CLAIM

1. The Plaintiff claims:

   (a) general damages as against the Defendants jointly and severally, in the amount of $500,000.00;

   (b) Restitution damages as against the University Defendants jointly and severally, in the amount of $1, 500,000.00 with respect to lab equipment and loss of grants and research funding;

   (c) aggravated damages as against the Defendants, jointly and severally, in the amount of $500,000.00;

   (d) punitive damages as against the Defendants, jointly and severally, in the amount of $500,000.00;

   (e) prejudgment and post judgment interest pursuant to s. 128 of the ***Courts of Justice Act*** R.S.O. 1990 c. C43; and

2. A Declaration that publicly-funded universities, governed by statute, and the conduct of their administration and personnel, are subject to constitutional review under, *inter alia*, ss.24(1) 32, and 52(1) of the ***Constitution Act, 1982***.

3. An interim and permanent injunction to be granted to the Plaintiff, ordering the University of Guelph to allow the Plaintiff to freely be present at the University campus, and in particular at his lab and office, in the Pathobiology Building, without conditions or interference from the University, to pursue his work.

4. costs of this action on a substantial indemnity basis and such further or other relief as this Court deems just.

THE PARTIES

The Plaintiff

- ***Dr. Byram Bridle***

5. The Plaintiff, Dr. Byram Bridle ("Plaintiff") is an Associate Professor of Viral Immunology in the Department of Pathobiology at the University of Guelph. He holds a MSc and PhD in immunology and a post-doctorate in viral immunology. His academic appointment as an independent researcher and faculty member of the Ontario Veterinary College at the University of Guelph commenced in January 2012. In December 2017, the Plaintiff was awarded tenure at the University of Guelph. He is a member of the University of Guelph Faculty Association ("UGFA").

6. The Plaintiff's research program at the University of Guelph focuses on the development of vaccines to prevent infectious diseases and to treat cancers, as well as studying host immune responses to viruses, for humans.

7. The Plaintiff has received and relies on numerous grants and funding to support his cancer research, and basic viral immunology research programs, including from the:

   (a) Canadian Institutes of Health Research;

   (b) Natural Sciences and Engineering Research Council of Canada (NSERC);

   (c) Terry Fox Research Institute;

   (d) Canadian Cancer Society;

   (e) Cancer Research Society;

   (f) Canadian Breast Cancer Foundation;

   (g) Ontario COVID-19 Rapid Research Fund;

(h) University of Guelph/Ontario Veterinary College/Department of Pathobiology COVID-19 Seed Funding;

(i) National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx);

(j) OVC Pet Trust;

(k) The Smiling Blue Skies Cancer Fund;

(l) Canadian Foundation for Innovation - John R. Evans Leaders Fund;

(m) Canadian Foundation for Innovation - Infrastructure Operating Funds;

(n) Ministry of Research and Innovation Ontario Research Fund - Research Infrastructure Program.

8. The Plaintiff currently has seventy-four (74) peer-reviewed publications in high-quality scientific journals that are indexed on "PubMed", which is operated by the United States National Institute of Health. Most of these publications involve long-term studies, often spanning several years. The average impact factor of the Plaintiff's publications far exceeds that of most of his colleagues at the University of Guelph. The Plaintiff routinely publishes in journals with impact factors exceeding five (5). As such, most of the Plaintiff's publications rank in the top 5-10% of the scientific literature, in terms of their importance. The Plaintiff has one additional manuscript that was recently accepted for publication in the journal *Frontiers in Immunology*, which has an impact factor of 7.561, as well as other manuscripts that are currently under review. The Plaintiff has published forty-one (41) peer-reviewed papers since the beginning of 2020 alone.

9. Since 2020, the Plaintiff has secured two grants to support COVID-19-focused research, which were exceptionally difficult to secure. In 2021, the Plaintiff was the only applicant from the Department of Pathobiology to successfully obtain funding from the Natural Sciences and Engineering Research Council of Canada (NSERC): a five-year grant.

10. The Plaintiff has brought millions of dollars of operating funds to the University of Guelph over his tenure as a faculty member. This included agencies that the University of Guelph had never received funding from before, including a very prestigious grant from the Terry Fox Research Institute, and another one from the Canadian Centre of Excellence in Biotherapeutics for Cancer Research. Furthermore, the Plaintiff has acquired more than one million dollars worth of research equipment, which included upgrading the University's core flow cytometry facility to the state-of-the-art facility it is today, and is a resource used by many labs across the campus.

11. The Plaintiff's research lab and office are located, on two different floors, in the Pathobiology Department building at the Ontario Veterinary College ("OVC") Pathobiology/Animal Health Lab Building (PAHL). Since its establishment in the Pathobiology building, his research lab has been one of the most active, productive, and successful in the Department.

12. The Plaintiff also teaches several courses at the undergraduate and graduate level on the topics of immunology, virology, and cancer biology at the University of Guelph. The Plaintiff has consistently received excellent ratings by students during their end-of-course evaluations, well above the faculty average. The Plaintiff has received many teaching awards. The Plaintiff has always executed his teaching responsibilities successfully at the University of Guelph. The Plaintiff has twice been elected as an honourary class president, meaning, he was voted top professor of the year (an honour which can only be held a maximum of once per four years.) He has also received the top teaching awarded by North American Veterinary Schools. The Plaintiff's overall average for teaching is 4.75/5.0 (or the equivalent of 95/100).

13. The Plaintiff also trains Canada's next generation of multidisciplinary researchers. Within the context of his research program, the Plaintiff has trained three (3) research associates, six (6) postdoctoral fellows, six (6) PhD students, ten (10) MSc students, nineteen (19) summer

undergraduate research assistants, seven (7) undergraduate research project students, three (3) students from the Work-Study program at the University of Guelph, and five (5) high school students as part of the Sanofi BioGENEius Challenge Canada program.

14. The Plaintiff is recognized as an outstanding reviewer of Health Research and for excellence in teaching in his field.

15. The Plaintiff is a member of the Canadian Oncolytic Virus Consortium (COVC). The COVC is a prestigious Pan-Canadian consortium of highly qualified and respected scientists and researchers in their respective fields.

16. The Plaintiff has served as an expert witness in the field of immunology and also has expertise in virology. He is one of the few Canadian scientists who have expertise in both fields.

17. Due to his expertise in **both** immunology **and** virology, in March 2020, the Plaintiff **received funding from the Government of Ontario and, on December 2020, from the Government of Canada to develop vaccines against COVID-19.** This funding was from the COVID-19 Rapid Research Fund, Ministry of Colleges and Universities and the federal government's Pandemic Response Challenge Program, National Research Council of Canada. The Plaintiff's COVID-19 research focuses primarily on the development of vaccines to prevent infectious diseases, as well as study the body's immune response to viruses. The Plaintiff's cancer research has progressed into four (4) human clinical trials.

18. As a senior viral immunologist and as a research and developer of vaccines, including COVID-19 vaccines, the Plaintiff is a strong proponent of using high quality vaccines in a correct and evidence-based manner.

19. Since the beginning of the COVID-19 pandemic declaration, the Plaintiff has closely followed the scientific research and evidence-based data on COVID-19. Based on his knowledge acquired from this research, the Plaintiff provided evidence-based, balanced scientific information to the

public and policy makers to assist members of the public with making fully informed decisions, as a public service, and, in response to requests from the public, including the media. All his statements are founded on scientific data. As an outstanding reviewer of health research he has, and continues to remain, informed of publications and studies related to COVID-19.

- **The Defendants**

- **University of Guelph**

20. The Defendant, The University of Guelph,a body under s,2 of the *University of Guelph Act S.O. 1964, C.136* (the "ACT"), is a public university and an educational institution as defined under s.1 of the *University of Guelph Act S.O. 1964, C.136* section 5.1(2) of the *Ministry of Training, Colleges and University Act,* R.S.O. 1990, and section 2(1) of the *Freedom of Information and Protection of Privacy Act,* R.S.O. 2005, and was at all material times the Plaintiff's employer. The objective and purpose of the Defendant University of Guelph is the advancement of learning and distribution of knowledge, and, *inter alia* the intellectual development of its members and of the betterment of society as set out in s.3 of the *University of Guelph Act*. The University has a duty to treat the Plaintiff in a fair, non-arbitrary fashion, in accordance with the civil and criminal law and is vicariously liable for mistreatment of the Plaintiff, by other University employees, particularly those who hold a supervisory role and power and control over the Plaintiff, particularly when the University President has been apprised of that mistreatment.

- **Dr. Jeffrey Wichtel**

21. The Defendant Dr. Jeffrey Wichtel ("Wichtel") was at all material times the Dean of the University of Guelph's Ontario Veterinary College as defined under s 11(b) and 12(b) of the *University of Guelph Act* and, as such a holder of public office. He studies animal nutrition, disease, production, and reproduction, and has specialized in trace element and vitamin nutrition

in ruminants and horses. Wichtel is not a viral immunologist. He holds a supervisory role, power and control over the Plaintiff, and in addition to being personally liable for his mistreatment of the Plaintiff, is vicariously liable by others under his supervision and control who mistreated the Plaintiff.

- **Laurie Arnott**

22. The Defendant, Laurie Arnott ("Arnott"), a lawyer by training, was at all material times the Vice President of Faculty Relations at the University of Guelph a senior administrative officer of the University of Guelph as defined under s,11(b) of the *University of Guelph Act*, and, as such a holder of public office. She was at all materials times employed by the University of Guelph. She holds a supervisory role, power and control over the Plaintiff, and in addition to being personally liable for her mistreatment of the Plaintiff, is vicariously liable by others under her supervision and control who mistreated the Plaintiff.

- **Charlotte Yates**

23. The Defendant, Charlotte Yates, ("Yates") is the President and holder of public office as set out in s.14 of the ***University of Guelph Act ("Act")***, and the Vice-Chancellor and CEO of the University of Guelph. As the president, Yates has supervision and direction of the academic work and general administration of the University including over the co-defendants, Arnott, Wichtel, Weese, Bienzle, Pyle, Peregrine, and Greer as set out in the ***Act***. It is her duty to supervise and regulate the conduct of Wichtel and Arnott to act in compliance of, not only the objectives of the University, as personnel and employees under the ***Act***, but also other legal requiremenst under the law. The University has a duty to treat the Plaintiff in a fair, non-arbitrary fashion, in accordance with the civil and criminal law and is vicariously liable for mistreatment of the Plaintiff, by other

University employees, particularly those who hold a supervisory role and power and control over the Plaintiff, particularly when the University President has been apprised of that mistreatment.

- **Dr. J. Scott Weese**

24. The Defendant, Dr. J. Scott Weese ("Weese"), is a veterinary internist and microbiologist, and was at all material times employed by the University of Guelph Ontario as a Professor , as defined under s.1(g) of the ***Act,*** at the Ontario Veterinary College. Weese's office is located in the Centre for Public Health and Zoonoses. Weese was appointed a member of the Ontario Science Table in January 2021. He is not a viral immunologist.

- **Dr. Glen Pyle**

25. The Defendant, Dr. Glen Pyle ("Pyle"), is a Professor, , as defined under s.1(g) of the ***Act,*** in the Department of Biomedical Sciences at the University of Guelph and has a PhD in Physiology and Biophysics. His research investigates the molecular basis of heart failure, and the development of novel therapies for the treatment of heart attacks and chronic heart failure, as well as how menopause increases the risk of heart disease in women, and sex differences in heart function. Pyle was at all material times employed by the University of Guelph. He is not a viral immunologist. His office at the University of Guelph is located at Biomedical sciences building, at Biomed 1646E.

- **Dr. Andrew Peregrine**

26. The Defendant, Dr. Andrew Peregrine ("Peregrine"), is an Associate Professor , as defined under s.1(g) of the ***Act,*** in clinical parasitology at the Ontario Veterinary College ("OVC"). Andrew Peregrine was at all material times employed by the University of Guelph. He is not a viral

immunologist. His office at the University of Guelph is in the Pathology building at PAHL 3825 where the Plaintiff's office and lab are located.

- **Dr. Dorothee Bienzle**

27. The Defendant, Dr. Dorothee Bienzle, ("Bienzle") has a Doctorate in Veterinary Medicine and has a PhD in Immunology. Bienzle's research focused on feline immunity and the role of the epitheliumn equine asthma and has diagnostic expertise in hemolymphatic neoplasia. Bienzle was, at all material times, also a Professor, as defined under s.1(g) of the ***Act,*** Researcher, and employed as a Veterinary Pathologist at the University of Guelph. She was at all material times employed by the University of Guelph. She is not a viral immunologist. Her office at the University of Guelph is in the Pathology building, at PAHL 3822, where the Plaintiff's office is located.

- **Dr. Amy Greer**

28. The Defendant, Dr. Amy Greer ("Greer"), is the Canada Research Chair in Population Disease Modelling and Associate Professor , as defined under s.1(g) of the ***Act*** . She was at all material times employed by the University of Guelph. She is not a viral immunologist. Her office at the University of Guelph is located in the Stewart Building.

- **Dr. David Norman Fisman**

29. The Defendant, Dr. David Fisman's ("Fisman"), is an Epidemiologist who researches the epidemiology of infectious diseases, including community-based and hospital acquired pneumonia, epidemiology of enteric infections, sexually transmitted infections, laboratory datasets as epidemiological resources, infectious diseases, seasonality, environment, and climate

change. Fisman was at all material times a professor of epidemiology at the University of Toronto, Dalla Lana School of Public Health. Fisman was a member of the Ontario Science Advisory Table (Science Table) until he resigned on or about August 23rd, 2022, claiming that the Science Table had become too political. However, on January 27, 2022, prior to resigning, the Ontario government raised concerns about a conflict of interest given his paid role at the Elementary Teachers' Federation of Ontario. Fisman has received research funding from Novartis Pharma Canada Inc, Novartis Vaccines Canada, GlaxoSmithKline Canada, and the Centre for Disease Control.("CDC"). Fisman is not a viral immunologist.

- **Nick Duley**

30. Nick Duley ("Duley") is a designated "Certified Human Resources Leader" and works for Northshore HR Consulting Inc. as a Workplace Investigator. On July 29, 2021, Duley was appointed by the University of Guelph to conduct an "investigation". On November 9, 2021, Duley prepared a report entitled "Re: Investigation of complaints against Dr. Byram Bridle Workplace Harassment Prevention Policy," which was addressed to Arnott. Duley owed a duty of care when investigating the incident and drafting the report. Duley was negligent in how he carried out his investigation, wilfully ignored relevant information, and further acted as a co-conspirator along with the other Defendants, to injure the Plaintiff.

- **John or Jane Doe "Junior Scientist" Creator(s)/Owner(s) of the Website Byrambridle.com and fake Twitter Account @ByramBridle**

31. These Defendant(s) are currently unknown to the Plaintiff, but are those individuals who colluded and/or conspired with the co-defendants, Fisman, Pyle, and Weese, and created the website byrambridle.com and the corresponding Twitter account @ByramBridle, as well as created and

published all content, in order to impersonate, harass, injure, and ruin the reputation and economic interests of the Plaintiff.

32. The Plaintiff states that all the University-employed Defendants, defined and set out by statutory reference under the ***Act,*** are public office holders.

33. The Plaintiff further states that, all the University-employed Defendants, beyond statute and fiduciary duty at common law with respect to his superiors, owe a fiduciary duty of care as colleagues under their Code of Conduct to the Plaintiff, not to engage in tortious or criminal conduct.

THE FACTS

34. The Plaintiff is an expert in immunology and in virology. None of the Defendants have the Plaintiff's expertise in both immunology and virology. None of the Defendants are viral immunologists.

35. Unlike the Plaintiff, none of the of the Defendants are involved in research or development of vaccines.

36. The Plaintiff is not, and has never been, "anti-vaccination". The Plaintiff studies, develops, and researches vaccines. His career is built on the creation of vaccines.

37. The Plaintiff has conducted research and development of vaccines at the University of Guelph for over a decade. This research is dependent on funding from third party donors/grantors.

38. In 2020 and 2021, the Plaintiff was granted funding by both Federal and Provincial governments to develop a Canadian COVID–19 vaccine. This research is ongoing, and consequently, the Plaintiff follows the scientific literature on COVID-19 in general, and COVID-19 vaccines, in particular, very closely.

39. Since the Declaration of the COVID-19 pandemic, and given his specialization in viral immunology and all aspects of the Severe Acute Respiratory Syndrome – Coronavirus V2 (SARS -CoV-2), the Plaintiff has provided scientific expertise, as a public service, to the community, including to the media, on research and science related to COVID-19 and public health policies and mandates when requested, including to CBC News, Global News, Fox News, and the Globe and Mail. As of July 2022, the Plaintiff has provided over two hundred (200) media interviews and speaking engagements on COVID-19 related issues.

40. On Monday August 17, 2020, the Plaintiff presented as a keynote speaker at an international conference on COVID-19 at the New Zealand's COVID-19 Science and Policy Symposium. At this symposium, the Plaintiff publicly raised concerns about the short-cuts in the research and development of the COVID-19 vaccines by international pharmaceutical companies for profit at the time.

41. Thereafter, the Plaintiff continued to participate as an independent scientific expert of COVID-19 vaccines in the media and on discussion panels and presentations.

42. The Plaintiff did not, and does not, have any conflicts of interests and his views were welcome as a scientist with deep integrity and independence. He performed the role of sharing his expertise as a public service and not for monetary compensation or gain. His candid and honest discussion of the scientific data gained popularity.

43. On November 25, 2020, the Vice President of Research for the University of Guelph, Dr. Malcolm Campbell, held a meeting with the Plaintiff and two of his close faculty colleagues, and warned the Plaintiff to censor his speech on COVID-19 matters and withdraw from public appearances altogether. This caused the Plaintiff mental anguish because he had performed this duty as a public servant, on request, to inform the public on matters within his field of expertise, but he was socially

and professionally chastised. Campbell did not give any reasons for his purported dictate which was not in keeping with academic freedom.

44. On November 27, 2020, the Plaintiff was invited by Dr. Forbes of the Public Health Agency of Canada to apply to join the National Advisory Committee on Immunization (NACI) as a volunteer to provide the Government of Canada with his scientific expertise on viral immunology on the COVID-19 vaccines and anti-bodies. NACI did not, and still does not, have a voting member with a specialization in virology and immunology, like the Plaintiff.

45. On December 1, 2020, CTV National News, interviewed the Plaintiff for an episode of W5, where the Plaintiff expressed concerns about the short research timelines in the development of COVID-19 vaccines, which had moved into human clinical trials at that time.

46. During the interview, the Plaintiff indicated:

(a) That he is a vaccinologist and therefore could not be, and was not "anti-vaccination";

(b) That he believes that vaccines are valuable for society and that, in fact, the Plaintiff's career depends on vaccine development; and

(c) That he was concerned about the duration of immunity, where, if the vaccination did not have a sufficient duration, that the populations who were vaccinated first would lose their immunity while other populations were still being vaccinated, and therefore there would be insufficient immunity, leading to the virus spreading again through the initially vaccinated people.

These concerns are true, as the COVID-19 vaccines are now understood to lose their effectiveness very quickly (90 days or so).

47. On December 9, 2020, Health Canada issued emergency authorization of the Pfizer-BioNTech vaccine, with the rollout efforts beginning on December 14, 2020. The agency later authorized the Moderna vaccine on December 23, 2020.

48. On January 2, 2021, the CTV media interview of the Plaintiff on W5 episode was televised nationally. This high-profile interview gained national and international attention.

49. On January 15, 2021, the Plaintiff was a keynote speaker at the Dalla Lana School of Public Health, "COVID-19 Panel Discussion: A Vaccine Recovery". He was invited by the Infectious Disease Working Group of the Dalla Lana School of public Health to be part of a panel discussing COVID-19 vaccines.

50. The panel discussion was open to the public and recorded. The Plaintiff provided candid discussions about some of his concerns with respect to the vaccines, which were then in development and, still in clinical trials. Ninety percent (90%) of all questions to the panel, from the public, were directed to the Plaintiff. The public interest in the Plaintiff's presentation was overwhelming.

51. On February 26, 2021, Health Canada authorized the Oxford–AstraZeneca vaccine for use, until its discontinuance on March 29, 2021, for ages 55 and under, for concerns over blood clots, which concerns about blood clots the Plaintiff had first raised on August 17, 2020.

52. On March 3, 2021, the Plaintiff co-authored a letter with his immunology and virology colleagues to University of Guelph President, the Defendant, Yates and the Provost, Dr. Chapman, to provide recommendations and to assist in developing a plan for in-person learning to restart again in the Fall 2021.

53. On March 5, 2021, a similar version of the letter was also sent to the Medical Officer of Health for Wellington-Dufferin-Guelph Public Health. On March 16, 2021, the letter was published as an "open letter" to the public.

54. On March 11, 2021, the Plaintiff, along with other senior immunologists at the University of Guelph, met with Dr. Cate Dewey, Vice-President Academic, to discuss the University of Guelph's position on vaccine mandates. At this meeting Dr. Dewey indicated that she was aware of the Plaintiff's concerns about the COVID-19 vaccines and would not support mandatory vaccination at the University of Guelph. The University confirmed it had consulted with a lawyer advising against mandatory vaccination. Furthermore, the University had created a system to allow students to report any concerns with respect to vaccine coercion. (However, eventually, on September 24, 2021, the University of Guelph implemented a mandatory COVID-19 vaccination policy, contrary to the March 11, 2021 assertions, and barred unvaccinated students and faculty members from attending campus).

55. On March 23, 2021, the Plaintiff co-authored an open letter with his University of Guelph immunology colleagues, Drs. Bonnie Mallard and Niel Karrow, setting out the safety and efficacy consensus of "COVID-19 vaccines," which had been authorized by Health Canada for interim emergency use and not approved. This letter was widely circulated, nationally and internationally.

56. On April 15, 2021, the Defendant, Weese, criticized the Plaintiff for the public statements he was making. Weese attempted to intimidate the Plaintiff at the monthly Pathobiology Department meeting, by telling him to curtail his discussions and that the Plaintiff and another colleague "needed to be careful about [their] messaging to the public".

57. On May 27, 2021, the Plaintiff was interviewed by Global News correspondent Alex Pierson on the program "On Point." The Plaintiff gave honest and unbiased answers, supported by multiple

peer-reviewed scientific papers. However, due to the time constraints of a nine (9) minute radio interview, the Plaintiff could not provide citations, references and quotes from his review of the research, during the aired interview, to refer to the evidence underpinning his oral assertions, conclusions and opinions. The three salient points the Plaintiff discussed in that interview are accepted principles in the peer-reviewed scientific literature.

58. Immediately following the 'On Point" interview, the Defendants, Pyle, Weese, and Fisman, began a targeted and vicious campaign of personal attacks and harassment aimed at the Plaintiff, over social media, in order to label the Plaintiff, a career vaccinologist, as an "anti-vaxx-er" and disseminator of "misinformation", in order to silence and discredit him. However, the Defendants, Weese, Pyle and, Fisman, did not identify any false information in the interview.

59. Email(s) from Fisman, to Pyle and Weese clearly manifest a conspiracy hatched and instigated by Fisman ,agreeing with Pyle and Weese to destroying the Plaintiff's reputation and work.

60. Since May 27, 2021, after every interview, speech or article written by the Plaintiff, the Defendants, Weese, Pyle, and Fisman would immediately post over social media, labelling him as providing "misinformation", and/or seeking to discredit the Plaintiff as an individual who provides "misinformation" . None of these Defendants, are themselves vaccinologists and viral immunologists. The Defendants, Weese, Pyle, and Fisman failed to identify any false information and distorted, misstated, and mischaracterized the Plaintiff's claims in order to lower his reputation and character as a vaccinologist and viral immunologist.

61. The Plaintiff has always demonstrated his desire to discuss and debate his scientific claims openly with these three (3) Defendants in particular, and others, and has invited those who

disagree with him to do so. These three (3) Defendants' conduct, however, is fundamentally removed from this type of scientific discourse, but simply aimed at personal, baseless, malicious attacks damaging the Plaintiff.

62. Importantly, the three (3) Defendants', Weese, Pyle, Fisman's personal attacks on the Plaintiff were deliberately made so that he would have no knowledge of their conduct given that he did not, and does not, operate on social media platforms. The Plaintiff only learned about these three Defendants' attack through third parties.

63. These three Defendants, Fisman, Pyle and Weese knew, or ought to have known, that the Plaintiff did not and does not have any social media accounts, including on Twitter, and that the Plaintiff was therefore unable to either participate in or defend himself against attacks on his credibility and expertise on social media.

64. In addition to tweets insulting the Plaintiff directly, Pyle, Weese, and Fisman, in their social media posts on Twitter, directed people to a false website, which had been falsely created in the Plaintiff's name, "byrambridle.com", which website was created on May 28th, 2021, within twenty-four (24) hours of the OnPoint Interview. This website's sole purpose was, and continues to be, to impersonate the Plaintiff in order to mock, defame, and damage the Plaintiff.

65. The headline of the website states, next to a large picture of a duck (with the innuendo "quackery"):

> "Byram Bridle is a "viral immunologist who is passionate about improving life"... Albeit not by reducing the spread of covid-19 misinformation".

66. The individuals, Jane or John Does, responsible for creating the website also created a false Twitter Account impersonating the Plaintiff, @ByramBridle, which twitter account also

directly linked to the website byrambridle.com, with the sole purpose of impersonating the Plaintiff in order to mock, discredit, attack, and damage the Plaintiff. For example, in just the first two weeks after it was created, a sample of the @byrambridle fake twitter account's posts were, as follows:

(a) On May 31, 2021, accusing the Plaintiff of dishonesty by putting out "misinformation' and as a purveyor of "myths", @byrambridle posted, as follows:

> Replying to @DFisman,
>
> And here's one more way in which folks everywhere are fighting the kind of misinformation that Dr. Bridle is putting out. @SabiVM made this amazing infographic debunking the myths.

(b) On June 4, 2021, about @byrambridle account's number of followers:

> Well dammit if Not Byram Bridle now has more followers than me. I must be doing something right keeping my message alive! Big pharma will try to silence me but they'll never win! Join my mailing list so big tech doesn't get me either! http://byrambridle.com

(c) On June 5, 2021, attempting to discredit the Plaintiff's recent interview, @byrambridle posted, as follows:

> Thanks for supporting my work! Make sure you go to my website to understand exactly what was said in the interview. This is essential to learning about the efficacy and safety of the vaccine. http://ByramBridle.com

(d) On June 6, about its authorship, in response to another person's tweet stating:

> The new http://byrambridle.com trolling website has been created with funding from the Public Health Agency of Canada.

@byrambridle posted, as follows:

> It hasn't, and there's a disclaimer to that effect there.
>
> If you want to support my work (of which I am the sole author, with some tips from those who have submitted feedback - thx!) you can find me on OnlyFans.
>
> See me strip… away misinformation.

(e) On June 9, 2021, about fact-checks, @byrambridle posted, as follows:

> And here comes the cavalry!
>
> Here's a USA today fact check on Bridle's claims: https://usatoday.com/story/news/factcheck/2021/06/08/fact-check-proteins-covid-19-vaccines-arent-dangerous-toxins/7505236002/
>
> And here's a PolitiFact fact check on the same claims: https://politifact.com/factchecks/2021/jun/07/facebook-posts/no-proof-researcher-claim-covid-19-vaccines-spike-/

(f) On June 13, 2021, @byrambridle posted, as follows:

> But why doesn't the media share our stories!! Oh yea, cause they're not yours, and you continuously misrepresent things until you become a joke.

(g) On June 14th, 2022, claiming it is allowed to impersonate the Plaintiff, @byrambridle posted, as follows:

> I know reading comprehension isn't generally anti-vaxxer's strong suit, but here are the impersonation rules.
>
> What one am I breaking?
>
> help.twitter.com- Misleading and deceptive identities policy

The Plaintiff states that these statements, and other statements quoted in the within Statement of Claim, are statements in furtherance of the conspiracy entered into, and perpetuated by Fisman, Pyle, and Weese.

67. If a person searches for Byram Bridle on the internet, they will be directed to this website, which website appears at first glance to be a website owned by the Plaintiff. If a person searches for Byram Bridle on social media, they are presented with this fake twitter account, which at first appears to be Dr. Byram Bridle's Twitter account. Both the website and the twitter platform use the reader's expectation that they are viewing a platform operated by the Plaintiff to draw readers seeking information in the expertise of the Plaintiff to discredit and smear him instead, for example:

(a) the @byrambridle account states, on June 15, 2021:

> If you're here for the Bridle interview, head to http://byrambridle.com
>
> But let's explore the vaccine disinformation campaign, featuring Peter McCullough, a prominent figure in the anti-vaccine movement. You'll recognize him from Tucker Carlson's & Laura Ingraham's shows…

(b) on September 23, 2022, the @byrambridle account states:

> A reminder, because I've had an influx of new followers. Go. Get. Vaccinated. If you followed this account thinking I don't approve of the vaccines, maybe you should consider how easily you were mistaken (and the implications for your position on vaccination).:

68. The Defendants, Fisman, Pyle, and Weese, knowingly, irresponsibly and intentionally reference this fake website in their social media posts. The Defendants were aware of the website's existence, almost immediately after the website was created. The false Twitter account @byrambridle.com also repeatedly reposts tweets made by the above Defendants. There was and remains a clear link between these Defendants, Fisman, Pyle, and Weese, and the false website and Twitter account.

69. Fisman, Pyle, and Weese's conduct in participating and promoting the impersonation of the Plaintiff was intended to injure and harm the Plaintiff, which it did.

70. The creation and operation of this website became and continues to be the subject of a police investigation which has hit road blocks due to its sophisticated set-up that crosses and is relayed across several countries and a few different continents.

71. On or about May 29th, 2021, the day after the website's creation, Pyle stated that he was in contact with and therefore was aware of the identity of the website's (and Twitter account's) creator. In response to another user's suggestion that a hacker had made the website, Pyle responded:

> "It's not a hacker. **The person who made it has contacted me. They are a scientist."**

When the other user responded by stating that creating a fake twitter account about a colleague was "embarrassing and unprofessional", Pyle further alluded to details about the identity of the website/fake account creator:

> "They [the creator of the website/twitter account] are not a colleague. I don't say that to be dismissive, just to clarify **that this is not someone who is at the same level & has legitimate reason to fear retribution.** You are certainly entitled to your opinion on the website & I'm not here to change anyone's mind on that…"

72. The Defendant, Pyle, deleted these posts to conceal the fact that he knows the identity of the impersonator when confronted with his knowledge of materials facts about the website and fake twitter account's creation separate and apart from the admission that he has knowledge of the creator on social media. Pyle also confided to several of his faculty colleagues including the Defendant, Greer, by email, that he knew the creator of the impersonating accounts. Pyle now falsely claims that he has no knowledge of the website's or twitter account's creation or creator(s).

73. The Defendants', Fisman, Pyle, and Weese's conduct acting together was directed towards the Plaintiff and constituted social media harassment, and furthering the conspiracy to harm the Plaintiff, as follows:

(a) On May 29th, 2021, Fisman's Twitter account, @DFisman, posted the following

> "I've had questions over the past 48h about vaccine safety concerns aired Dr Bryam Bridle at @UofGuelphOAC in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here: byrambridle.com"
>
> …."

(b) On May 29th, 2021, Glen Pyle also posted the following tweets attempting to disparage the Plaintiff's claims made during a nine (9) minute interview, where Pyle mischaracterises the Plaintiff's statements and cites the wrong papers in order to discredit the Plaintiff. For example, Pyle tweets:

> "The paper Byram cited doesn't support his claim. That's pretty telling that a study cited to support his claims actually goes against those claims."

In the tweet, Pyle irresponsibly cities a completely different study than the study Dr. Bridle referred to in his interview.

(c) On May 28th, 2021, in a response to a Twitter user discussing the Plaintiff's OnPoint Interview, where the user posted, the following:

> From Late Last Night: Mechanism of injury explained by Canadian Prof Dr. Byram Bridle at University of Guelph. Includes description of spike protein damage and mobility (including passing through breast milk to cause GI bleeding in infant).

Glen Pyle responded over Twitter:

…"No, this is a hypothesis, and nothing is reviewed or published. A few points:

1. Claims the first access to biodistribution studies. In fact EMA reported these data last year & updated in Feb 2021. (ema.europa.eu/en/documents/a…)…."

In making these tweets, Pyle owed the Plaintiff a duty of care and knew, or ought to have known, that Dr. Bridle could not cite or quote from his scientific references in a nine-minute oral radio interview. Pyle was irresponsible and reckless since he further was not aware of which paper the Plaintiff was referring to and did not make any attempts to apprise himself as to which paper the Plaintiff was referring to, both prior to and after his posts. Pyle failed to notify or speak with the Plaintiff about his concerns, or

ask which study the Plaintiff was referring to, prior to posting remarks he knew were inapplicable, which harmed the Plaintiff's expertise and qualifications, and which did not promote any debate or discussion. Pyle also emailed other faculty members at the Ontario Veterinary College telling them not to respond to the Plaintiff and to ignore him causing the Plaintiff to be further isolated and suffer harm.

(d) On May 30th, 2021, Fisman, through his Twitter account, @DFisman, posted a tweet requesting that his followers follow @glenpyle, and refers to the Plaintiff as a prevaricator:

> "An excellent follow for good immune science from @UofGuelphOAC is Dr @glenpyle, who has addressed some of the misinformation in his own tweets,"
>
> [and here Fisman reposted Pyle's tweet below:
>
> > "The paper Byram cited doesn't support his claim. That's pretty telling that a study cited to support his claims actually goes against those claims."
>
> And etc.]

(e) On May 30th, 2021, Weese, from his Twitter account @weese_scott, replied, on May 30th, 2021, as follows:

> "It's tough but misinformation has to be challenged. More misinformation and confusion during a pandemic are dangerous and causing harm."

74. The Plaintiff states, and the fact is, that all the above-noted posts to, and from, and through these fake cites, are statements made in furtherance of the Defendants', Fisman's, Pyle's, and Weese's conspiracy to injure the Plaintiff, and harass him online.

75. On May 29, 2021, upon becoming informed by concerned colleagues and students at the University, the Plaintiff immediately brought the fake Twitter account and website to the

attention of the University of Guelph and informed the University of Guelph, through the Defendant Wichtel, that he was being personally targeted by the creation of this fake website and the Defendants Pyle and Weese were, along with Fisman, promoting fraudulent and impersonating internet forum attacking his credibility and expertise, causing him harm. The Plaintiff further indicated in the email to his colleagues that the online harassment was causing him to fear for his safety as well.

76. The Defendant, Wichtel, as his Dean, owed the Plaintiff a duty of care to investigate the information, and in particular Pyle's role and conduct in harming his reputation and character as a scientist and vaccinologist.

77. The Defendant, Wichtel, refused to investigate, assist or intervene in any manner whatsoever to stop the harassment.

78. The Plaintiff states, and the fact is that, at this point the Defendant Wichtel , by his refusals, and green light to Weese and Pyle to continue with the harassment and conspiracy, joined the already on-going conspiracy along with Fisman, Pyle and Weese to injure the Plaintiff.

79. On May 30, 2021, Pyle emailed a response to the Plaintiff, copying Wichtel, falsely claiming that he had no knowledge of the website.

80. On May 30, 2021, the Plaintiff requested the three Defendants, all academics, discuss and debate scientific disagreements with him directly, instead of posting comments claiming he is a liar, or purveyor of lies on social media covertly. None responded and failed to identify a false utterance.

81. On May 31st, 2021, the Plaintiff became aware that the Defendant, Weese, continued to conspire with Fisman and Pyle in accusing him of falsifying science on social media. The Plaintiff wrote to Weese directly over email, while copying the Defendant, Wichtel. The Plaintiff asked Weese to set out what information he was accusing the Plaintiff of distorting as "misinformation" and provide him with the scientific evidence supporting Weese's claim that the Plaintiff was falsifying information. The Plaintiff attached scientific publications in defence of his statements as truthful and accurate and invited Weese to respond and debate with him about the science. Weese failed to respond to the Plaintiff or identify a false utterance.

82. The fake byrambridle.com website, along with the fake twitter account @byrambridle, have remained live and are both extremely active from the date of creation until the present date. The Twitter account, @ByramBridle has tweeted over 1434 tweets as of October 1, 2022, all attempting to attack, discredit, and diminish the Plaintiff's reputation, credentials and expertise, in the eyes of his academic, research and professional communities, the general public, and the world at large.

83. In addition to posting and or promoting the two fake accounts, the Defendants, Pyle, Weese, and Fisman, continued to smear the Plaintiff's reputation online, hiding behind their social media accounts and refusing to identify any "fake information" . These Defendants continue to refer to the Plaintiff, a vaccinologist, as an "anti-vaxxer," and who is an eminent scientific researcher, as a purveyor of "misinformation." These Defendants continue to harass the Plaintiff in order to destroy his position, profession and, standing as a vaccinologist and viral immunologist.

84. On June 2, 2021, the Defendant, Wichtel provided faculty, including the Plaintiff, with a University of Guelph "approved" "official" statement with respect to the Plaintiff's media engagements, titled "Bridle Response". The statement reiterates, in general terms, the

University's objective of dissemination of knowledge, advancement of learning and academic freedom and freedom of expression.

85. Notwithstanding this official statement for all faculty to respond to media inquiries regarding the Plaintiff, the Defendant Fisman, co-conspired with the Defendants, Weese and Pyle to personally malign the Plaintiff as "dangerous" and harass the Plaintiff as a purveyor of "misinformation" to the public at large through social media and to the press. Email(s) from Fisman, and Pyle, dated on or around June 2nd, 2021 to a USA TODAY journalist indicate false statements that the Plaintiff was distorting scientific evidence and that the Plaintiff was part of a "disinformation operation" to shake vaccine confidence, and that the Plaintiff was becoming "more and more" "anti-vaxx." It further promoted the fake website to media and injured the Plaintiff.

86. On June 2, 2021, the Plaintiff filed a workplace harassment report against his academic colleagues, Pyle and Weese, and included the Defendant, Fisman, based on directions and instructions from University of Guelph administration, including the Defendant Wichtel, regarding the three (3) Defendants' social media posts and impersonating website and Twitter account. The Plaintiff requested the complaint to be given high priority.

87. The Plaintiff's June 2, 2021 harassment complaint against the Defendants, Pyle and Weese, set out the full facts and instances of the conspired harassment by the three Defendants, Pyle, Weese, and Fisman.

88. The Defendants, the University of Guelph, Wichtel, and Arnott, failed to respond urgently, **or at all**, until June 23 2021, at which point they dismissed the complaint entirely without providing any reasons whatsoever. The Plaintiff states, and fact is, that not only is this further

evidence in furtherance of the Defendants' Fisman's, Pyle's, Weese's , and Wichtel's conspiracy against the Plaintiff, but an overt manifestation of Arnott's entry into the conspiracy to harm and destroy the Plaintiff's work, and intention to try to drive him out of the University.

89. Both Wichtel and Arnott owed the Plaintiff a duty of care to respond urgently, and guide and support him in accessing the correct resources and process, which they refused. As a result of the Defendants, Wichtel and Arnott's, refusls to act, inaction and failure, the harassment of the Plaintiff continued unabated. In or around June 2021, the Defendant, Fisman, posted the following tweet:

> David Fisman @DFisman
>
> "The website debunking Dr. Bridle's covid-19 vaccine claims has been updated with lots of peer-reviewed science that attests to the safety of vaccines.
>
> Byrambridle.com
>
> And for those who think I made or organized this website: nope. But grateful to the scientists who did."

> David Fisman @DFisman
>
> "A friend indicates that Dr Bridle's interview caused his parents to cancel their vaccine appointments. This is not ok."

Again, statements in furtherance of their conspiracy, and continuance of their on-line harassment. The Plaintiff states, and re-iterates, that all social media posts extracted in the within Statement of Claim are statements pled as statements in furtherance of the Defendants' conspiracy and on-line harassment against the Plaintiff.

90. On June 12 and 14, 2021, as the Defendants continued to attack the Plaintiff over social media, the Plaintiff sent emails to the Defendants Pyle, Weese and Fisman to again request that they

debate with him directly, provide him with proof of false information, and cease attacking him behind his back. However, the Defendants chose not to respond, or identify any falsehoods.

91. On June 14, 2021, the Plaintiff emailed Pyle, Weese and Fisman documents written by the inventor of mRNA vaccine technology, Dr. Robert Malone, corroborating the Plaintiff's statements, to disabuse the Defendants of the notion that the Plaintiff was making false claims about COVID-19 vaccines. These three Defendants refused to respond to the Plaintiff, and instead contrived, and conspired, and continued to further smear and harass the Plaintiff.

92. On June 15, 2021, the Plaintiff published the "Covid-19 Vaccines and Children: A Scientist's Guide for Parents". This report was produced in response to overwhelming number of requests to the Plaintiff, from members of the public, for detailed references to scientific data and the most current independent research on COVID-19 variants due to his expertise. The Plaintiff specifically sent his publication to the Defendants, Weese, Pyle, and Fisman's attention as well as many other University of Guelph faculty. The Defendants were made aware of the scientific underpinnings relied on by the Plaintiff were not false or misleading. The Defendants Pyle, Weese, and Fisman, did not refute or identify any false information in the report. In forwarding this report, the Plaintiff asked the Defendants to review the guide, and specifically again wrote that he was open to discussion of this research.

93. That same day, on June 15, 2021, the Defendant Weese, responded to another person discussing the Plaintiff's report "COVID-19 Vaccines and Children: A Scientists Guide for Parents" on Twitter. Weese responded by posting an image of a man shovelling manure along with the following text:

> "spreading it…[picture of shovelling manure]"

In doing so, the Defendant Weese smeared the Plaintiff, by innuendo, as a "bullshitter," again a statement in furtherance of the conspiracy and online harassment against the Plaintiff.

94. On June 17, 2021, the Plaintiff was invited to speak at a news conference in the Press Gallery of Parliament Hill. Immediately after the News conference, the Defendant Weese, posted on Twitter:

> "An[sic] far right politician, anti-vaxxer and guy who compared public health measures to the Holocoaust walk into a press room…
>
> I wish there was an actual joke in there. The real story's too sad/frustrating/maddening
>
> Misinformation kills. We need to address and remember that.

Again, a statement made in furtherance of the Defendants' conspiracy and online harassment.

95. The Defendant Weese publicly refers to the Plaintiff, who is a vaccinologist, and whose research and program, and publication record focuses on vaccine development, as an "Anti-vaxxer," purveyor of false information and "killer."

96. The Plaintiff claims, and the fact is, that the Defendant Weese, has continued to attack and on-line harass the Plaintiff personally on Twitter, as follows:

(a) On June 21st, 2021

> Rachel Green @4bbhb • Jun 20, 2021
>
> Replying to @MDinCanada
>
> "Shame on the #cpso for not investigating @dfisman for harassing and bullying Dr Byram Bridle, and the sharing of confidential medical information his parents"
>
> Diana C #TrudeauMustGo @diana_c2021 • Jun 20, 2021
>
> Replying to @MDinCanada @4bbhb and @DFisman

> "Here's website and account discrediting Bridle that Fisman tweets about and RTs. Proof that personal info was released about his parents seems to have been disclosed by Bridle in the recent cpac conference organized by Derek Sloan. He did not name names…"
>
> J Scott Weese @weese_scott
>
> Replying to @diana_c2021 @4bbhb and @DFisman
>
> "It seems like Bridle (surprise, surprise) misinterpreted a comment and (surprise, surprise) continues to spew misinformation about it.
>
> I've seen nothing supporting it and how would the person he's accusing have access to Bridle's parents' info?
>
> Just more misdirection.
>
> 6:41 AM • Jun 21, 2021 • Twitter Web App

Again, statements made in the furtherance of the Defendants' conspiracy and online harassment.

97. On June 22, 2021, the Plaintiff, once again, sought to end the harassment and the harmful allegations made by Weese about him on social media via an email request to his academic colleagues, including the Defendants, Weese and Pyle, and proposed a manner of engaging on public interest issues which would be respectful and not harmful to his personal reputation and profession.

98. On June 23, 2021, the Plaintiff provided a request from an internationally renowned scientist and the inventor of mRNA, Dr. Robert Malone, to the Defendant Wichtel, and the Defendants, Weese and Pyle for the University to end the harassment of the Plaintiff and, which request fully supported the Plaintiff's scientific assertions as sound.

99. The Defendants, Arnott, Wichtel, Weese, and Pyle were thus aware and had knowledge of this letter, and were also aware, or ought to have been aware of how their actions and inactions injured the Plaintiff and harmed his expertise. The Defendants, Arnott and Wichtel, were aware

that the Plaintiff's harassment was apparent and obvious to all who viewed/read the comments both inside and outside of the University.

100. Notwithstanding this fact, on June 23, 2021, the Defendants Wichtel and Arnott having refused to investigate the Plaintiff's concerns, instead dismissed the Plaintiff's workplace harassment complaint against the Defendants, Fisman, Pyle, and Weese as 'frivolous" summarily and verbally with no written reasons or decision, as being outside the scope of the jurisdiction of the collective bargaining agreement because the online harassment was taking place outside the campus grounds. The Defendant Wichtel, in verbally dismissing the Plaintiff's complaint, feigningly suggested to the Plaintiff that the Plaintiff engage in "open discussions" directly with the Defendants, Pyle and Weese, as the only way left to deal with them. This, notwithstanding the numerous attempts to do so, by the Plaintiff, had fallen on deaf ears and knowing that this foreseeably would cause the Plaintiff more harm and injury and/or escalate the disagreements within the Faculty. The Plaintiff again states that these actions by these Defendants were in furtherance of their conspiracy to harm the Plaintiff.

101. As a result of the dismissal of his complaint and request for formal resolution, the Plaintiff again requested the Defendants Pyle and Weese, engage with him to solve and end the ongoing harassment. This onus of engaging in "open discussions" was placed on the Plai by the University of Guelph, through Wichtel, and Arnott.. Following the dismissal of the Plaintiff's complaint, the Plaintiff pursued a criminal complaint against Weese and Pyle.

102. On June 24, 2021, a peer-reviewed scientific paper was published[1] that independently drew very similar conclusions to those drawn by the Plaintiff, months earlier. The Plaintiff's Guide

[1] Citation: Walach, H.; Klement, R.J.; Aukema, W. The Safety of COVID-19 Vaccinations—We Should Rethink the Policy. Vaccines 2021, 9, 693. https:// doi.org/10.3390/vaccines9070693

therefore outlined the scientific basis for the US-FDA caution of risks posed to children and adding warnings to the labels for the Pfizer and Moderna vaccines regarding the association with myocarditis (inflammation of the heart) and pericarditis (inflammation of the sack surrounding the heart). The relevant text is:

> Today, the FDA is announcing revisions to the patient and provider fact sheets for the Moderna and Pfizer-BioNTech COVID-19 vaccines regarding the suggested increased risks of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the tissue surrounding the heart) following vaccination. For each vaccine, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) has been **revised to include a warning about myocarditis and pericarditis** and the Fact Sheet for Recipients and Caregivers has been revised to include information about myocarditis and pericarditis.[2]

103. On June 24, 2021 **the Plaintiff formally invited the Defendant Weese and Pyle to publicly** discuss the issue of COVID-19 vaccines for children instead of personally attacking him on Twitter in light of his new publications. The Defendants, Wichtel and Pyle, refused to respond, retract or apologize.

104. The Defendant Wichtel contributed to the escalation of the conflict between the Plaintiff and the Defendants, Weese and Pyle, by placing the onus of conflict resolution on the Plaintiff, and paying 'lip service' to academic freedom. The Defendant Wichtel contradictedly sided and collaborated with the Defendants Pyle and Weese, **and prohibited the Plaintiff from contacting these two Defendants** through email, which was the only medium open to the Plaintiff .

105. The Plaintiff has never mentioned the names of, or personally attacked, the Defendants, Weese, Pyle, or Fisman, in a public forum. He has always maintained the position of open discussion of

[2]): https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-june-25-2021

science, even in the face of their continued personal attacks to his name, qualifications and expertise.

106. The Defendants', Fisman's, Weese's and Pyle's posts reached members of the University, as well as members of the general public through the world wide web. The University permitted a malicious, castigating, and reckless double-standard to apply, in which the Defendants, Pyle and Weese, could continue to smear the Plaintiff unabated to the public at large, but the Plaintiff was to immediately cease and desist the only avenue of direct electronic communication while being directed to solve the issue through "open discussion." The Plaintiff states that this conduct, by Wichtel was in furtherance of the conspiracy against the Plaintiff, and online harassment against him..

107. Furthermore, as a result of banning the Plaintiff from emailing the Defendants, Weese and Pyle, the Defendant, Wichtel, further knew, or ought to have known that prohibiting email communication would result in the continuation of a one-sided and ongoing personal attack against the Plaintiff on social media by the Defendants, Weese and Pyle, aiding, abetting, and co-conspiring with the harassment against the Plaintiff.

108. The Plaintiff pointed out this unfair treatment and collusion between the Defendants in an email to Wichtel on June 24, 2021.

109. The Defendants, Wichtel together with Arnott thus, collaborated, colluded and co-conspired with the Defendants, Weese and Pyle, to harm the Plaintiff. The University's actions and inactions through Wichtel and Arnott emboldened the Defendants Weese and Pyle to continue to injure the Plaintiff, and thus knowingly, conspire to cause him harm and to conscript other University of Guelph faculty to join in the harassment, and injuring of the Plaintiff.

110. On or around June 30, 2021, the Municipal Police commenced a criminal investigation of the fake website and Twitter accounts impersonating and damaging the Plaintiff. The Municipal Police required and requested the collaboration and cooperation of the University of Guelph Campus police to do so. While the investigation was ongoing, the Defendant, Arnott interfered with and re-directed the inquiries ,with respect to criminal investigation between Guelph University Police and the Municipal Police, to herself under the pretext of Human Resources.

111. On July 6, 2021, notwithstanding the "Official June 2, 2022 University Statement on Dr. Bridle" the Defendants Greer, Bienzle, Weese, and Pyle, co-authored an open letter and solicited seventy-six (76) other faculty to sign it, some under pressure. These Defendants are the Plaintiff's academic contemporaries, co-faculty at the University of Guelph, and owed the Plaintiff a duty of care. The Defendant Peregrine, in particular, has historically relied upon, benefited from and deferred to the viral immunology expertise of the Plaintiff. The letter personally attacks the Plaintiff's credibility and expertise in viral immunology and accuses the Plaintiff of deception and falsification as a vaccinologist and scientist. The Plaintiff states, and fact is, that this was the first overt manifestation of the Defendants Greer, Bienzle, and Peregrine's joining the conspiracy against the Plaintiff in knowingly causing injury through false statements and accusations, to damage the Plaintiff's work and career. These Defendants acted in furtherance of an agreement to injure the Plaintiff and was directed to the Plaintiff .

112. The July 6, 2021 letter was posted on-line, published both inside and outside the University of Guelph, circulated widely on the internet by the Defendants Greer, Weese, Bienzle, Peregrine and Pyle, and the Defendant Fisman, who conspired to harm the Plaintiff.

113. The July 6, 2021 letter, caused the Plaintiff to suffer harassment and harm to his standing, profession and research, both on campus and off campus, as a viral immunologist, vaccinologist

and expert in his field as evidenced by the reliance of the letter in court proceedings to discredit the Plaintiff's expertise and cause harm to his reputation.

114. The Defendants' harassment of the Plaintiff and damage to him was apparent to the wider Canadian community. Scientists requested that the University of Guelph, and the co-conspirator Defendants, cease their conduct intended to silence the Plaintiff, cause him harm, and push to remove him from campus.

115. Due to the Defendants', Wichtel's and Arnott's decision and, complicity in allowing the on-line harassment of the Plaintiff to continue unabated and escalate, and further to permit the Defendant faculty members, instigated by Greer to malign the Plaintiff, his life at the University became increasingly toxic and harmful. In an effort to resolve the toxic relationships in his immediate work environment, being his lab and office at the Pathobiology Department, prior to the commencement of the academic teaching team, the Plaintiff invited some of the drafters and signatories of the July 6, 2021 open letter to meet with him at his campus office, and provide them with evidence of his position, which they harmfully and generally claimed was false and inaccurate.

116. On July 20, 2021, the Plaintiff provided four of his departmental colleagues, with offices in the same building, including the Defendants, Peregrine and Bienzle, with a document package consisting of articles, from government sources, as evidence to demonstrate to the Defendant signatories that he was not a prevaricator or "spreading misinformation" regarding "COVID-19 vaccines" for children, in order for them to retract the damaging and harmful July 6, 2021 open letter. He also provided the same package to the Defendants Weese and Greer whose offices were not in the Pathobiology building. The three articles the Plaintiff presented to his colleagues were as follows:

(i) Headline from U.K. newspaper "The Telegraph", dated July 19, 2021:

> "Covid vaccines on hold for most children amid fears they could trigger heart conditions"
>
> "Joint Committee on Vaccination and Immunisation says small risks from virus do not outweigh potential risks from vaccines"

(ii) Press Release Publication from Public Health England, JCVI issues advice on COVID-19 vaccination of children and young people, dated July 19, 2021:

> "As evidence shows that COVID-19 rarely causes severe disease in children without underlying health conditions, at this time the JCVI's view is that the minimal health benefits of offering universal COVID-19 vaccination to children do not outweigh the potential risks."

(iii) Publication of the "Royal College of Pediatrician and Child Health," dated July 19, 2021:

> "The JCVI advice reiterates what the evidence tells us - that most children are at minimal risk of being made seriously ill by COVID. Having looked at the available national and international data, the Committee has weighed in the balance the benefit to children over 12 of being vaccinated, against the very small but important risk of potential side effects from the vaccine. They have decided that for children who are otherwise healthy, the risk is not outweighed by the benefit."

117. The Plaintiff chose references to governmental policy as a point to initiate discussion on the science of which he had expertise and included a personal covering note accompanying this document package. The personal note stated:

> "Are you sure that you are on the right side of history? **My door is always open if you would like to chat about the science instead of making false assumption about my intentions and expertise**. My foresight is based on following the science. I genuinely care about the health and well-being of children. Immature behaviour is unbecoming of a professional. I have been deeply hurt by your profound disrespect. Byram"

118. The Plaintiff delivered the document package by leaving a copy **under the office doors** of the Defendants, Greer, Bienzle, and Peregrine, and two other faculty members within the

Department of Pathobiology, and in the departmental mailbox of the Defendant Weese, well after regular office hours.

119. Upon receipt of this note and documents, the Defendants, Weese, Pyle, Peregrine, Bienzle, and Greer, turned the Plaintiff's harassment allegation against them, into an opportunity to remove the Plaintiff from campus. These five (5) Defendants entered into an agreement to falsely characterize the above personal note, and invitation to talk they received on July 21, 2021, as well as the Plaintiff's presence, as "threatening."

120. By email , on July 21, 2021, the Defendants Bienzle, Pyle, Peregrine, Weese and Greer entered into an agreement and conspired with one another, plotting to portray the Plaintiff's gesture to resolve the alleged scientific disagreements which the Defendants, Wichtel and Arnott, had allowed to become personal and acrimonious, into a "threat to their physical safety" to effect his removal from campus.

121. On Wednesday July 21, 2021, by email, the Defendant Pyle, encouraged by the Defendants, Weese, Greer and Bienzle, distorted, fabricated, and exaggerated the Plaintiff's efforts by involving campus police.

122. Emails between these Defendants, dated July 21, 2021 and July 22, 2021 manifest concrete evidence that the Defendants communicated this intent, with each other, both over the phone and through email correspondence. Instigated by Weese, the Defendants Pyle, Greer, Peregrine and Bienzle planned to file multiple and separate criminal complaints with the University of Guelph's Campus Police, **prior to** and contemporaneous with any actual encounter with the Plaintiff.

123. In furtherance of this plan, on the morning of July 22, 2021, **before she saw the Plaintiff,** Bienzle emailed Campus Police a harassment complaint against the Plaintiff on the pretext that

she received the above documentary package and a "threatening note", referring to the cover note described above, under her door. The Plaintiff was unaware that Bienzle had complained to Campus Police prior to seeing her in his office space.

124. On July 22, 2021, **after** emailing Campus Police, when Bienzle and Peregrine saw the Plaintiff in his office building, seized the opportunity to fabricate a physical threat and safety risk when the Plaintiff asked them if they had read his report, or, the articles that he had left under their doors. Both Defendants acted as if they were under physical attack by slamming the office door on the Plaintiff and barricading themselves in the office while simultaneously recording an emergency call to the Campus Police unnecessarily causing a commotion. Students present in the building questioned why it was necessary for the Plaintiff to speak to the Defendants, Bienzle and Peregrine through the closed door, instead of by email, unaware that the Plaintiff was prohibited from sending an email by the Defendant, co-conspirator, Wichtel.

125. When two Campus Police officers attended the building, Bienzle and Peregrine fabricated allegations that the Plaintiff physically threatened them and was a risk to their safety in the Pathobiology office building as per the plan made with their co-conspirators, Weese and Pyle. Constable Beckmann interviewed the Defendants Bienzle and Peregrine. The Plaintiff was interviewed by Sargent O'Connell. During his interview the Plaintiff described in detail the on-line and workplace harassment he endured since May 2021 from the Defendants Pyle and Weese, which culminated in the harmful July 6, 2021 letter being circulated widely by them and the Defendant's Bienzle, and Peregrine and Greer. The Campus Police officers made contemporaneous notes of these interviews.

126. Both officers concluded the Plaintiff did **not** pose a safety risk or threat to anyone in the Pathobiology building and the Plaintiff could remain and resume his work in the building. The

officers, upon concluding that the situation was "safe," left the Plaintiff to remain at his office, immediately after the incident, to carry on in the Pathobiology lab and in his office. The Campus Police then proceeded to investigate the Defendants, Pyle and Weese after being apprised by the Plaintiff of the full historical context of their on-line harassment and personal attacks on his expertise on vaccines.

127. The Defendants, Weese, Bienzle, Pyle, and Peregrine, not satisfied with the failure of their scheme to frame the Plaintiff's physical presence in the Pathobiology building as a threat to their safety and a form of personal harassment in order to remove him from campus, entered into an overlapping conspiracy with the Defendants, Wichtel and Arnott, to falsely allege "workplace harassment." The "workplace harassment" is based on the exact same facts, incidents, and allegations. In substance it is exactly the same, but in form it is a different process to achieve the same end which was to remove the Plaintiff from his office, lab, and the campus.

128. The Defendants, Arnott and Wichtel, as manifested from email correspondence, subsequently interfered with, and terminated the Campus Police's investigation into the Plaintiff's allegations of harassment against the Defendants Pyle and Weese together with the harassment complaints reported to them by Pyle, Peregrine, and Bienzle. The Campus Police Report states that the University administration ended the Campus Police investigation. The Defendant, Arnott instead commenced a private, one-sided investigation, under the pretext of "workplace harassment" on July 22, 2021. The Defendants, Wichtel and Arnott, colluded and conspired with the Defendants Pyle, Peregrine, Bienzle, Weese, and Greer, to isolate, and banish the Plaintiff from campus resulting in harm to his research and reputation as an expert vaccinologist.

129. The Defendants, Wichtel and Arnott, further knew that the Defendants, Greer, Pyle, Peregrine, Weese, and Bienzle, had and continued to harass the Plaintiff at the University, and also online,

and to the public at large through the letter dated July 6, 2021, describing the Plaintiff as a falsifier and liar on the scientific area of his expertise, over which the Defendants had **no** expertise.

130. The University of Guelph, particularly Wichtel and Arnott, engaged in a distorted and biased acceptance of the Defendants' claims of "harassment", while abusing their power to dismiss the Plaintiff's own, much stronger, harassment claim, entirely, and with no reasons. The false allegations of threats (of violence and to safety) set out in their own emails to Witchel, by the Defendants, Pyle, Bienzle and Peregrine, was criminal in nature (threat to physical and psychological safety) and lacked statutory authority.

131. On Friday July 23, 2021, the Defendants, Wichtel and Arnott engaged in an abuse of public office and an abuse of their authority and powers as University administrators to prohibit the Plaintiff from attending his research lab, office and the University campus by falsely labelling the Plaintiff as a "real and present danger" to the University community and/or property, without any evidence, or without providing reasons, in order to nullify the decision of Campus Police officers to permit the Plaintiff to remain in his office, lab and on University property. This decision, to prohibit the Plaintiff from continuing to conduct research at his lab by illegally invoking an "interim measure" was intended to injure the Plaintiff. The Defendant, Wichtel, **took less than a few hours to** endorse the Defendants', Pyle, Bienzle, and Peregrine's plan to remove the Plaintiff on the basis of a spurious "harassment" claim, while he took 21 days before responding to, and summarily dismissing, the Plaintiff's harassment claim against Weese and Pyle, as a further abuse of his public office.

132. The Defendant, Wichtel, in prohibiting the Plaintiff from attending University Property, acted maliciously with the knowledge that the Plaintiff's work is the most lab research intensive of all

the departments. Witchel's conduct lacked authority and interfered with the Plaintiff's professional, academic and research obligations and rendered him unable to complete his work in a remote capacity. The Defendant, Wichtel, knew that the Plaintiff was and is the **only person on campus** who could perform some of the procedures required to be completed in person, for the animal-based experiments at his lab. The Defendant, Wichtel, further aggravated this injury because he knew the importance of the Plaintiff's access to his lab in July up to December 2021, in particular. The Plaintiff's research was immeasurably damaged by the decision. As a result of his removal from the University, the Plaintiff lost control over the materials necessary to continue his research and development of the COVID-19 vaccines and irreparably harmed his research and collaboration with funders and other researchers.

133. The Plaintiff states, and fact is, that the Investigation, conducted from July 22, 2021 to November 6, 2021was *ultra vires* the University's powers.

134. On Friday, July 29, 2021, the Defendant, Nick Duley of Northshore HR Consulting Inc., was hired by the Defendant University of Guelph as the private investigator for the "workplace harassment complaint," filed by the Defendants, Pyle, Peregrine and Bienzle to post-facto rubber stamp the Defendants', Wichtel's and Arnott's, decision and the Defendants', Weese's, Pyle's, Peregrine's, Beinzle's and Greer's, conspiracy. The Defendant, Arnott, lacked authority to mandate the consultant to investigate essentially criminal allegations. In order to do so, the Defendant, Arnott, interfered with and halted the Campus Police criminal investigation and recharacterized it as a "workplace harassment," exclusively focused on the allegations against the Plaintiff, to the exclusion of the allegations against the Defendants Pyle, Weese, and the July 6, 2021 letter.

135. The Defendant, Duley, knew or ought to have known, that he was hired to determine criminal allegations made by the Defendant Pyle, including allegations of physical threat and physical safety which had already failed to be substantiated by the Defendants Pyle, Peregrine and Bienzle, upon investigation by Campus Police. The Defendant, Duley failed to investigate the root causes of the friction between the Plaintiff and the Defendants, Pyle, Peregrine, and Bienzle despite the clear, convincing and credible evidence presented to him by witnesses, including Sargent O'Connell, from the University of Guelph Campus Police, during this interview of Sargeant O'Connell. Among other things this evidence included the ongoing and related criminal investigation by Municipal Police commenced one month **prior** to the Defendants" harassment allegation.

136. The Defendant, Duley, failed to connect and assess the preceding mistreatment inflicted against the Plaintiff by the Defendant, Pyle and Weese, to the complaint of harassment filed against him. The Plaintiff states that this is all indicia of Duley joining the conspiracy against the Plaintiff, whether knowingly and/or as a "duped" co-conspirator, as well as his negligence and the lack of jurisdiction in conducting an essentially criminal investigation, given his knowledge of the role played by Pyle and Weese in the criminal conduct against the Plaintiff that goes beyond the scope of the collective agreement despite their status as co-workers. As a result, the Plaintiff did not participate in the investigation, because of its clearly "Kangaroo Court" set up and framed premise and origin which lacked statutory authority. The Plaintiff states and the fact is, that Nick Duley was a "hired gun", with the knowledge,complicity and intent to produce a pre-set result to Arnott's plan.

137. The Defendants, Duley, Wichtel, and Arnott turned a blind eye to the continuous and increasing on-line harassment of the Plaintiff by the Defendants, Weese and Pyle throughout the duration of the investigation from August to November, 2021.

138. The Defendant, Weese, posted on July 24 and on August 6, 9, 13, 19, 22, 24, 25, 27, 28 and 31 wherein he referred to the Plaintiff as a "liar and grifter," an "anti-vaxxer" and as being "harmful to society." The Defendant University knew or ought to have known about this harassment and failed to take any action.

139. On August 12, 2021, the Plaintiff retained private legal counsel.

140. On August 19, 2021, the Plaintiff attended an on-line meeting for instructors in the Ontario Veterinary College's DVM program to discuss logistics of the upcoming 2021/2022 school year regarding in-person campus attendance.

141. On September 7, 2021, the Plaintiff made the Defendants, Wichtel and Arnott, aware of the Defendant Weese's harassment, but the University failed to address it and the Defendant Duley also failed to assess it.

142. On September 8, 2021, the Defendant Weese continued to post harmful, hateful and harassing comments about the Plaintiff online.

143. On September 15, 2021, the Plaintiff through legal counsel, requested the Defendant Weese cease and desist from harassing the Plaintiff. On September 30, 2021 the Defendant, Weese, was again requested to cease and placed on notice, of impending civil action if he did not.

144. On September 17th, 2021, further to his March 3, 2021 letter, the Plaintiff wrote directly to the Defendant Yates, regarding the implementation of vaccine mandates, which set out:

    (a) That the Plaintiff had clinically proven natural immunity, which natural immunity provided stronger immunity from the COVID-19 than vaccine acquired immunity. The

Plaintiff had participated in a clinical trial that had been testing his antibodies and immunity with respect to COVID-19. The Plaintiff referred to various peer-reviewed scientific journals to demonstrate that his naturally acquired immunity against COVID-19 is likely superior to that conferred by vaccination only. Immunity acquired through vaccination only lasts 4.5 months;

(b) That the Plaintiff was therefore immune, if not more immune, than vaccinated University members and therefore did not pose a risk to other members on campus;

(c) That immunity acquired as a result of vaccination has only short-term duration, as compared to natural immunity, and that therefore banning those with naturally acquired immunity, who are known and can provide evidence through anti-body testing that they are immune, but not banning those who had received two doses of the COVID-19 vaccine, whose immunity may have expired as the result of the passage of time, did not make sense;

(d) He reminded Dr. Yates, that the University and the Plaintiff, along with other individuals, had meet to offer immunity testing to the campus community, and/or making an antibody test available as an alternative to mandatory vaccination, as a result of the above studies;

(e) That for those students or staff who had naturally acquired anti-bodies, studies have shown that vaccination results in greater side effects to those individuals, and given their greater protection from their natural immunity, their forced vaccination might be reconsidered;

(f) He presented scientific research and evidence about some of the concerns he had with the current COVID-19 vaccines, and, as a result, the concerns he had about forced vaccination of students.

145. On September 24, 2021, the University of Guelph implemented a mandatory vaccine policy.

146. On or around October 2021, the Defendants, Arnott and Wichtel in response to the Plaintiff's counsel's request to cease Weese's harassment, instead, offered to protect Weese from criminal and civil liability flowing from **his off-campus, off-work conduct** harming the Plaintiff, and further offered to protect and insulate Weese from any further accountability or liability, by promising to provide legal counsel at the University's expense.

147. The Defendant, Arnott, also sought to interfere with the Defendant, Duley's report and investigation by recommending Weese provide the Plaintiff's legal counsel's letter as an indicium of harassment against abuse, even though this was a matter the University through, the Defendants, Arnott, Wichtel, and Duley, maintained were outside the jurisdiction of the University, as it involved events outside the physical confines of the campus, when requested to deal with complaints about Weese's and Pyle's social media posts. The Plaintiff states that Arnott's biased, malicious, one-sided treatment, and complicity, was in furtherance of the conspiracy against the Plaintiff, and further abuse of her office.

148. The Defendant, Arnott, contrary to the position she took with respect to the Plaintiff's June 2, 2021, online harassment complaint, advised the Defendant, Weese, that his social media posts would qualify as job-related and constitute academic discussions, and legal defence of his on-line harassment of the Plaintiff would be covered by the University's insurance.

149. The Defendant, Arnott thus contributed to and encouraged the Defendant Weese to continue harassing the Plaintiff online causing him injury.

150. As a result, on October 26, 2021 Weese posted another harmful tweet harassing the Plaintiff.

151. On November 10, 2021 the online harassment by Weese escalated when he re-posted an old post from the Defendant Fisman inviting the public to link "anti-vaxxers," to **neo-Nazi White**

Supremists. Then he falsely posted that the Plaintiff is an "anti-vaxxer". The link on Weese's post goes directly to the name and photograph of the Plaintiff and foreseeably places the Plaintiff at risk of his safety and causes him harm. Sargeant O'Connell of Campus Police expressed his concerns about what he considered criminal conduct in these posts, and further instructed that someone should read the definition of criminal harassment (inciting hatred) to Weese. Sargeant O'Connell also expressed concern that Pyle had not responded to the safety plan forwarded after their attendance on the incident of July 22, 2021.

152. On November 11, 2021, the Plaintiff was advised by the Municipal Police investigating the harassment to take pre-cautions for his safety and that the Defendant Weese's link between the Plaintiff, allegation of lies, and White Supremist neo-Nazis has the potential to incite hate.

153. On November 11, 2021, the Plaintiff received a letter from the Defendant Wichtel placing the Plaintiff on temporary partially unpaid leave, as a result of the mandatory vaccination policy contrary to the Defendant Yates and her administrators agreement that the Plaintiff's natural immunity status would be considered. The Defendant, Yates knew or ought to know that the vaccination policy was unreasonable, because it failed to ensure health and safety by testing for immunity after multiple admissions by the University that it would foster in natural immunity in its policy. The Defendant, Yates, owed the Plaintiff a fiduciary duty to address the Plaintiff's natural immunity, afford him equal treatment, and uphold his common law rights and ***Charter*** rights under sections 2, 7 and 15 of the ***Charter***, with respect to the choice to decide on any and all medical treatment, and the requirement of consent.

154. On or around November 16, 2021, the Municipal Police investigation into the criminal conduct of Weese required cooperation and assistance from the Campus Police. The Defendant, Arnott interfered with, obstructed, and halted the cooperation of University of Guelph Campus Police

officers in the criminal investigation of the Defendant Weese and directed that all matters be referred to Human Resources to her attention. As a result, Arnott acted unlawfully and failed to take steps to investigate the conduct of the Defendant, Weese, which she had re-directed from the police to herself. Arnott acted with malicious intent in abuse of her power and authority to injure the Plaintiff, in furtherance of the two over-lapping conspiracies with respect to social media posts to injure the Plaintiff, and the conspiracy to have the Plaintiff removed as a Professor and off-campus.

155. The University through its administrator Arnott, is vicariously liable for the abuse of power and authority to interfere with and obstruct the criminal investigation and collaboration between Campus Police and Municipal Police in order to conceal and encourage the criminal conduct of the Defendant Weese in causing harm to the Plaintiff. In doing so, the University breached its fiduciary duty to the Plaintiff.

156. On November 26, 2021, the Plaintiff received the Nick Duley report of the "harassment" allegation by the Defendants Pyle, Peregrine and Bienzle which had failed to examine the ongoing and past harassment of the Plaintiff, and also failed to address the ongoing police investigation against the Defendants Weese and Pyle, and failed to address the collusion of the Defendants, Weese and Arnott in perpetuating the harassment against the Plaintiff or uncover the conspiracy among them.

157. The vexatious conduct of the University is evidenced by the fact that the Defendant Weese was added to the harassment complaint exclusively on the basis that the Plaintiff placed the same note and copies of the same three publications in his on-campus mailbox and for no other reason whatsoever.

158. The Defendant, Arnott, committed misfeasance of public office by halting and usurping the criminal investigation by Campus Police into the Plaintiff's harassment allegations and by controlling the parameters and outcome of the contrived, biased, "3rd party investigation" against the Plaintiff.

159. The Defendant University and its employee co-Defendants, Yates, Arnott, and Wichtel, owed a duty to the Plaintiff to investigate the false website, byrambridle.com, and the evidence that showed Pyle knew or ought to have known who made the website impersonating Dr. Bridle. The Defendant Arnott and Wichtel's conduct and decision to not deal with the online harassment of the Plaintiff on the pretext that the University did not have jurisdiction, was false and contradictory of the University's position on Weese's tweets generally, and of on-line harassment investigations by the Defendant Nick Duley conducted for the University in other matters.

160. The Defendant, Wichtel and Arnott, showed clear and intentional bias in inconsistent and selective application of the University Harassment Policy. The Defendant, Wichtel, accepted the self-serving statements of the Defendants, Pyle, Peregrine, Weese and Bienzle and failed to inform the investigator that the alleged "unsolicited emails" sent by the Plaintiff were in response to the "unsolicited tweets" posted by the Defendants on social media where he had no presence or participation, and at the direction of Witchel to enter "open discussion". The Defendant Arnott ensured the investigation was bent and one-sided, in line with participation in the overlapping conspiracies.

161. The Defendants', Arnott's and Wichtel's, decision to prohibit the Plaintiff from working at his office and lab from July 23, 2021 to the present, constitutes a misfeasance of public office, for

which the Defendant, Yates, and the University of Guelph are vicariously liable, in that they have, or ought to have, knowledge.

162. The prohibition from being able to attend campus resulted in the Plaintiff's pay and course load being reduced. The Plaintiff furthermore was unable to access his lab or conduct research, causing the loss of grants and funding from external sources, to be calculated at trial. It was further aggravated by the fact that the Defendant Wichtel and Arnott and Yates knew the Plaintiff was on research leave until December 30, 2021, and unable to conduct research off-site.

163. On December 3, 2021 the Plaintiff was informed that the Defendant, University of Guelph, was advertising a job for his teaching position. The Defendant, University of Guelph, owed the Plaintiff a duty to discuss the Plaintiff's teaching or discuss alternative solutions (such as remote learning), as it had promised to do so in July 2021, in breach of its fiduciary duty.

164. The Defendants, Wichtel and Arnott, knew that the Defendants, Pyle and Weese, continued the *ad hominin* attack and on-line harassment against the Plaintiff throughout the entire duration of the investigation in which they claimed that they felt "unsafe". While feeling "unsafe" they continued, and continue to date, to maliciously bait and harass the Plaintiff with the Defendant Wichtel and Arnott's knowledge, complicity, and support, including support to mount a legal defense for their offensive off-campus activity.

165. The conduct of the Defendants who conspired together to prevent the Plaintiff him from working at his office and lab irreparably damaged his research, and his collaboration, and relationships with both internal and external scientists and researchers, including on the COVID 19 vaccines.

166. The Defendant, Yates is vicariously liable for the actions of the Defendants, Wichtel and Arnott, and also vicariously liable for failing to address the harassment of the Plaintiff, by the Co-Defendants, Pyle and Weese, which complaints Yates wholly ignored.

167. On December 14, 2021, the University prohibited the Plaintiff from accessing the University and put him on partial unpaid leave, effective January 5, 2022.

168. The Plaintiff's exclusion from campus for five (5) months from December 14, 2021 to May 1, 2022 was a breach of his common-law, constitutional and statutory rights to informed consent to medical treatment. The Plaintiff was deprived of his rights under sections 2, 7 and 15 of the ***Charter*** by the Defendant Yates' decision in carrying out and enforcing a policy which forced COVID-19 vaccines over natural immunity. The Defendant Yates knew or ought to have known that the policy denied the Plaintiff the right to consent and to have autonomy over medical treatment, all of which was not in accordance with the principles of fundamental justice.

169. The Plaintiff's COVID-19 research was, and is, considered "essential," but his cancer research was considered "non-essential", except for literature based and data analysis, is also laboratory research intensive. His research cannot and could not be conducted remotely. The Plaintiff's research requires presence in the laboratory and animal facility because it involves cell-based and animal-based research. The Defendant University and the Defendant, Wichtel, knew or ought to have known, from the Plaintiff's Research Management Plan that the vast majority of his research would need to be conducted on campus.

170. Notwithstanding the policy of general application and given the strong evidence of immunity and health and safety presented by the Plaintiff to the Defendant University, and, in particular, directly to the Defendant Yates, the Plaintiff was owed a duty of care. The Defendant Yates decision to exclude the Plaintiff from campus for five (5) months is contrary to the policy's rationale which fails to ensure health and safety by recognizing immunity and using vaccination as the only measure of a substitute for immunity and ignoring adverse side effects from vaccines. The Defendant Yates, failed to guard against damages that were foreseeable and the violation of

the Plaintiff's common-law, statutory, and ss. 2, s.7 and s.15 ***Charter*** rights, breach of right to medical consent to treatment and failure to provide a reasonable system of exemption arising from natural immunity.

171. he September 17, 2021 letter, confirmed multiple admissions by the University that it would factor in natural immunity. The Plaintiff had explained that natural immunity is more robust, longer lasting and broader than vaccine immunity. The Defendant, Yates exercised her discretion and authority arbitrarily and for improper motives. Further, the Defendant Yates selectively denied access to campus to the Plaintiff, a disfavoured minority violating equal protection under s.15 of the ***Charter***.

172. On January 4, 2022, the Defendant, Wichtel, caused the Plaintiff mental anguish and suffering by threatening further "non-disciplinary" measures would be implemented without cause, basis or evidence, which was above and beyond the discipline of five (5) days of paid suspension.

173. The Defendant Wichtel's claim that the Plaintiff is allowed to attend anywhere and everywhere on campus beginning January 4, 2022 **except his office or his lab is** a direct interference with his economic interests. The Defendants, Wichtel and Arnott's, assertion that the Plaintiff was prohibited to attend his office and lab is directly contradictory to their representations on many occasions, including on November 30, 2021 and January 4, 2022 that, but for the non-compliance with the vaccination policy he can return to work. The Defendant, Wichtel, abused his powers in public office in exceeding his authority in an arbitrary and capricious manner by prohibiting the Plaintiff from pursuing his economic interests exclusively related with and requiring his physical presence at his office and lab at the University. The Defendant, Wichtel, engaged in a public misfeasance of office and unjustifiably interfered with the Plaintiff's research and pursuit of economic interests by prohibiting him from his lab when he knew, or

ought to have known, the damages which would ensue during the period of his research leave. a The Defendant, Wichtel, personally approved the Plaintiff's and therefore knew the Plaintiff's inability to access his lab for six months undermined the purpose and objective of the leave and aggravated the losses and damages resulting from his abuse of authority.

174. On February 21, 2022, the Defendant, Wichtel, created a new impediment by proposing relocation of the Plaintiff's lab and office from the Pathobiology building. The Defendant, Wichtel, breached his duty of care to the Plaintiff by also failing to reconfigure the Defendants, Peregrine and Bienzle's, and the Plaintiff's work schedule and environment to minimize and prevent contact rather than uproot the Plaintiff causing harm.

175. The Defendant, Wichtel, knew or ought to have known that the Plaintiff is more likely to encounter the Defendants, Bienzle and Peregrine, in other locations on campus, especially the cafeteria and lecture halls than his office or his lab. Particularly because the Plaintiff does not share a lab with Bienzle and Peregrine's research it is far less intensive than the Plaintiff's not requiring Peregrine's presence in the lab when the Plaintiff is there.

176. On February 23, 2022, the Plaintiff rejected Witchel's proposal to move his lab and/or office for valid reasons which the University has ignored.

177. On February 25, 2022, Wichtel issued a two-year no contact order between the Plaintiff and the Defendants, Pyle, Peregrine, and Bienzle knowing that this would only injure the Plaintiff from accessing his lab and office and not to prevent physical contact with the three Defendants on campus. The Plaintiff had no contact with them since July 22, 2021.

178. The Defendant, Wichtel, further engaged in public misfeasance of public office when he indicated that "The University has retained Protect International to undertake a workplace **violence** risk assessment," despite the fact that neither the Campus Police, nor the

privately retained investigator, Nick Duleyfound any evidence of violence, as a false pretext to continue to prolong and prevent the Plaintiff to access his lab, and his office and investigate the damages caused by the prohibition from July 23, 2022.

179. On March 22, 2022, the Defendants, Wichtel and Arnott, without statutory authority demanded the Plaintiff submit to an interview for a workplace "violence risk assessment," circumventing the Plaintiff's solicitor, abusing their power and authority and acting outside their jurisdiction and authority over what are essentially criminal allegations.

180. On March 24, 2022, due to the Plaintiff's legal counsel's ICU hospitalization, requested a postponement.

181. The Defendants, Wichtel and Arnott, subsequently knowingly and falsely conflated complications with scheduling the interview because of the Plaintiff's legal counsel's illness, as the Plaintiff refusing to attend the interview, and on April 29th, 2022, the Plaintiff received correspondence from Witchel indicating that the workplace violence and risk assessment had been completed in the Plaintiff's absence, and findings and next steps had been made pursuant to this report. Under the pretext of this risk assessment report, the Defendant, the University of Guelph, and its employees Arnott and Wichtel, unilaterally decided to move the Plaintiff's lab and office from the Pathology building and prohibited the Plaintiff from access the Pathology building where all of the Plaintiff's research equipment and materials are present, and academic workis performed causing immense harm to his future lab research and productivity, as well as his teaching career.

182. No "risk assessment report" was ever provided to the Plaintiff or his legal counsel.

183. On May 1, 2022, the vaccine mandates exclusion ended on campus. The Defendants, Wichtel and Arnott without justification still prohibited the Plaintiff from attending his office and lab on

campus, despite the fact that other faculty members who are "unvaccinated" were allowed to attend physically on campus and continue in person teaching. This was an arbitrary decision intended only to interfere with the Plaintiff's research productivity and success and not to prevent contact with the Defendants, Pyle, Peregrine, and Bienzle .

184. On August 11, 2022, the Defendant, Arnott, orally informed the Plaintiff that the risk assessment concluded that the Plaintiff was **a psychological safety risk** to "other members," in an arbitrary and capricious manner because at the same time she also requested that the Plaintiff enter into a "facilitated discussion" , without any further particulars or details, despite a request from Plaintiff's counsel.

185. On the August 11, 2022 at a virtual meeting between the Plaintiff, his legal counsel, and the Defendants, Wichtel and Arnott, the Plaintiff formed a reasonable expectation that the University would act in good faith to permit him to return to his lab and office immediately, based on the representations made by Arnott.

186. On September 20, 2022, by letter, the Defendant Arnott made the return of the Plaintiff to his office and lab at the Pathobiology building conditional upon the Plaintiff developing a safety plan with the Campus Safety Office (Campus Police) and requested his legal counsel to advise as to how he wishes to proceed, despite the fact that Campus Police had made a safety plan following the July 22, 2021 incident, which Pyle and Arnott ignored. Arnott further required, as conditions, agreement that the Plaintiff would not pursue criminal or civil proceedings against the Defendants.

187. On November 4, 2022, the Plaintiff proposed a plan in good faith and in the interests of immediately to returning to his office and lab, which included the development of a safety plan, given the Plaintiff's own concerns about his safety and psychological well-being due to the

continued on-line harassment and conduct of the Defendants, Pyle and Weese. The University neither rejected nor accepted this proposal, and in fact never responded. The University breached its duty of care to consider and respond to the very reasonable proposal.

188. Instead, on December 8, 2022 at 4:29 PM the Defendant, Wichtel, circumventing the Plaintiff's solicitor and ignoring the November 4, 2022 proposal, and contrary to Arnott's position of August 11 and September 20, 2022, directly and unilaterally notified the Plaintiff that his office would be moved, without his consent, within eight (8) days on December 16, 2021 to a building in closer proximity to the Defendant Weese, knowing that Weese's harassment of the Plaintiff had escalated, in a move to further entrap, frame, and set him up for more conflict. The Defendant University of Guelph is vicariously liable for the Defendant, Wichtel, who is acting in bad faith. Both Defendants are aware that the location of the Plaintiff's laboratory had been strategically selected by the chair of his department at the time he was hired to promote inter-disciplinary collaborations, which it has since achieved, and that any relocation or movement would harm this overall and important objective as well as immeasurably injure the Plaintiff's academic and research career.

189. The Defendant, Wichtel breached the duty of care owed to the Plaintiff as his Dean to ensure he could return to productivity and successfully work in a lab and office knowing he had shared equipment which other programs used, and worth over one million dollars, which equipment was attached to the building infrastructure. The removal, even if possible, would be to the detriment of the Plaintiff's research and other programs. By continuing to prohibit the Plaintiff from the Pathology building the Defendants, Wichtel and Arnott, prevented the Plaintiff from performing any and all research and work.

190. On December 6, 2022, the Plaintiff became aware of the Defendant Weese's December 1, 2022 post which incited hate against him as follows:

> "It's bad enough that misinformation scared people away from vaccination (causing lots of death).
> Now they're scaring people away from blood transfusions....with no accountability."

Due to the fact that the Defendant Weese accused the Plaintiff of "causing lots of death," called for him to be held "accountable," posted directly above the Plaintiff's name, contact information, and a full photograph of the Plaintiff, the Municipal Police cautioned the Plaintiff to take measures for his own safety and informed him that the Defendants, Weese and Pyle, would be notified of their arrest for *inter alia* criminal harassment. The Plaintiff took immediate steps to secure a personal escort trained and experienced in law enforcement for his own safety and that of his family.

191. Now that the Plaintiff had an escort, a retired police officer, for his own safety, on December 12, 2022, the Plaintiff submitted an urgent proposal , through his legal counsel,to access his office and lab, as he would be accompanied by a former law enforcement officer, and this would allay any safety concerns, purported or real. The Plaintiff advised he would need to attend on December 14, 2022, to commence preparation for his courses in January 2023.

192. In response, on December 13, 2022, Arnott , in a letter to Plaintiff's legal counsel, prohibited the Plaintiff from attending at his lab and office, without justification and in an unreasonable manner, under threat that if the Plaintiff entered the Pathobiology building, he would be forcibly barred and/or removed. The Defendant, Arnott, acted maliciously in an abuse of public office.

193. On or about December 14, 2022, the Defendant Pyle was issued notification of pending arrest for criminal harassment by Municipal Police. He was asked to attend the police station for processing. He refused. Instead, he contacted his Faculty Association representative, who, along

with the University, located a friendly Ontario Provincial Police (OPP) officer apparently in a cozy relationship with the University, who called the Municipal Police Officer heading the investigation and case, to intimidate and threaten the Municipal Officer to drop or withdraw the charges. The OPP officer had absolutely no prior involvement with the investigation whatsoever, thus constituting an obstruction of justice.

194. As a result of the impending criminal charges, on December 16, 2022, at approximately 11 a.m., the Defendant, Pyle, put his account on "protected status" allowing only those Pyle permits to access it.

195. Furthermore, the University of Guelph Defendant(s) spread a prevalent, false rumour over the course of December 16-17, 2022 that the Plaintiff, Dr. Bridle, had been arrested and criminally charged, which was untrue, and further evidence of the Defendants' conspiracy and on-line harassment.

196. The Defendants, Wichtel and Arnott knew, or ought to have known, that as a result of prohibiting the Plaintiff access his office and lab, he would not be able to teach his course in January 2023. He would not be able to recruit new graduate students, which would mean that there would be no overlap between old graduate students teaching the next generation of graduate students. Therefore, there will be no continuity of the Plaintiff's research program, which has, and will, result in irreparable damage to his research and academic career, reputation, and relationships. As a result of the University's conduct and, in particular, the conduct of the Defendants Wichtel and Arnott barring the Plaintiff from his office and lab for approximately 1.5 years, and the University Defendants' continued conduct to date, his vaccine and cancer research has been set back 10 years.

197. As a result of the Defendants' actions, as set out above, the Plaintiff has suffered extensive damages, including but not limited to:

(a) Significant loss of standing as a virologist, immunologist, scientist, and academic;

(b) Loss of income, equipment and lab and materials;

(c) Damage to his teaching career and research program, including

(i) at least ten years set back to his research programs, which he was conducting at the University of Guelph;

(ii) Loss and missed opportunities to apply for research grants;

(iii) Inability to recruit new graduate students for over two consecutive academic years, and therefore a loss of memory carryover and of expertise in his research team, resulting in harm to his vaccine and cancer research; and

(d) Mental anguish and suffering.

LIABILITY OF DEFENDANTS

- **Online Harassment**

198. Based on the facts and elements of tortious conduct pled above, the Plaintiff states that the conduct of the Defendants, Fisman, Weese and Pyle constitutes the newly-recognised tort of (online) harassment as delineated by the Ontario Superior Court in ***Caplan v Atas 2021 ONSC 670*** at paragraph 171. The test for online harassment being as follows:

(a) The defendant maliciously or recklessly engaged in communications and conduct so outrageous in character, duration, and extreme in degree, so as to go beyond all possible bounds of decency and tolerance;

(b) The defendant intended to cause fear, anxiety, emotional upset or to impugn the dignity of the plaintiff; and

(c) The plaintiff suffered such harm.

Which are all present in this case.

199. The Plaintiff states, and the fact is, that the conduct of the Defendants, Pyle, Fisman, and Weese, along with parties currently unknown to the Plaintiff, but responsible for the creation and, authorship of Byrambridle.com and @byrambridle, are harassment, in that the above-cited statements published on Byrambridle.com and Twitter, @byrambridle, are/were false, and untrue statements, and further were explicitly, and by innuendo, injurious to the Plaintiff's work and reputation and relationships as an academic, research scientist and vaccinologist, and further knowingly inflicted mental pain and anguish , fear , anxiety and emotional upset, on the Plaintiff.

200. The Plaintiff states, and the fact is, that the Defendants, Fisman, Weese, Pyle, have engaged in:

(a) Repeated and serial publications of false, malicious, reckless, and, derogatory material, extreme in degree and beyond all possible bounds of decency and tolerance, damaging the Plaintiff and inciting hatred against him;

(b) Harassment intended to affect the economic interests and reputation and relationships of the Plaintiff;

(c) With respect to these Defendants, in the fake accounts, byrambridle.com and @byrambridle (twitter), harassment designed to impersonate (personate) and thereby cause specific harm to the Plaintiff's reputation and relationships;

(d) Intentional infliction of fear, anxiety and misery, and mental pain and anguish on the Plaintiff, and his family which in turn causes more pain and anguish to the Plaintiff;

(e) As a result of the above, the Defendant has suffered extensive damages, including injury to reputation and relationships with funders and grant agencies;

201. Furthermore, these false statements were designed to interfere with the Plaintiff's contractual obligations and economic interests, and ability to publish.

202. The statements were published on the internet, through the fake website ByramBridle.com, and over Twitter, using the false handle @byrambridle, as well as over social media.

203. As a result of the statements and conduct of these Defendants, Fisman, Pyle, and Weese, the Plaintiff suffered damage as follows:

(a) considerable financial damages;

(b) damage to reputation;

(c) loss of funding and donor support for his scientific research and graduate programs;

- **Conspiracy**

204. The Plaintiff states and fact is, that all the named Defendants, Fisman, Pyle, and Weese, as well as other "duped co-conspirators", engaged in the actionable tort of conspiracy in order to discredit and therefore silence the Plaintiff, and damage his reputation and relationships.

205. The Plaintiff states that the Defendants, Arnott, Wichtel, Weese, Pyle, Peregrine, Bienzle, Greer, Fisman, and Duley engaged in the overlapping conspiracy to discredit, and falsely malign and damage the personal and professional standing, reputation, and work of Plaintiff with a view, aim, and objective to force and/or remove the Plaintiff as a researcher and tenured professor at the University.

206. The Plaintiff states that the Defendants further conspired to interfere with the Plaintiff's economic interests, pursuant to civil conspiracy as set out by the Supreme Court of Canada, in, inter alia, ***Hunt v. Carey Canada Inc., 1990 CanLII 90 (SCC), [1990] 2 SCR 959,*** which set out that the tort of the conspiracy comprised of the following elements:

(a) In the first place there will be an actionable conspiracy if two or more persons agree and combine to act unlawfully with the predominating purpose of injuring the plaintiff.

(b) Second, there will be an actionable conspiracy if the defendants combine to act lawfully with the predominate purpose of injuring the plaintiff.

(c) Third, an actionable conspiracy will exist if defendants combine to act unlawfully, their conduct is directed towards the plaintiff (or the plaintiff and others), and the likelihood of injury to the plaintiff is known to the defendants or should have been known to them in the circumstances.

207. The Plaintiff states that the overlapping conspiracies, of the social media online harassment, and the conspiracy to remove the Plaintiff from the University, are manifest by, *inter alia*:

(a) The false and malicious statements made in furtherance of the conspiracy as set out in the within Statement of Claim, which were pre-planned by Fisman, Weese, and Pyle;

(b) The creation of a false website and Twitter account to further that conspiracy;

(c) The concerted and co-ordinated actions of online harassment designed to destroy the Plaintiff;

(d) The contrived, false allegations of the plaintiff being a "violent threat" and "clear and present danger" on campus, which were preplanned by the Defendants as pleaded above;

(e) The persistent false allegations and conduct in attempting to, and in fact, physically removing and barring the Plaintiff from campus and in particular, his office and lab by Arnott and Witchel;

(f) The wholly arbitrary and illegal conduct creating the conditions that have made it impossible for the Plaintiff to continue his work;

(g) The arbitrary and different treatment of complaints made by the Plaintiff, by the Defendants, Arnott, Wichtel, and Yates;

(h) Interfering and stopping the Campus Police Investigation;

(i) The University Defendants' malicious biased, and singularly obsessive targeting at every turn, to force and/or remove the Plaintiff from his campus office and lab; and

(j) The Defendants', Greer, Bienzle, Weese, and Pyle, in organizing and publishing the July 6, 2021 letter to injure the Plaintiff.

- **Interference with Economic Interest**

208. The Plaintiff states that, through their conduct and actions, all the Defendants have engaged in interference with the Plaintiff's economic interests as set out by the facts, pleaded above, and set out by the jurisprudence in that:

(i) the Defendants intended to injure the Plaintiff's economic interests;

(ii) the interference was by illegal or unlawful means; and

(iii)the Plaintiff suffered economic harm or loss as a result.

- **Breach of Fiduciary Duty**

209. The Plaintiff further states that the Defendants, the University of Guelph, Yates, Arnott, and Wichtel, in addition to the duties of fairness and reasonableness, at common law, Administrative Law, and under statute, further owe a fiduciary duty to the Plaintiff, in that the Defendants assumed a fiduciary relationship, and owed a corresponding fiduciary duty of care to the Plaintiff, for the following reasons:

(a) The Defendants were, and are, in a position of power over the Plaintiff, and were able to use this power and their authority so as to control and affect the Plaintiff's interests;

(b) The Plaintiff was, and is, in a corresponding position of vulnerability toward the Defendants. The Plaintiff was, and is, therefore in a class of persons vulnerable to the control of the Defendants;

(c) There was, and is, a special position of trust between the Defendants and the Plaintiff, governed by statute, the ***Charter***, and the common law;

(d) The Defendants University of Guelph, Yates, Wichtel, and Arnott undertook to act in the best interests of the Plaintiff equal to other faculty members;

(e) The Defendants breached this fiduciary duty;

And, as a direct result of this breach, the Plaintiff has suffered loss and damages, which include, ***inter alia:***

(a) Damage to reputation and interference with the economic interests of the Plaintiff

(b) Loss of grants and funding for his research;

(c) Immeasurable loss of research productivity and progress, in fact, his research has been set back at least ten years;

(d) Loss of graduate students, graduate student retention, future opportunities with graduate students;

(e) Loss of opportunity with research collaborators and projects;

(f) Loss of dignity; and

(g) Violation of the Plaintiff's psychological integrity guaranteed and protected by s.7 of the ***Charter***, as well as violation of the Plaintiff's dignity of equal treatment under s.15 of the ***Charter***;

(h) Pain and anguish

- **Negligence**

210. The Plaintiff further and alternatively states, that the Defendants, the University of Guelph, its President, and the Plaintiff's Dean, Witchel, are vicariously, and in fact, liable in negligence, along with Wichtel, and Arnott, in that:

(a) They owe a duty of care to the Plaintiff to ensure a safe and non-hostile and harassment-free environment from other University Faculty, and to be safe from tortious and criminal

conduct, and ensure the viability of the plaintiff's academic freedom (of speech) and work as a professor and scientist;

(b) That they breached this duty of care by choosing and/or failing to:

(i) Put an end to the tortious and criminal conduct and harassing of the Plaintiff by the Co-Defendants;

(ii) Properly train and supervise subordinates under their control;

(iii) With respect to Nick Duley, the duty to assume jurisdiction only if statutorily authorized, and to conduct a competent investigation, which he failed to do in conducting a negligent investigation as set out in the within Statement of Claim;

(c) And that, as a result of that breach in the Defendants' duty of care, the Plaintiff suffered damages as follows:

(i) Damage to reputation and interference with the economic interests of the Plaintiff;

(ii) Loss of funding for his research;

(iii) Loss of research productivity and set back to research program of at least ten years;

(iv) Loss of graduate student, graduate student retention, future opportunities with graduate students;

(v) Loss of dignity; and

(vi) Violation of the Plaintiff's security of the person, bodily autonomy and autonomy of medical treatment psychological integrity guaranteed and protected by s.7 of the ***Charter***, as well as violation of the Plaintiff's right to equal treatment under s.15 of the ***Charter***;

(vii) Pain and anguish.

For which the Defendants are liable in damages.

- **Intentional Tort of Abuse of Authority and Misfeasance of Public Office**

211. The Plaintiffs state, and fact is, that the Defendants, Yates, Wichtel, and Arnott, Weese,Pyle, and all other University Defendants, have knowingly engaged in misfeasance of their public office, and abuse of authority, through their public office, as contemplated and set out by the Supreme Court of Canada in, ***inter alia, Roncarelli v. Duplessis, [1959] S.C.R. 121 Odhavji Estate v. Woodhouse [2003] 3 S.C.R. 263, 2003 SCC 69.***

212. The Plaintiff states that, through their conduct and actions, the Defendants, Wichtel, and Arnott, abused their positions of public office, exceeding their authority, in the following arbitrary and capricious manner:

(i) Wichtel and Arnott acted with malice towards the Plaintiff with the knowledge that their conduct lacked statutory authority in initiatiing a "workplace harassment" claim on allegations which were criminal and which had been dismissed by Guelph Campus Police;

(ii) The Defendant, Arnott for interfering and obstructing and halting the Campus Police investigation against Weese and Pyle, as well as the Municipal Police's investigation;

(iii)The Defendant Arnott by interfering with the Campus Police cooperation with Municipal Police investigation on the criminal conduct of the Defendants, Pyle and Weese;

(iv)The Defendant Yates is vicariously liable for the Defendant Arnott's abuse of public office, as well as the conduct of Weese, Pyle, and Arnott, and the other Professor co-Defendants, by not controlling their tortious conduct even though Yates was apprised.

And the Plaintiff further states that, in engaging in this abuse of authority and misfeance of public office, the Defens\dants have not injured the Plaintiff, but also undermined, breached and subverted the objective and purposes of the University of Guelph, as set out under s. 3 of the *Act*.

- **Vicarious Liability**

213. The Plaintiff further states that the Defendants, University of Guelph, Yates, Wichtel, and Arnott are vicariously liable for the action and inaction of the administrators, and the professors Weese, Pyle, Peregrine, Bienzle, and Greer who are all "teaching staff" of the University. The University and Yates are vicariously liable for:

(i) Arnott's use and abuse of her power, authority, and position at the University, take control of, interfere with, and obstruct the criminal investigation and, to defend and encourage the criminal conduct of the Defendant Weese, all of which caused harm to the Plaintiff;

(ii) Arnott and Wichtel's conduct of criminal investigation under the guise of disciplinary proceedings without lawful authority and jurisdiction;

(iii) The Defendants, Arnott's and Wichtel's, decision to prohibit the Plaintiff from working at his office and lab from July 23, 2021 until January 4, 2022, and from May 1, 2022 to present, constituted a misfeasance of public office, for which the Defendant, Yates, and the University of Guelph had knowledge and are vicariously liable, in that they had, or ought to have, knowledge;

(iv) For the Defendants, Arnott and Wichtel, failing to address the harassment of the Plaintiff, by the Co-Defendants, Pyle and Weese, as well as Peregrine, Bienzle, and Greer, which complaints Yates wholly ignored;

(v) For allowing the Defendants, Arnott and Wichtel, to unilaterally decide to move the Plaintiff's lab and office from the Pathology building and prohibiting the Plaintiff from access to the Pathology building where all of the Plaintiff's research equipment and academic work performed causing immense harm to the Plaintiff's present and future lab research and productivity, as well as his teaching career.

- **Endangerment of Plaintiff's Life**

214. The Plaintiff states that the Defendants, Fisman, Pyle and Weese, and in particular Pyle and Weese, have placed the Plaintiff in physical and psychological danger, culminating with Weese's latest post in which they accompany a photograph of the Plaintiff, and incite hatred by stating that he is causing harm and death to others, and must be held accountable which post was dated December 1, 2022, as well as Fisman's labelling the Plaintiff as an "anti-vaxxer," white "Neo-Nazi."

215. The Plaintiff states that these vile posts, which incited hatred, make the Plaintiff vulnerable to physical and psychological attack and knowingly inflicts harm, aguish and pain.

- **All Documents referred to in within Claim**

216. The Plaintiff further pleads any and all documents mentioned in this Statement of Claim as documents referred to in the pleadings herein.

217. The Plaintiff therefore seeks the relief set out in paragraphs 1 to 5 of the within statement of claim.

218. The Plaintiff proposes that this action be tried in Toronto.

Dated at Toronto this 19th day of December, 2022.

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Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

Court File No.:

Dr. BYRAM BRIDLE

Plaintiffs

-and-

Glen PYLE et al

Defendants

ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDING COMMENCED AT TORONTO

STATEMENT OF CLAIM

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TAB 2

Court File No. CV-22-00691880-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N :

DR. BYRAM BRIDLE

Plaintiff

- and –

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

STATEMENT OF DEFENCE OF THE DEFENDANTS, UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE, YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, AND NICK DULEY

1. The Defendants University of Guelph, Jeffrey Wichtel, Laurie Arnott, Charlotte, Yates, Scott Weese, Glen Pyle, Andrew Peregrine, Dorothee Bienzle, Amy Greer, and Nick Duley (collectively hereinafter “these Defendants”), specifically deny that the Plaintiff is entitled to the relief claimed in paragraphs 1, 2, 3 and 4 of the Statement of Claim, and put the Plaintiff to the strict proof thereof.

2. These Defendants plead that the Defendants John or Jane Doe Junior Scientist were never University of Guelph employees and therefore the University of Guelph did not have care, control or management over them at any material time in issue and cannot be responsible in law for any actions they may have committed as against the Plaintiff, as alleged in the Statement of Claim, which are not admitted but specifically denied. These Defendants further plead that none of Dr. David Fisman, Dr. Glen Pyle or Dr. Scott Weese colluded, cooperated, or assisted the Defendants John or Jane Doe Junior Scientist in any

way, as has been baldly alleged in the Statement of Claim. In this respect, the Defendants put the Plaintiff to the strict proof thereof.

3. Except as may hereinafter be expressly admitted, these Defendants do not admit any of the allegations contained in the Statement of Claim, and put the Plaintiff to the strict proof thereof.

The Parties

4. The Defendant, the University of Guelph, is a post-secondary educational institution in Ontario with a campus located at 50 Stone Road East in Guelph, Ontario.

5. The Defendant Dr. Jeffrey Wichtel, at all material times, has served as the Dean of the University of Guelph's Ontario Veterinary College.

6. The Defendant Laurie Arnott, at all material times, has served as the Assistant Vice-president, Faculty and Academic Staff Relations, at the University of Guelph.

7. The Defendant Dr. Charlotte Yates, at all material times, has served as the President & Vice Chancellor of the University of Guelph.

8. The Defendant Dr. Scott Weese, at all material times, has served as a Professor with the University of Guelph's Ontario Veterinary College.

9. The Defendant Dr. Glen Pyle, at all material times, has served as a Professor with the University of Guelph's Ontario Veterinary College.

10. The Defendant Dr. Andrew S. Peregrine, at all material times, has served as an Associate Professor with the University of Guelph's Ontario Veterinary College.

11. The Defendant Dr. Dorothee Bienzle, at all material times, has served as a Professor of Veterinary Pathology and the University Research Leadership Chair with the University of Guelph's Department of Pathobiology.

12. The Defendant Dr. Amy Greer, at all material times, has served as Canada Research Chair in Population Disease Modeling and Associate Professor & Graduate Program Coordinator, at the University of Guelph.

13. The Defendant Nick Duley is a Certified Human Resources Leader employed by the non-party North Shore HR Consulting Inc., who was appointed on or about July 29, 2021, by the Defendant University of Guelph to conduct an investigation into concerns raised about the conduct of the Plaintiff. Nick Duley's investigation report was delivered on or about November 9, 2021.

14. The Defendant, Dr. David Fisman, serves as a Faculty Member with the Dalla Lana School of Public Health at the University of Toronto.

The Plaintiff's Action is Without Merit

15. These Defendants plead that the Plaintiff's claim is frivolous, vexatious, and an abuse of process, and should be struck in its entirety.

16. These Defendants plead that this action is being used as a means of unduly limiting expression on matters of public interest and, in particular, to discourage these Defendants from participating in and contributing their expertise to matters of public interest. These Defendants therefore plead that the Plaintiff's action is barred by section 137.1 of the *Courts of Justice Act*, R.S.O. 1990, c. C. 43.

17. These Defendants plead, and the fact is, that at all material times each of them acted reasonably, professionally, properly, and in accordance with the University of Guelph's academic and other policies and procedures, throughout their involvement with the Plaintiff.

18. These Defendants deny that there was any misrepresentation, breach of duty, want of care, or negligence on their part or on the part of any of their servants, agents, or employees which caused or contributed to the damages alleged by the Plaintiff, which damages are not admitted but expressly denied, and put the Plaintiff to the strict proof thereof.

19. These Defendants, and Dr. Weese and Dr. Pyle in particular, deny that any of them engaged in any form of online harassment and/or bullying of the Plaintiff, as is alleged, or at all, and put him to the strict proof thereof.

20. These Defendants deny that there was, at any time, a "conspiracy" as against the Plaintiff, as is alleged in the Statement of Claim, and put the Plaintiff to the strict proof thereof.

21. These Defendants deny that any of them owed the Plaintiff a fiduciary duty, under the circumstances. In the alternative only, these Defendants deny that any of them breached any fiduciary duty that may have been owed to the Plaintiff.

22. These Defendants further deny that any of them are public office holders, and put the Plaintiff to the strict proof thereof. In the alternative, these Defendants plead that at all material times they acted appropriately and fairly in carrying out their duties.

23. These Defendants further deny that any of them endangered the Plaintiff's life in any way, and put him to the strict proof thereof.

24. These Defendants further deny that any of them interfered in any way with the Plaintiff's economic interests, and put him to the strict proof thereof.

25. These Defendants specifically deny that any of their actions, or the actions of their servants, agents, or employees, were motivated in any way whatsoever by bad faith or malice, and put the Plaintiff to the strict proof thereof.

26. These Defendants further plead that the essential nature of the dispute between the Plaintiff and these Defendants, in particular but without limitation as described in the Statement of Claim, is an employment dispute. These Defendants plead that by virtue of the collective bargaining agreement that the dispute complained of is within the exclusive jurisdiction of the processes established by the collective agreement, and not within the jurisdiction of this Court. As such, these Defendants plead that the collective agreement, and the processes established therein, serves as a complete bar to the Plaintiff's action as against them.

27. These Defendants plead that the Statement of Claim does not contain a precise statement of material facts. Rather, it is replete with evidence, and should therefore be struck.

28. These Defendants deny that the Plaintiff has suffered, due to any acts or omissions of these Defendants, their servants, agents or employees, damages as alleged, or at all, and put the Plaintiff to the strict proof thereof.

29. These Defendants plead that any injuries, conditions or illnesses from which the Plaintiff may be suffering, as alleged, were caused or contributed to by incidents or health conditions unrelated to matters at issue in this claim, and are in no way causally related to such issues.

30. These Defendants deny that the Plaintiff suffered any damages as a result of any negligence, breach of duty, act or omission on the part of these Defendants or any of their servants, agents or employees, and put the Plaintiff to the strict proof thereof.

31. In the alternative only, these Defendants plead that any damages sustained by the Plaintiff are excessive, exaggerated and remote in law.

32. These Defendants further plead that the Plaintiff has failed to mitigate his damages, if any.

33. These Defendants plead that the Plaintiff's damages, if any, will be assessed in an amount not exceeding $200,000.00 and, as such, these Defendants plead and rely upon the cost consequences contained in Rule 76.13 of the *Rules of Civil Procedure*, as this matter ought to have proceeded by way of the *Simplified Procedure*.

34. These Defendants specifically deny that any of them acted in a manner which would warrant an award of punitive or aggravated damages, as alleged, and put the Plaintiff to the strict proof thereof. These Defendants specifically deny that their conduct, or the conduct of anyone for whom they are in law responsible, was improper, abusive, unjustifiable, high-handed, or vindictive, and put the Plaintiff to the strict proof thereof.

35. These Defendants allege that a number of the Plaintiff's allegations are statute barred, and plead and rely upon the *Limitation Act*, 2002, SO 2002, c. 24 Sched. B.

36. These Defendants plead and rely upon the *Courts of Justice Act*, RSO 1990, c. C.43, *Negligence Act*, RSO 1990 c. N.1, *Human Rights Code*, RSO 1990 c. H.19, *Occupiers' Liability Act,* RSO 1990, and *Limitation Act*, 2002, SO 2002, c. 24 Sched. B c. O.2, as amended.

37. These Defendants therefore submit that the Plaintiff's claim should be dismissed, as against them, with costs and applicable HST thereon.

February 24, 2023

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Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

DR. BYRAM BRIDLE
Plaintiff and University of Guelph et al
Defendants

Court File No.: CV-22-00691880-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceeding commenced at TORONTO

STATEMENT OF DEFENCE

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TAB 3

Court File #: CV-22-0069-1880-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

REPLY

1. The Plaintiff Dr. Byram Bridle Replies to the Defendants' Statement of Defence as set out below.

2. The Plaintiff Dr. Byram Bridle relies on the facts set out in his Statement of Claim, and, unless expressly admitted, denies the Defendants' assertions.

3. With respect to paragraph 2 of the Statement of Defence, and the John or Jane Doe junior scientist, the Plaintiff states that this statement draws the inescapable conclusion that the Defendants know the identity of this John or Jane Doe and request the Defendants provide his/her identity forthwith.

4. With respect to paragraph 13 of the Statement of Claim the Plaintiff states that if so, the lawyer on record for the Defendants is in a (potential) conflict of interest in representing Mr. Duley and furthermore, given that fact, gives reasonable inference that Mr. Duley colluded, as pleaded, with the other Co-Defendants.

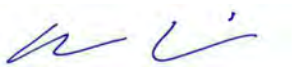
5. The Plaintiff, with respect to paragraphs 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, contest those assertions.

6. In particular, with respect to paragraph 26, this bald assertion is contradicted by the Defendants' own assertion that anything ("physically") done outside the university campus, including online harassment, was not within the Universities jurisdiction, to remedy. The issues of the intentional torts are not a matter of a labour dispute as it deals with intentional tort and criminal activity against the Plaintiff, by the Defendants.

7. With respect to paragraph 27 the Plaintiff contests this assertion and further states that the "evidence" alleged, much of which is the Twitter tweets by the Defendants, are necessarily plead as statements in furtherance of the conspiracy.

8. The Plaintiff further contests the statements and assertions set out in paragraphs 28, 29, 30, 31, 32, 33, 34, 35 of the Statement of Defence.

Dated at Toronto this 8th day of March , 2023.



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Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No.: **CV-22-0069-1880-0000**

Dr. BYRAM BRIDLE
Plaintiffs

-and-

Glen PYLE et al
Defendants

.

ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDING COMMENCED AT TORONTO

REPLY

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TAB 4

Court File #: CV-22-0069-1880-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

DR. BYRAM BRIDLE

Plaintiff

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

AFFIDAVIT OF DR. BYRAM BRIDLE

I, Dr. Byram Bridle, of the City of Guelph, in the Province of Ontario, MAKE OATH AND SAY:

1. I am the Plaintiff in this proceeding, and as such, have knowledge of the matters contained in this Affidavit.

Professional, Academic and Research background

2. The Defendant, Dr. David Fisman, states in the within Motion that I am a veterinarian.[1] This statement is false. It is one of many attempts by Dr. Fisman to smear my academic credentials, scientific knowledge and expertise on issues related to COVID-19, to the public at large, and now, also to the Court in this motion. I am **not**, nor have I ever been, a veterinarian. I do not even hold a Doctor of Veterinary Medicine degree.

[1] Motion Record of the Defendant Fisman, Notice of Motion, dated May 24, 2023, page 2, paragraph (e)

3. I am an Associate Professor of Viral Immunology in the Department of Pathobiology at the University of Guelph. I hold a BSc in biomedical sciences, MSc and PhD in immunology, and a post-doctorate in viral immunology. I conduct research on the development of vaccines to prevent infectious diseases and to treat cancers, as well as studying host immune responses to viruses, **for humans**[2]. I have held and still hold many patents in this area. One of my novel vaccination strategies progressed into testing in four **human** clinical trials[3].
4. My academic appointment as an independent researcher and faculty member of the Ontario Veterinary College at the University of Guelph commenced in January 2012. To begin my career as an independent researcher, I received competing offers from the Ottawa Hospital Research Institute and University of Guelph. I strategically opted to locate my research program at the Ontario Veterinary College to conduct unique translational research with advanced animal models to short-list the most promising medical interventions for testing in human clinical trials. An association with a medical school would have limited my research program to primarily working with rodent models and human samples. I can work with both at the Ontario Veterinary College. But I have the unique advantage of being able to work with animals that simulate the genetic diversity of the human population and that spontaneously develop the same diseases that people do. These advanced models are veterinary patients. The uniqueness and value of my human-focused research program at the Ontario

[2] Bridle BW, Stephenson KB, Boudreau JE, Koshy S, Kazdhan N, Pullenayegum E, Brunellière J, Bramson JL, Lichty BD, Wan Y. Potentiating cancer immunotherapy using an oncolytic virus. *Molecular Therapy*. 2010 Aug;18(8):1430-9. doi: 10.1038/mt.2010.98. Epub 2010 Jun 15. PMID: 20551919; PMCID: PMC2927075.
[3] clinicaltrials.gov; trial #s NCT02285816, NCT03618953, NCT03773744, NCT02879760

Veterinary College was recognized by the Terry Fox Research Institute providing a prestigious research award to me to fund my program, under the title of "Evaluation of oncolytic immunotherapy in canine cancer trials: a stepping stone towards successful translation into human patients". This was the first time that the University of Guelph had ever received funding from the Terry Fox Research Institute. I also received funding from the former Canadian Breast Cancer Foundation to run a veterinary clinical trial in cats with mammary carcinomas to accelerate progress towards testing in human trials. This was the first time that the Canadian Breast Cancer Foundation had funded a veterinary clinical trial. This provided additional evidence of the unique value that my research program offers to the scientific community. A portion of this research was published[4], with another publication in preparation. It was this research that accelerated progress into the aforementioned four human clinical trials. My research program has brought much fame to the University of Guelph, which they have proudly advertised on many occasions. I have listed a few of the almost one hundred articles that the university publicized[5].

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[4] Hummel J, Bienzle D, Morrison A, Cieplak M, Stephenson K, DeLay J, Woods JP, Lichty BD, Bridle BW. Maraba virus-vectored cancer vaccines represent a safe and novel therapeutic option for cats. *Scientific Reports*. 2017 Nov 16;7(1):15738.

[5] "U of G Vaccine Researcher Makes Headlines", https://news.uoguelph.ca/2020/06/u-of-g-vaccine-developer-to-appear-on-the-west-block/; "Vaccine Research Targets Cancer Cells", https://guides.uoguelph.ca/2012/02/vaccine-research-targets-cancer-cells/; "OVC Clinical Trial Treats Breast Cancer in Cats", https://news.uoguelph.ca/2014/10/ovc-clinical-trial-treats-breast-cancer-in-cats/; "Immunologist Pens Commentary on Kids' Health in COVID-19", https://news.uoguelph.ca/2021/03/immunologist-pens-commentary-on-kids-health-in-covid-19/; "U of G COVID-19 Vaccine Research Awarded Provincial Funding", https://news.uoguelph.ca/2020/05/u-of-g-covid-19-vaccine-research-awarded-provincial-funding/; "OVC Cancer Breakthrough Leads to Human Clinical Trials", https://news.uoguelph.ca/2016/07/ovc-cancer-breakthrough-finding-leads-human-clinical-trials/; "National Geographic Consults U of G Immunologist", https://guides.uoguelph.ca/2020/06/national-geographic-consults-u-of-g-immunologist/

5. I also teach several courses at the undergraduate and graduate level on the topics of immunology, virology, and cancer biology at the University of Guelph. I received excellent ratings, evaluations, and teaching awards. I was elected as an honourary class president twice; I was voted top professor of the year (an honour which can only be held a maximum of once per four years) by students enrolled in all four phases of the doctor of veterinary medicine program. For this, I received the top teaching award for North American Veterinary Schools. My overall average for all the years that I have taught and across all teaching categories evaluated is 4.75/5.0 (or the equivalent of 95/100).

6. I have eighty-five peer-reviewed publications in high-quality scientific journals that are indexed on "PubMed", in my area of expertise; which is, immunology, virology, vaccinology, and cancer biology. PubMed is operated by the United States National Institutes of Health. The average impact factor of my publications far exceeds that of most of my colleagues at the University of Guelph. My publications rank in the top 5-10% of the scientific literature, in terms of their importance. I point this out to illustrate the depth of my expertise on vaccines and vaccine immunology. I have also been recognized on multiple occasions as a top-tier scientific reviewer for the Canadians Institutes of Health Research, resulting in my admission into their college of reviewers and invitations to serve on their Cancer Biology and Therapeutics grant review panel, and a three-year term on their Virology and Viral Pathogenesis panel, where I was specifically recruited to provide expertise for reviewing vaccine-related applications. Attached as **Exhibit A** to my affidavit is a copy of my curriculum vitae.

My expressions on COVID-19 science curtailed and censored after Dr. Fisman's posts

7. Since the declaration of the COVID-19 pandemic in March 2020, I provided information in the area of my scientific expertise as a public service. Specifically, I provided information about research and science related to COVID-19 and public health policies when requested. It is an expectation of my university that I address questions posed to me by the public in areas of my expertise. This falls under the "Service to the Community" portion of my distribution of effort. I gained popularity with mainstream media networks such as CBC News, Global News, Fox News, and the Globe and Mail, because of my specialization in viral immunology and all aspects of the severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2). I answered questions in a factual manner based on my research of the primary scientific data regardless of the dominant or prevailing messages conveyed to the public by government officials. This is evidenced for example, in my radio interview with Alex Pierson. My engagements were announced on the University of Guelph website, attached as **Exhibit B**.

8. As one example, on January 2, 2021, I raised concerns about the short research timelines in the development, and insufficient duration of immunity, of the COVID-19 vaccines on a CTV episode of W5. That interview was televised nationally and gained national and international attention. https://www.ctvnews.ca/w5/rush-to-vaccinate-citizens-by-rich-countries-leaves-much-of-the-world-awaiting-coronavirus-vaccines-1.5250596

9. On February 10, 2021, I published an article in The Conversation entitled "5 factors that could dictate the success or failure of the COVID-19 vaccine rollout"[6]. In this article I predicted that achieving the publicly stated goal of herd immunity against SARS-CoV-2 would not be possible if the duration of immunity conferred by COVID-19 vaccines was too short. Specifically, I stated, "If immunity declines before "herd immunity" is achieved, previously vaccinated individuals will become susceptible to infection again and the rollout could fail." Questioning the duration of immunity of the COVID-19 vaccines was countervailing to the government messages that they were "effective" at the time. But my questions proved to be valid because multiple peer-reviewed scientific publications confirmed that any protection against infection induced by COVID-19 vaccines wanes sharply after only four months[7].

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[6] https://theconversation.com/5-factors-that-could-dictate-the-success-or-failure-of-the-covid-19-vaccine-rollout-152856

[7] Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, Al Khatib HA, Coyle P, Ayoub HH, Al Kanaani Z, Al Kuwari E, Jeremijenko A, Kaleeckal AH, Latif AN, Shaik RM, Abdul Rahim HF, Nasrallah GK, Al Kuwari MG, Al Romaihi HE, Butt AA, Al-Thani MH, Al Khal A, Bertollini R, Abu-Raddad LJ. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021 Dec 9;385(24):e83. doi: 10.1056/NEJMoa2114114. Epub 2021 Oct 6. PMID: 34614327; PMCID: PMC8522799.

Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, Frankland TB, Ogun OA, Zamparo JM, Gray S, Valluri SR, Pan K, Angulo FJ, Jodar L, McLaughlin JM. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021 Oct 16;398(10309):1407-1416. doi: 10.1016/S0140-6736(21)02183-8. Epub 2021 Oct 4. PMID: 34619098; PMCID: PMC8489881.

Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, Gallagher E, Thelwall S, Groves N, Dabrera G, Myers R, Campbell CNJ, Amirthalingam G, Edmunds M, Zambon M, Brown K, Hopkins S, Chand M, Ladhani SN, Ramsay M, Lopez Bernal J. Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines. N Engl J Med. 2022 Jan 27;386(4):340-350. doi: 10.1056/NEJMoa2115481. Epub 2022 Jan 12. PMID: 35021002; PMCID: PMC8781262.

Indeed, breakthrough infections are commonplace, and SARS-CoV-2 has become endemic. The attempt to achieve herd immunity against SARS-CoV-2 failed. It is now commonplace knowledge that the COVID-19 vaccines were never tested for their potential to stop transmission of SARS-CoV-2 and they can't. This failure to confer immunity guaranteed that herd immunity could never be reached by mass vaccination. Worse, there are publicly available data, such as those provided by Public Health Ontario that showed cases of COVID-19 being disproportionately diagnosed among people that had received COVID-19 vaccines. This is shown in the figure of data from Ontario that I made, which is presented in **Exhibit I.** Also in Exhibit I are shown a graph of confirmational data from Quebec that shows cases of COVID-19 being diagnosed disproportionately among people who received COVID-19 vaccines, and a graph of data from Quebec showing hospitalizations occurring due to COVID-19 being disproportionately higher among those that received COVID-19 vaccines. Similar findings have also been reported in the peer-reviewed scientific literature[8]. The authors of this paper published a figure, included in Exhibit I, that shows cases of COVID-19 being diagnosed disproportionately among people that received COVID-19 vaccines, with a dose-response effect opposite to what a vaccine is intended to accomplish. Specifically, the more doses that people in this study received, the greater their risk of being diagnosed with COVID-19.

[8] Shrestha NK, Burke PC, Nowacki AS, Simon JF, Hagen A, Gordon SM. Effectiveness of the Coronavirus Disease 2019 Bivalent Vaccine. Open Forum Infect Dis. 2023 Apr 19;10(6):ofad209. doi: 10.1093/ofid/ofad209. PMID: 37274183; PMCID: PMC10234376.

The authors concluded, "…it is possible that a substantial proportion of individuals may be unlikely to derive any meaningful benefit from a bivalent vaccine.". This raises the possibility of negative effectiveness of COVID-19 vaccines in some scenarios. For comparative purposes, Health Canada defines an ideal vaccine (*i.e.*, one that can be used to achieve herd immunity) as one that "is effective in providing lifelong protection against disease after a single dose."[9] In short, as an expert vaccinologist, I knew exactly what was required for an attempt to achieve herd immunity to succeed or fail.

In the same article published in The Conversation, I also predicted failure of achieving herd immunity with SARS-CoV-2 vaccines should too many variants of the virus emerge. Among my accurate predictions on this topic was the following quote, "If a variant emerges that has altered its spike protein enough to bypass vaccine-induced immunity, the vaccine rollout could fail. If this happens, vaccines may need to be re-engineered to express a novel version of the spike protein, preferably with other proteins added to broaden immunity." Once again, with the ongoing use of reformulated COVID-19 booster vaccines, this expert prediction came to pass. I can make accurate predictions like this when it comes to vaccines because a person with deep expertise in an area can identify disconcerting patterns within data sets that are too limited for others to discern.

[9] https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-14-basic-immunology-vaccinology.html#a9

10. I continued to provide commentary on the COVID-19 pandemic based on my scientific knowledge and studies, attached as **Exhibit C** is a partial list of my media interviews. I raised many of the same concerns in several "Open Letters" I co-authored with my senior immunology colleagues at the university, dated, March 3, 2021, March 5, 2021, and March 16, 2021, attached as **Exhibit D**. I consider it my duty to objectively comment on matters within my expertise of vaccinology in the public interest when called upon to do so.
11. On March 23, 2021, the I co-authored another open letter with my immunology colleagues at the university, setting out the safety and efficacy concerns we all had about AstraZeneca's COVID-19 vaccine, which had been authorized by Health Canada for interim emergency use and not approved. This letter was widely circulated, nationally and internationally, attached as **Exhibit E**. Raising valid questions in my field of expertise was never considered misinformation or disinformation. In fact, our concerns about the safety of AstraZeneca's COVID-19 vaccine proved to be legitimate when the use of this vaccine was subsequently discouraged due to its linkage to potentially fatal blood clots, which did end up killing several Canadians.
12. On April 15, 2021, however, I was openly and directly criticized about "messaging to the public" that was contrary to public health at the monthly Pathobiology Department meeting by Dr. Scott Weese. Dr. Bonnie Mallard, the most senior immunologist at the University of Guelph, was present. Dr. Weese also criticized Dr. Mallard for expressing scientific views that were contrary to the government message. We were both surprised not only by Dr. Weese's objection to our public speaking, but also by the Dean of our Department, Dr. Jeff Wichtel's reaction in silencing any further

scientific discussion. These behaviours are very atypical in publicly funded academic institutions. In fact, I had never experienced nor witnessed these kinds of behaviours previously in my scientific career.

13. Dr. Scott Weese is a Defendant in this Claim. He is a veterinarian and microbiologist at the University of Guelph. Dr. Weese does not have a PhD, he has a DVSc. The DVSc is not a recognized degree in many countries, and it typically involves research conducted at a level roughly equivalent to a MSc degree. Dr. Weese operates a website blog "Worms and Germs": https://www.wormsandgermsblog.com/

14. Dr. Weese and Dr. Fisman share the same goal of labelling scientific criticism of COVID-19 vaccines and public health policies as "misinformation", even if the information is accurate. Dr. Weese was a member of the Ontario COVID-19 Advisory Science Table (now called Ontario Public Health Emergencies Science Advisory Committee) when Dr. Fisman was also a serving member.[10]

15. After Dr. Fisman's social media posts, which I describe below, on June 2, 2021, the University issued an announcement regarding my media interviews and ceased posting any future media appearances. Attached as **Exhibit F** are emails between Drs. Weese, Pyle, and Wichtel. None of my public presentations are announced on the University website after May 17, 2021. The final story that the University of Guelph carried about me was entitled "The Guardian Consults Virologist on Children's Immunity Concerns".[11] This was highly unusual because prior to this, the University of Guelph had run almost 100 stories about me as part of their ongoing media

[10] https://www.publichealthontario.ca/en/About/External-Advisory-Committees/OPHESAC
[11] https://news.uoguelph.ca/2021/05/the-guardian-consults-virologist-on-childrens-immunity-concerns/

campaign and I continued to submit many potential stories to be run. Never had any of my news-worthy messages been denied. In fact, people involved with media relations at the University of Guelph simply ceased communicating with me. Worse, I even submitted stories to promote the careers of members of my research team and these were never published also under Exhibit F. This is a form of academic harm to innocent trainees that are trying to establish their careers.

Fisman's social media messages about me are false and malicious

16. On May 27, 2021, I was interviewed by Global News correspondent, Alex Pierson, for the radio program "ON Point", attached as **Exhibit G** is the complete interview transcript.

17. Within 48 hours of my interview, I received an email from a graduate student, with a screenshot of a message posted by Dr. Fisman on his Twitter account. I immediedtly brought the matter to the attention of my Dean. Attached as **Exhibit H** is my email. ***I do not have a Twitter account*** or any other on-line microblogging social network service account.

18. Dr. Fisman's May 29th, 2021, post on @DFisman was:

> "I've had questions over the past 48h about vaccine safety concerns aired Dr Bryam Bridle at @UofGuelphOAC in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here:
>
> **byrambridle.com**"

19. On May 31, 2021, Dr. Fisman, posted the following Tweet:

> David Fisman @DFisman
>
> "The website debunking Dr. Bridle's covid-19 vaccine claims has been updated with lots of peer-reviewed science that attests to the safety of vaccines.
>
> **Byrambridle.com**
>
> And for those who think I made or organized this website: nope. But grateful to the scientists who did."

20. I unequivocally deny providing any information on the radio interview that was not based on scientific evidence or data. Dr. Fisman did not specify which of my claims are "not data based", either in his online posts or subsequently. During my interview, I made it clear that I could only present some of the information that I had in-hand, and could only do it superficially, since I was addressing a lay audience, and had no way to show any evidence via radio airwaves. Specifically, I stated, "the science that, that I am going to be talking about, um, I don't have the time here to describe exactly the scientific data", and "I have all of this information, ah, in-hand. I am in the process of madly trying to put it all into a, a, a, a document that I, I can hopefully circulate widely". By failing to communicate with me, anybody who judged what I said was knowingly doing it based on incomplete and superficial information. I made it clear that I could provide the information. Dr. Fisman, as an academic colleague never asked for it prior to accusing me of dishonesty. I followed through on my promise

stated in the interview and subsequently published an article entitled "COVID-19 Vaccines and Children: A Scientist's Guide for Parents".[12]

21. My life was turned upside down after Dr. Fisman's allegations that I was dishonest and my interview comments were not based on data and his promotion of a website that impersonates me and smears my name was underhanded.

Fisman asserts unsubstantiated and false allegations of scientific fraud

22. In the May 29, 2021, post, Dr. Fisman juxtaposes the term legitimate immunologist, with making illegitimate claims. His statement acts as a smear on my reputation as a credible scientist. It is not a disagreement about the science, or my scientific views. He makes no statement about scientific evidence, and he offers no scientific views of his own.

23. With respect to Dr. Fisman's allegation that "some claims were not data based". Dr. Fisman never identified ***any*** scientifically invalid claims. I deny making any invalid claims. I gave honest and unbiased answers, supported by multiple peer-reviewed scientific papers during the interview. All these references are cited in my article "COVID-19 Vaccines and Children: A Scientist's Guide for Parents".

24. Due to the time constraints of a nine (9) minute radio interview in which I was presenting to a lay audience using simplified jargon, I could not provide citations, references, and quotes from my review of the research to support my oral assertions, questions, and opinions.

[12] https://www.canadiancovidcarealliance.org/media/children-and-covid-19-vaccines-full-guide/

25. The three salient points made in that interview are accepted principles in the peer-reviewed scientific literature, also referenced in the Affidavits of Dr. Pelech, Dr. Speicher, Dr. Bonnie Mallard, Dr. Niel Karrow, and Dr. Harvey Risch, filed in this motion. Attached as **Exhibit I** are further studies and evidentiary basis for my interview comments.

26. Contrary to Dr. Fisman's post, the scientific claims I made during the 9 minute interview are not rebutted on the website. I have seen the website. The messages and discussions posted on the website about the points I made in the ON Point interview are mostly innuendo and opinion about me. I could rebut every accusation with primary scientific evidence, if given a chance to engage in a discussion about the accusations made there. In fact, many of the messages posted on the website demonstrate fundamental misunderstandings about immunology by its anonymous author(s). For example, I was criticized for citing a paper as evidence that the spike protein circulating in blood might be able to cause harm. But I highlighted in my interview that the study in question used a tiny sample size and focused on people with robust health. Specifically, I said, "thirteen, ah, young health care workers". I merely cited this study as **proof-of-principle** that the spike could get into circulation (in 11 of these 13 people). Was the spike at very low concentrations in this study. Yes, as I would expect because the people were healthy. I didn't have time to express my concern that the concentrations might be much higher in people diagnosed with severe adverse events after getting the shot. Indeed, a case study was published showing the concentration was >100-fold higher in a person that suffered a severe consequence

from the shot[13]. After all, Canada shut down the AstraZeneca COVID-19 vaccine program because of a reported 1:55,000 incidence of potentially fatal blood clots. So, I wouldn't expect to see high concentrations of the spike in the blood of only 13 young healthy people. In fact, we would need to look at many tens of thousands of people to have a reasonable chance of finding a person suffering a severe adverse event (according to Health Canada's statistics for blood clots associated with the AstraZeneca vaccine).

27. There are numerous Fact Check citations about spike proteins, all denying any possible toxicity of the vaccine spike. However, Fact Checks are not scientific references. Moreover, there is substantial evidence about the role of the vaccine spike protein circulating to and causing pathogenic reaction in various organs.[14]

    I wrote an article detailing behind-the-scenes details about so-called 'fact checking' and how they cannot be relied upon as accurate sources of information. The article is entitled "The Façade of 'Fact' Checking".[15]

Introduction and promotion of impersonating website in my name

28. Dr. Fisman provides a website bearing my name to the public; it is not my website. He never asked me about the website. It is not authorized by me, and I had no knowledge of it prior to receiving Dr. Fisman's post.

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[13] Appelbaum, J. et al. SARS-CoV-2 spike-dependent platelet activation in COVID-19 vaccine-induced thrombocytopenia. Blood advances 6, 2250-2253 (2022).
[14] Parry et al. https://www.mdpi.com/2227-9059/11/8/2287

[15] https://open.substack.com/pub/viralimmunologist/p/the-facade-of-fact-checking?r=109bxj&utm_campaign=post&utm_medium=web&showWelcome=true

29. There are serious ethical problems with an academic of Dr. Fisman's profile offering the public reference to and endorsement of a website of anonymous authorship. It does not consider conflicts of interest or malicious intent to damage my reputation and career.

30. The website's sole purpose is to impersonate me with the malicious intent to mock, defame, and damage my reputation and career as a vaccinologist and viral immunologist. The headline of the website states, next to a large picture of a duck (with the innuendo "quackery"):

> "Byram Bridle is a "viral immunologist who is passionate about improving life"... Albeit not by reducing the spread of covid-19 misinformation".

31. The website is the subject of an ongoing criminal investigation for identity fraud and impersonation. Attached as **Exhibit J** is a copy of the "Open Source Police Investigation Report", a draft affidavit prepared by the detective for my review as a victim, the search warrants issued and emails provided to me during police interview, in conjunction with the criminal investigation. (the names of officers are redacted to prevent social media harassment by members of the public)

32. Dr. Fisman's post introduces and guides followers to the website, which was created on the same day he announced it Attached as **Exhibit K** is a Cyber Security Report. Dr. Fisman directs and promotes a website, created with malicious intent to harm my reputation and career as a scientist, to the public at large within 36 hours of domain registration.

33. To my knowledge, Dr. Fisman was the ***first to announce the defamatory impersonating website and did so on the same date that it was created,*** on his Twitter account.

34. There is also another unauthorized online profile fraudulently created in my name, Twitter account @byrambridle ("Not Dr. Byram Bridle") was generated by unknown persons. It is also under criminal investigation for identify fraud and described under Exhibit J.

35. The website promoted by Dr. Fisman is also promoted on the fake @byrambridle Twitter account. The timeline of both systems appearing on-line together was the same on or around May 29, 2021.

36. On June 18, 2021, Dr. Fisman tagged the fake @byrambridle Twitter account:

> @Reuters fact check: claims that covid-19 vaccines are toxic == (bull) (shit) With @SabiVM @bad_epi@ByramBridle

37. Because the Twitter handle is my name, Dr. Fisman gives the public the impression that it is my account, but when you click on it, the user is directed to the impersonating account, attached as **Exhibit L** is a screenshot of both.

38. Dr. Fisman was aware that the website and Twitter profile impersonating me were not generated or authorized by me. This was also apparent to and pointed out by members of the public on May 29, 2021, in Twitter messages, captured by the police, on page 8 and 9 of Exhibit J:

> "Wait, you are citing a website, created by an Icelandic hacker who hijacked Byram's name & put it as a web domain, as your rebuttal that Dr. Bridle's claims are not supported by data?
> …
> "hmmm…I'm a scientist too (and a UofG grad, at that). As fellow scientist, I am embarrassed for this "scientist" to have crafted such an unprofessional way to engage a colleague…."

39. After these posts Dr. Fisman continued to promote the defamatory website, both on his Twitter account, and in reply to posts on the impersonating Twitter account, to members of the public. He also promoted it to the media, as set out in his own affidavit.

40. To my knowledge, Dr. Fisman was the ***first*** to introduce, actively promote and then subsequently repeatedly promote the impersonating website to 128,700 of his followers with the knowledge that the creator, or author of the website, is not me and is not known.

41. Dr. Fisman does not provide evidence of how he discovered the existence of the website as the first one to post it.

42. Dr. Fisman now asserts in his affidavit that the above post was to "direct the public to evidence-based information related to COVID-19 vaccines", but in his May 29 and 30, 2021 posts, he specifically states the reference is to refute my "claims" in the interview. However, there is no rebuttal of the questions I posed and the concerns I raised in the May 27, 2021, radio interview on the defamatory website promoted by Dr. Fisman.

43. He has not retracted or apologized for his false allegations and misleading referral.

Conspiracy with co-Defendants Drs. Pyle, Weese and Greer

44. Dr. Fisman engaged in the smear of my reputation in concert with three of the Defendants, Drs. Glen Pyle, Scott Weese and Amy Greer who are faculty members at my university.

45. Dr. Pyle is a professor of Molecular Cardiology in the Department of Biomedical Sciences at the University of Guelph. He holds a PhD in physiology and biophysics. Dr. Pyle also shares Dr. Fisman's goal of silencing any dissenting comments on COVID-19 public policy as "misinformation". He is a member of COVID19 Resources Canada Science Explained: https://covid19resources.ca/about-us/

46. Dr. Greer is an associate professor in population disease modelling. Dr. Greer and Dr. Fisman are both epidemiologists and have a long history of close collaborations as detailed in his resume[16]. Dr. Greer also shares Dr. Fisman's goal of censoring dissent and criticism of COVID-19 public policy, made apparent in the letter she wrote with Drs. Pyle, Weese and the co-Defendant Dr. Bienzle, July 6, 2021, below.

47. On June 2, 2021, Dr. Fisman received an email from a *USA Today* reporter, Daniel Funke, for comment regarding my ON Point interview. Dr. Fisman replied and copied Drs. Weese, Pyle, and Dr. Greer. In his reply email, Dr. Fisman personally maligned me as "dangerous" and as a purveyor of "misinformation". Dr. Fisman stated without any reference that a) I was distorting scientific evidence; b) I was part of a "disinformation operation" to shake vaccine confidence, and that c) I was becoming "more and more" "anti-vaxx." He did not provide any evidence for these bald assertions and name-calling. It is shocking to me that Dr. Fisman would refer to me as "anti-vaxxer" when my career is built on researching and developing vaccines. Attached under **Exhibit J**, are emails dated June 2, 2021, between them.

48. Dr. Fisman referred the reporter to the defamatory website impersonating me.

49. Dr. Fisman also referred Mr. Funke to Drs. Pyle, Weese and Greer for expertise.

50. None of the three professors are viral immunologists, let alone vaccinologists. They do not research or develop vaccines. They have no expertise that is relevant to comment on my radio interview. Their training has involved only the most superficial learning of immunology. The immunological sub-discipline of vaccinology is so complex that only immunologists holding advanced graduate degrees in the field can

[16] Motion Record, Affidavit of David Fisman, Exhibit A, pages -

comprehend the sophisticated mechanistic nuances of vaccine technologies. Remember, the COVID-19 vaccines are far from meeting Health Canada's definition of an ideal vaccine, which closely aligns with textbook definitions. And it is the definition of an ideal vaccine that non-vaccinologists are familiar with when disseminating their information.

51. The University of Guelph's media guide is a resource that directs people from outside the institution to faculty members based on their listed expertise.

52. Dr. Weese submitted the following expertise to the guide: "Antimicrobial resistance, Bacterial infections in animals and humans, Clostridium difficile, COVID-19 in pets, Emerging infectious disease in animals, MRSA, Rabies, Tick-borne diseases, Zoonosis"[17]. Dr. Weese does not list immunology or vaccinology as being within his realm of expertise. Dr. Greer listed: "COVID, Disease modelling, Infectious disease, Influenza, Outbreaks, Pandemics"[18].

53. Dr. Greer does not list immunology or vaccinology as being within her realm of expertise.

54. Dr. Pyle does not have a faculty profile listed in the media guide but does have one on the website of the Office of Graduate & Postdoctoral Studies, which states, "Our laboratory is interested in the molecular basis of heart failure, and the development of novel therapies for the treatment of heart attacks and chronic heart failure. We are investigating the mechanisms by which menopause increases the risk of heart disease in women, and sex differences in heart function. Together our research covers causes,

[17] https://experts.uoguelph.ca/scott-j-weese
[18] https://experts.uoguelph.ca/amy-greer

molecular mechanisms, and treatments of heart disease."[19]. Dr. Pyle does not list immunology or vaccinology as being within his realm of expertise.

55. These co-Defendants have no expertise in immunology, let alone the immunological sub-discipline of vaccinology. But I ***do*** have colleagues in the immunology program at the University of Guelph, and throughout Canadian universities, who are much better qualified. It is highly suspicious for Dr. Fisman to forward the request for media comment on my area of expertise to Drs. Pyle, Weese, and Greer.
56. It is my opinion that he did so because they disliked the public attention I had gained since the beginning of the declaration of the COVID-19 pandemic. Like him, they referred to my scientific commentary to the media as "misinformation" without evidence, discussion or debate with me. They called for the university to prohibit my public expressions because, in their opinion, it reflected "poorly" on the university. Attached as **Exhibit M** is the Open letter dated July 6, 2021. Dr. Pyle, Weese and Dr. Greer are also associated with the impersonating website. Their involvement is described in the detective notes under Exhibit J on pages 19 to 21.
57. As such Dr. Fisman's objective was not to connect Mr. Funke with a scientist with relevant expertise to comment, but rather to discredit my expertise and label as "misinformation" my public expressions on COVID-19 vaccines.
58. The Fact Check article written about me is inaccurate. Attached as **Exhibit N** is a rebuttal I submitted to fact checkers that was never published, nor was the article retracted.

[19] https://graduatestudies.uoguelph.ca/people/glen-pyle-0

59. Dr. Pyle was dishonest in his response to Mr. Funke. He is an academic who knows that citations and/or quotes from scientific references cannot be made in a nine (9) minute oral radio interview, especially when it is directed at a lay audience. Dr. Pyle acted recklessly and did not make any attempts to contact me about which paper I was referring to, both prior to and after his posts.
60. Dr. Fisman's statements to Mr. Funke were intended to discredit and defame me as a legitimate viral immunologist at a reputable academic institution. It was to deter the public from gaining knowledge about independent and objective scientific evidence regarding COVID-19 vaccine performance and immunology.
61. It is ironic that Dr. Fisman brings this motion to evade liability for damaging my reputation and career based on public interest since his statements and actions have caused more harm to public health, medical science, and professional ethics for his role in preventing public access to my independent and objective expert scientific perspective and expressions.

Conspiracy with Dr. Pyle and Dr. Weese on-line harassment

62. Drs. Pyle and Weese were successful in tarnishing my reputation on social media because Dr. Fisman granted them a larger audience and higher profile than they would have had without Dr. Fisman, as documented by Cyber Support Services under Exhibit J. Dr. Pyle and Dr. Weese had no prior communication about me on their social media accounts prior to Dr. Fisman's May 29th, 2021 investigation.
63. Due to his large following on Twitter and public prominence as a member of the Ontario Science Table and government advisor on COVID-19, Dr. Fisman gave Drs. Pyle and Weese the platform and amplified their objective of discrediting my expert

opinion as a vaccinologist and, also provided Dr. Weese the audience for his deliberately insulting *ad hominem* attacks on my character online.

64. I had no knowledge, presence, or ability to respond to either Drs. Pyle or Weese on-line because they restricted their communications about me to a platform that they knew I did not exist in. This was underhanded. Dr. Fisman's instigated and encouraged my university colleagues to abandon academic discourse, discussion, and debate *with* me in favour of a one-sided, exclusively social media-driven campaign *against* me.

65. On May 30th, 2021, @DFisman, posted a Tweet requesting that his followers follow @glenpyle:

> "An excellent follow for good immune science from @UofGuelphOAC is Dr @glenpyle, who has addressed some of the misinformation in his own Tweets,"
>
> [and here Fisman reposted Pyle's Tweet below:
>
> > "The paper Byram cited doesn't support his claim. That's
> >
> > pretty telling that a study cited to support his claims actually goes against those claims."
>
> And etc.]

66. Dr. Fisman does not specify or identify "some of the misinformation". An unfounded accusation of spreading misinformation is not an expression of scientific opinion or views.

67. On May 30th, 2021, Weese, from his Twitter account @weese_scott, replied to Dr. Pyle, as follows:

> "It's tough but misinformation has to be challenged. More misinformation and confusion during a pandemic are dangerous and causing harm."

68. Dr. Weese's Tweet above is malicious because he knew that the COVID-19 vaccines posed an increased risk of myocarditis and pericarditis in adolescents and young adults when he posted that message. On May 28, 2021, he received an email from the United States Centres for Disease Control and Prevention confirming my statements were not misinformation. He intentionally continued to make public claims that I was spreading misinformation when he had evidence and knew that was not true. Attached under **Exhibit J**, on pages 37 and 38, is reference to the email. These were the same concerns I had expressed one day earlier in my May 27, 2021, interview and that I subsequently expressed my COVID-19 vaccine Guide for parents.

69. On May 29th, 2021, Dr. Pyle also posted the following Tweets on the heels of Dr. Fisman's posts:

> "The paper Byram cited doesn't support his claim. That's pretty telling that a study cited to support his claims actually goes against those claims."

70. I have reviewed the paper that Dr. Pyle referred to in this Tweet and can confirm he distorted my claims when he accused me of misunderstanding a published paper that contained data that I had briefly discussed in my interview, it was he who misunderstood the significance of the data. Since he is not a viral immunologist with a subspecialty in vaccines, Dr. Pyle failed to appreciate that upon receipt of a first dose of a COVID-19 vaccine, **there are no spike-specific antibodies in circulation**. This demonstrates that the paper that I referred to in my radio interview was relevant to the context in which I framed my concerns. It also shows how a scientist lacking expertise in the area can draw incorrect conclusions when they fail to understand important immunological nuances like the fact that neutralizing antibodies don't exist

prior to nor immediately after receipt of a vaccine. The problem is that many members of the public do not understand the degree to which someone like Dr. Pyle fails to understand these aspects of vaccinology, hence the ability to cause massive damage to my reputation. This highlights the importance of engaging dissenting experts in discussions prior to publicizing rash non-expert judgements.

71. Dr. Fisman's referral to Dr. Pyle was irresponsible.

72. Dr. Fisman's referral to Dr. Pyle is moreover in bad faith because he is being investigated for his knowledge of the impersonating website by police. On or about May 29, 2021, the day after the website's creation, Pyle stated that he was in contact with and therefore was aware of the identity of the website's (and Twitter account's) creator. In response to another user's suggestion that a hacker had made the website, Pyle responded:

> "It's not a hacker. **The person who made it has contacted me**. **They are a scientist."**

73. Pyle further alluded to details about the identity of the website/fake account creator:

> "They [the creator of the website/twitter account] are not a colleague. I don't say that to be dismissive, just to clarify **that this is not someone who is at the same level & has legitimate reason to fear retribution.** You are certainly entitled to your opinion on the website & I'm not here to change anyone's mind on that…"

74. Dr. Pyle deleted these posts to conceal his admission of knowledge about the impersonator. I provided the screenshots of the original and deleted Tweets in my workplace harassment complaint. **Attached as Exhibit O**.

75. On May 31, 2021 and June 2, 2021, in an email exchange between Dr. Pyle and his faculty colleagues, including the Defendant Dr. Greer, they each refer to the fact that

the creator of the website is a student and "its not hard to figure out who did it though". "I figured it was someone in the dept….", under Exhibit J, page 19-20.

76. Pyle now falsely claims that he has no knowledge of the website's or twitter account's creation or creator(s) as does Dr. Fisman in his affidavit. Yet they both knew of the website's existence before anyone else having posted on May 29, 2021, the same day as its anonymous creation.

77. Finally, Dr. Fisman's statement to Mr. Fanke that I was referring to an "odd" document is both ignorant on his part and malicious. The document provided by the Japanese health regulatory agency had far more detailed information about the biodistribution of lipid nanoparticles. It was indeed the first time that scientists could access such detailed information. The data contained in the report form the European Medicines Agency was an overly brief summary of the document that I publicized. Since then, it was discovered that even the document from the Japanese health authority was a truncated version of the overall study that was only revealed after a court compelled the Food and Drug Administration to release it[20]. The full version of the study disclosed data that was even more concerning than what I was able to relay following review of the Japanese version.

78. On June 22 and 24th, 2021, I requested all academics discuss and debate scientific disagreements with me directly, instead of posting comments claiming I am committing academic fraud, on social media where I have no notice or ability to

[20] https://open.substack.com/pub/viralimmunologist/p/a-moratorium-on-mrna-vaccines-is?r=109bxj&utm_campaign=post&utm_medium=web&showWelcome=true

comment. It is underhanded for academics to insult another academic covertly. None responded and failed to identify a false utterance. Attached as **Exhibit P** is the email.

79. In sequence with Drs. Pyle and Weese, on May 31, 2021, Dr. Fisman posted:

> David Fisman @DFisman
>
> "A friend indicates that Dr Bridle's interview caused his parents to cancel their vaccine appointments. This is not ok."

80. The post is so ambiguous that it can be interpreted as a reference to my parents. Indeed, the way I became aware of this Tweet is because my mother contacted me to ask why a member of the public told her that she had been doxxed online. I took it this way and filed a complaint with the College of Physicians and Surgeons for his comments about my parents. Dr. Fisman now claims it was a reference to "a friend". One of the skills that scientists and physicians are expected to develop in order to avoid public harms is the ability to relay information unambiguously. Dr. Fisman's Tweet was not a statement about science or an opinion about a scientific issue. It is just a smear and innuendo without causation. Attached as **Exhibit Q** is the complaint that was filed to the College of Physicians and Surgeons of Ontario.

81. On June 12, June 14, June 22 and June 23, 2021, I emailed Drs. Pyle, Weese, and Fisman documents written by the inventor of mRNA vaccine technology, Dr. Robert Malone, and a link to a video, corroborating my statements, to disabuse them that I was dishonest or making false claims about COVID-19 vaccines without evidence or data. I also provided them with a link to an interview in which I rebutted every false allegation against me on the defamatory website that was repeatedly referenced and

promoted by Dr. Fisman. Dr. Fisman failed to acknowledge, respond or retract the allegation of "misinformation". Attached as **Exhibit R** are the emails.

82. On June 15, 2021, I published the "COVID-19 Vaccines and Children: A Scientist's Guide for Parents" (Guide). This report was produced in response to an overwhelming number of requests from members of the public for detailed references to scientific data and the most current independent research on COVID-19 vaccines due to my expertise. I made Dr. Fisman aware of the scientific underpinnings for all my statements on the ON Point Interview. Attached as **Exhibit S** is the Guide.

83. That same day, on June 15, 2021, Dr. Weese, responded to another person discussing my report "COVID-19 Vaccines and Children: A Scientists Guide for Parents" on Twitter. Dr. Weese responded by posting an image of a man shovelling manure along with the following text. The post is attached, with several others, as **Exhibit T**:

> "spreading it…[picture of farmer shovelling a truck full of manure]"

84. Dr. Weese's post is malicious because he knew or ought to have know that my Guide did not contain any invalid claims because he had received an email from CDC.

85. On June 17, 2021, I was invited to speak at a news conference in the Press Gallery of Parliament Hill. Immediately after the news conference, Dr. Weese, posted on Twitter, attached under **Exhibit J**, page 25:

> "An[sic] far right politician, anti-vaxxer and guy who compared public health measures to the Holocaust walk into a press room…
>
> I wish there was an actual joke in there. The real story's too sad/frustrating/maddening
>
> Misinformation kills. We need to address and remember that.

86. The reference to "anti-vaxxer" is to me. Dr. Weese recklessly, maliciously and hatefully referred to me as an "anti-vaxxer," purveyor of false information and killer.

87. I provided a request from an internationally renowned scientist and the inventor of mRNA, Dr. Robert Malone, to Drs. Wichtel, Weese and Pyle, presenting support for my expert opinions and to end the on-line harassment initiated and encouraged by D. Fisman. Attached as **Exhibit U** is Dr. Malone's letter.

88. On June 24, 2021, a peer-reviewed scientific paper was published[21] that independently drew very similar conclusions to those drawn by me months earlier. My Guide had outlined the scientific basis for the US-FDA's caution of risks posed to children and adding warnings to the labels for the Pfizer and Moderna vaccines regarding the association with myocarditis (inflammation of the heart) and pericarditis (inflammation of the sack surrounding the heart). The relevant text is:

> Today, the FDA is announcing revisions to the patient and provider fact sheets for the Moderna and Pfizer-BioNTech COVID-19 vaccines regarding the suggested increased risks of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the tissue surrounding the heart) following vaccination. For each vaccine, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) has been **revised to include a warning about myocarditis and pericarditis** and the Fact Sheet for Recipients and Caregivers has been revised to include information about myocarditis and pericarditis.[22]

89. Dr. Fisman, therefore, knew that I was not spreading misinformation.

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[21] Citation: Walach, H.; Klement, R.J.; Aukema, W. The Safety of COVID-19 Vaccinations—We Should Rethink the Policy. Vaccines 2021, 9, 693. https://doi.org/10.3390/vaccines9070693

[22]): https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-june-25-2021

90. On May 30, 2021, at 11:29 am, Dr. Weese wrote in an email to Dr. Pyle expressing his intention to provoke me with more offensive on-line posts, attached under **Exhibit J** emails:

> "… I should ramp up what I'm saying so he can come after me at the same time"

91. On July 24 and on August 6, 9, 13, 19, 22, 24, 25, 27, 28 and 31, Dr. Weese proceeded to do just that with the collabaroration and assistance of Dr. Fisman's posts on May 10th, and August 19th, 2021. Dr. Fisman did nothing to mitigate that I was referred to as a "liar and grifter," an "anti-vaxxer" and as being "harmful to society". Attached as **Exhibit V** in his email and are the Tweets.

92. On September 8, 2021, Dr. Weese posted more harmful, hateful and harassing comments about me on-line. On September 30, 2021, my legal counsel sent Dr. Weese a cease-and-desist letter to stop the on-line harassment, attached as **Exhibit W**.

93. On the same day, Dr. Weese wrote to the Defendant, Laurie Arnott. On or around October 2021, Ms. Arnott advised that his social media posts would qualify as job-related and constitute academic discussions, and legal defence of his on-line harassment would be covered by the University's insurance, attached under **Exhibit J**, emails:

> "…We sought a legal opinion on the Tweets/posts we could find (outside of insurer general statement – to understand how we could push them if necessary) and think, though it isn't without risk of coverage denial, that they qualify as job related and would be covered."

94. Subsequently, Dr. Weese "ramped up" the posts as he stated he would by linking me to Dr. Fisman's post of May 10, 2021, and allegations of "anti-vaxxer" and "white

supremist", attached under **Exhibit V** is the post linking Dr. Fisman's Tweets to Dr. Weese. Dr. Fisman did not post a retraction or an apology.

Endangerment of Life

95. On May 29, 2021, I brought the impersonating Twitter account and website to the attention of my university, through the Defendant Dr. Jeff Wichtel, with a request for an expedited investigation, assistance given the chaos and turmoil it had wreaked on my life, my family and the toll it took on my emotional and mental state.

96. On June 23, 2021, Dr. Wichtel and Ms. Arnott dismissed the complaint orally, without investigation or reasons. Attached as **Exhibit X** is the email invitation to hear the orally delivered decision on-line. My university was unsympathetic and not motivated to assist or mediate a resolution to the increase in tension amongst faculty.

97. On June 30, 2021, I registered a formal police complaint, as set out under **Exhibit J**.

98. Due to the relentless Twitter posts beginning in May 2021 over a period of 6 months and the escalation of hateful messages, on November 11, 2021, I was advised by the Municipal Police investigating the harassment to take precautions for my safety.

99. Dr. Weese's link between me, allegation of lies, and white supremist, neo-Nazis have the potential to incite hate and violence.

100. On November 16, 2021, Campus Police Officer Larry O'Connell wrote to the Supervisor of the University Police, Garry Male in an email. Attached as **Exhibit Y**:

> "As you can see Scot Weese an employee of the university continues to Tweet about bridle. It appears the university of Guelph is not interested in doing anything to stop this behaviour. Can you please pass this on to Human Resources who will be receiving some attention in the near further. Scott Weese who uses social media and identifies himself as a university employee

> need to read the definition of criminal harassment and save himself and the university some embarrassment. To refer to Bridle as an anti-vaxxer and white supremacy is crossing the line. Again Weese has never responded to my email about a safety plan. Larry."

101. On December 6, 2022, I became aware of the Dr. Weese's December 1, 2022, post, which had the potential to incite more hate:

> "It's bad enough that misinformation scared people away from vaccination (causing lots of death).
> Now they're scaring people away from blood transfusions….with no accountability."

102. Dr. Weese accused me of "causing lots of death," called for the public to hold me "accountable," he posted directly above my name, contact information, and a full photograph of me. Municipal Police cautioned me verbally to take measures for preventative protection. I was required to secure a personal escort trained and experienced in law enforcement for my own and family's safety.

Substantial and Serious Harms Suffered by false claims of "spreading misinformation"

Harm to Reputation

103. Beginning on May 29, 2021, Dr. Fisman initiated an online smear campaign to damage my reputation as a viral immunologist, to undermine my standing as an expert in vaccine development, performance, and safety to the media and the public at large.

104. Since the introduction and promotion of the fraudulent website and allegation of "misinformation" by him, my reputation as a credible scientist with government funders has been destroyed.

105. Prior to May 2021, the only on-line presence I had was for scholarly matters. I did not participate or have any interest in social media.

106. After Dr. Fisman's post on May 29, 2021, a search for my name "Byram Bridle" on the internet, directs users to the defamatory website, which website appears at first glance to be a website owned by me. The X (Twitter) account registered in my name also appears. In October 2023, I became aware that there is now a defamatory dating site that is impersonating me. Attached as **Exhibit Z**.

107. Since the false allegation by Fisman that I am a purveyor of "misinformation" I am no longer referred to as an expert in my field. Prior to Dr. Fisman's post on May 29, 2021, my expertise in viral immunology was never questioned by the media. I was always referred to as an expert in the areas of immunology, virology, and vaccine-related research and development. After Dr. Fisman's "misinformation" and "disinformation" allegations, I am referred to as an "expert" in parentheses. Attached as **Exhibit AA** are two media articles in the same publication pre- and post-May 2021.

108. Dr. Fisman's alignment with and referral to Drs. Pyle and Weese with his followers and the media granted them access to a larger audience. He instigated them to attack me on social media as the first to post about me on his Twitter account, knowing I had no presence there.

109. Dr. Fisman added his comments to Dr. Weese and Dr. Pyle to support my removal from campus, which has caused irreparable harm to my career, research and academic programme. On August 19, 2021, Dr. Fisman posted in response to Dr. Weese:

> "UofG administration has been absolutely bizarre for months now.
> They've coddled spreaders of vaccine misinformation on campus, even as they have created safety issues (not just related to vaccinations) for others in the UofG university community."

110. On August 31, 2021, Dr. Pyle posted that the University was not doing enough to sanction me for "expressing views that are in direct contrast to their mission and

values". November 15, 2021, Dr. Weese posted another message to University of Guelph calling for the University to sanction me, under **Exhibit J**, page 29.

Harm to Research Lab and Funding

111. I am not, and have never been, "anti-vaxx". I have studied, developed, and researched vaccines for well over a decade. My career is built on the creation of vaccines. This research is dependent on funding from third party donors/grantors.

112. Since its establishment at the University of Guelph, Department of Pathobiology my research lab has been one of the most active, productive, and successful in the department and the entire campus.

113. In May 2021 I directed a team of eight scientists. At present I only direct one.

114. Loss of graduate students and an inability to recruit new graduate students, means that I no longer have the human resources required to maintain a functional, let alone productive research program. Without trainees, I cannot apply for grants. No grants will be awarded to a principal investigator lacking the human resources needed to conduct the proposed research. This has resulted in a massive loss of productivity and has negated my ability to write grant applications.

115. Historically I have been extremely successful in obtaining funding and grants for my research. Funding is essential to maintain the operation of my research lab and to recruit and retain personnel. Funding is based on three criteria: 1) the proposed research, 2) the research team and 3) the reputation of the scientist.

116. In the past I received numerous grants to support both cancer and basic viral immunology research programs, including to support COVID-19-focused research, which were exceptionally difficult to secure. For example, I was the only applicant

from the Department of Pathobiology to successfully obtain funding from the Natural Sciences and Engineering Research Council of Canada (NSERC) in the funding cycle that I competed in. This was a five-year grant. I have also brought prestigious funding to the University of Guelph that they had never received in their history, such as monies from the Terry Fox Research Institute.

117. Since May 2021, I have not been able to obtain a grant. I even tried applying in conjunction with collaborators who could cover my missing human resources, to an agency that I had never applied to in the past, namely the Ontario Ministry of Agriculture, Food, and Rural Affairs.

118. On June 15, 2021, the Terry Fox Research Institute expressed concern about the social media posts. I relied on the Terry Fox Research Institute to consistently provide funding for my research and have successfully obtained funding as evidenced in my CV attached under **Exhibit A**, for seven (7) consecutive years.

119. Without graduate students I have been unable to maintain my research program. Two of my graduate students left my group due to concerns about the negative publicity that was instigated beginning with Dr. Fisman's initial Tweet about my ON Point interview. Since then, all but one of my remaining graduate students have completed their program. I cannot, in good faith, recruit new graduate students for research-intensive training when my university will not allow me to mentor them in-person. The result of this, and broad damage to my academic reputation, among granting agencies, where colleagues can determine the outcome of my applications behind closed doors, I have now lost my funding.

120. My research career, which was on a steep upward trajectory has now been destroyed.

121. Over the past three years, these harms have amounted to a loss of approximately $250,000 in annual operating funds, or $750,000 in total funding. Worse, I now face having to re-start my research program from scratch whenever the administration of my university allows me to resume it. To establish a research program typically takes five years. This is the why faculty members are referred to as 'early career faculty members' for the initial five years of their independent research career.

122. Further, the start-up of a research program requires time to obtain funding and time to recruit and intensively train new students. So, early career researchers get relief from teaching and service duties to facilitate this. Following this period, maintaining a research team is much less arduous because the group maintains functional memory, meaning that skills that have been acquired over the years get passed from senior to junior lab members to ensure that the skills are never lost within the group.

123. In my case, my research program has lost this continuity, which means that I will be responsible for most of the training of an initial team of new trainees. Therefore, for me to rebuild my research program, I require the following: for apologies to be issued publicly by the Defendants to clear my reputation. This will allow me to attach these documents to grants to allay any concerns that granting agencies and their reviewers may have because of the damage done to my reputation. I will also need an initial two-year reprieve from teaching and service, $500,000 in the first year of my re-start-up to cover the replacement of materials lost over the past three years and to cover the operating costs of the first year. I would also need approximately $250,000 per year to cover operating costs in years 2-5. At the end of this period, I anticipate that my productivity and reputation could be restored to where they were prior to May 2021.

No evidence of Dr. Fisman's public expressions being limited or curtailed

124. Dr. Fisman has not provided any evidence in his affidavit of how his expressions have been curtailed or limited since the commencement of this claim in December 2022.

125. There is evidence from X (Twitter) that Dr. Fisman's expressions have ***increased*** since May 2021, when he had 72, 600 followers, July 2021, 83,600 followers, December 2021 105, 000 followers and December 2023, 128, 400 followers. Attached as **Exhibit BB** are Dr. Fisman's twitter profile screenshots from May 2021 to December 2023.

126. Dr. Fisman's public expressions and views cannot be characterized as dissent, countervailing or minority. He represents opinions that are in accordance with the dominant government discourse and policies.

Continuation of Dr. Fisman's Smear of my reputation in these proceedings

127. I have spoken about science when I have been invited to do so by members of the public.

128. With respect to Dr. Fisman's affidavit, I state that:

(a) I speak at gatherings, conferences, or public events to which I am invited, I am invited to, and speak about the science;

(b) At many of those conferences, rallies, and public gatherings, hundreds to thousands of people may be present.

129. The validity and accuracy of my exposés on the science has nothing to do with the fact that one, two, or even a handful of the attendees are not to Dr. Fisman's political liking, and is trying to smear me, in a guilt-by-association, with non-scientists. This, to my view is simply an indication of his malice.

SWORN BEFORE ME by Byram)
Bridle in the City of Guelph, in the)
Province of Ontario, on this 15th day of)
December, 2023, in accordance with)
O. Reg. 431/20 Administering Oath)
Or Declaration Remotely)

A Commissioner for Taking Oaths
Rocco Galati B.A., LL.B., LL.M.

Dr. Byram Bridle

This is Exhibit " A " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

Canadian Common CV commun canadien

Protected when completed

Date Submitted: 2023-12-04 09:43:37
Confirmation Number: 1722007
Template: Full CV

Dr. Byram W. Bridle

Correspondence language: English
Sex: Male
Date of Birth: 12/02
Canadian Residency Status: Canadian Citizen
Country of Citizenship: Canada

Contact Information

The primary information is denoted by (*)

Address

Primary Affiliation (*)

Room #4834, Building #89
Department of Pathobiology
University of Guelph
50 Stone Road East
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Canada

Telephone

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Email

Work (*)	bbridle@uoguelph.ca

Website

Corporate	https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

Canadian Common CV commun canadien

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Dr. Byram Bridle

Language	Read	Write	Speak	Understand	Peer Review
English	Yes	Yes	Yes	Yes	Yes

2005/9 - 2011/12	Post-doctorate, Post-doctoral fellowship, Viral Immunology, McMaster University Degree Status: Completed
	Supervisors: Dr. Yonghong Wan, 2005/9 - 2011/12
	Research Disciplines: Immunology, Virology
	Areas of Research: Vaccine and Cancer, Immunotherapy, Vaccination, Virus, Auto-Immune Diseases, Cerebral Tumors
	Fields of Application: Biomedical Aspects of Human Health
2000/1 - 2005/10	Doctorate, Doctor of Philosophy, Immunology, University of Guelph Degree Status: Completed Thesis Title: Suppression and modulation of rat immune responses against porcine cells.
	Supervisors: Dr. Bonnie A. Mallard, 2000/1 - 2005/10
	Research Disciplines: Immunology
	Areas of Research: Transplantation and Graft Rejection
	Fields of Application: Biomedical Aspects of Human Health
1994/9 - 1997/4	Master's Thesis, Masters of Science, Immunology, University of Guelph Degree Status: Completed Thesis Title: The influence of age and strain on the peripheral blood lymphocytes of commercially raised chickens.
	Supervisors: Dr. Azad Kaushik, 1994/9 - 1997/4
	Research Disciplines: Immunology
	Areas of Research: Immune System
	Fields of Application: Pathogenesis and Treatment of Diseases
1990/9 - 1994/4	Bachelor's Honours, Bachelors of Science, Biomedical Sciences, University of Guelph Degree Status: Completed

Credentials

2018/8	Awarded Tenure, University of Guelph
2018/1	Associate Professor, University of Guelph

2012/1 - 2017/12 Assistant Professor, University of Guelph
Named to the Regular Graduate Faculty in the Department of Pathobiology by the Board of Graduate Studies, University of Guelph.

Research Disciplines: Immunology

Areas of Research: Vaccine and Cancer, Immunotherapy, Vaccination, Virus, Cerebral Tumors, Leukemia, Lymphoma, Auto-Immune Diseases

Fields of Application: Biomedical Aspects of Human Health

Recognitions

2021/5 Recognized as an outstanding reviewer for the Canadian Institutes of Health Research
Canadian Institutes of Health Research
Distinction
CIHR's Review Quality Assurance (RQA) Process recognizes outstanding contributions to peer review. Through feedback and observations from Committee Chairs, Scientific Officers and CIHR staff, the RQA process captures contributions that exemplify the very best of peer reviewers. It is my pleasure to inform you that you are among a select group of reviewers who have been identified through this process as an Outstanding reviewer in recognition of your exemplary contribution to peer review for the Fall 2020 Project Grant competition. Among the 1107 reviewers that participated in the competition, only 12.6% obtained this recognition. On behalf of CIHR and the College of Reviewers, thank you for your selfless generosity volunteering your time and expertise and for your commitment to excellence in peer review. Your institution will be informed of your achievement as part of the College of Reviewers' Institution Activity Report planned to be sent to your institution's Vice-President.

2020/11 Invited to be a member of the Canadian Institutes of Health Research College of Reviewers (Canadian dollar)
Canadian Institutes of Health Research
Honor
"On behalf of the Canadian Institutes of Health Research (CIHR), we are very pleased to invite you to become a member of the College of Reviewers (College). This invitation is made in recognition of your accomplished career, demonstrated track record of excellence, and dedication to peer review."

2020/11 Identified as an outstanding reviewer for the Canadian Institutes of Health Research
Canadian Institutes of Health Research
Distinction
CIHR's Review Quality Assurance (RQA) Process recognizes outstanding contributions to peer review. Through feedback and observations from Committee Chairs, Scientific Officers and CIHR staff, the RQA process captures contributions that exemplify the very best of peer reviewers, such as providing reviews that exceeded expectations, completing additional tasks on short notice, and participating constructively in discussions about applications that were not assigned to them. It is my pleasure to inform you that you are among a select group of reviewers who have been identified through this process as an outstanding reviewer in recognition of your exemplary contribution to peer review during the fall 2019 Project Grant competition. On behalf of CIHR, thank you for your selfless generosity volunteering your time and expertise and for your commitment to excellence in peer review. Feel free to inform the Vice-President of Research or equivalent at your institution on this achievement.

2020/4	Honourary class president of the Ontario Veterinary College's Doctor of Veterinary Medicine class of 2023 University of Guelph Honor Voted by class as professor of the year (for teaching immunology)
2020/3	Zoetis Award for Research Excellence - 1,000 Zoetis Prize / Award This award recognizes outstanding research effort and productivity.
2019/6	Donation made on behalf of my research program. - 25,000 (Canadian dollar) Canadian Cancer Society Research Institute Honor Hawkesbury Regional Catholic High School, via the Relay for Life Youth program, donated $25,000 to the Canadian Cancer Society in support of my research program.
2019/6	Donation made on behalf of my research program. - 75,000 (Canadian dollar) Canadian Cancer Society Research Institute Honor The Arts and Science Undergraduate Society at Queen's University donated $75,000 to the Canadian Cancer Society to support my research program.
2019/4	Monetary donation made in Dr. Bridle's honour by the DVM class of 2020 to the Down Syndrome Research Foundation. University of Guelph Honor Done in recognition of teaching excellence.
2018/7	Promotion to the position of Associate Professor University of Guelph Distinction Based on meritorious performance as an Assistant Professor, I was promoted to the position of Associate Professor, effective July 1, 2018.
2017/12	Tenure University of Guelph Distinction Based on meritorious performance as an Assistant Professor, I was awarded tenure in December 2017.
2015/6	Carl J. Norden Distinguished Teaching Award The highest teaching award given by each North American Veterinary College; the recipient is chosen based on a vote of the second, third and fourth year veterinary classes. - 1,000 University of Guelph Prize / Award The highest teaching award given by each North American Veterinary College
2015/4 - 2018/3	Terry Fox Research Institute New Investigator Award - 449,587 (Canadian dollar) Terry Fox Research Institute Prize / Award To provide outstanding young researchers with support as they develop their career as independent research scientists or clinician scientists and to undertake high-quality research into cancer in close collaboration with established research teams.

2015/4	Was one of three nominees for honourary class president for the Doctor of Veterinary Medicine class of 2018. University of Guelph Honor The honourary class president is voted by the students as the professor of the year.
2014/6	Junior Investigator Grant Panel Travel Award Canadian Cancer Society Research Institute Prize / Award An travel award provided to successful applicants by the Canadian Cancer Society to attend and observe a grant review panel meeting.
2014/4	Monetary donation made in Dr. Bridle's honour by the DVM class of 2017 to the Guelph Giants Special Hockey organization. University of Guelph Honor Done in recognition of teaching excellence.
2014/3	Honourary class president of the Ontario Veterinary College's Doctor of Veterinary Medicine class of 2017 University of Guelph Honor Voted by class as professor of the year (for teaching immunology).
2010/12	Next generation of cancer researchers Ontario Institute for Cancer Research Distinction Featured in the Ontario Institute for Cancer Research 2010 annual report as one of the "next generation of cancer researchers" that is a "rising star" that should be retained in Ontario (see page 20 of report). Research Disciplines: Immunology Areas of Research: Vaccine and Cancer Fields of Application: Biomedical Aspects of Human Health
2010/10	Best oral presentation McMaster University Prize / Award 1st Annual McMaster University Faculty of Health Sciences Post-Doctoral Research Day Research Disciplines: Immunology Areas of Research: Vaccine and Cancer Fields of Application: Biomedical Aspects of Human Health
2009/3	Poster award Ontario Institute for Cancer Research Prize / Award Award for poster presented at the OICR annual scientific meeting. Research Disciplines: Immunology Areas of Research: Vaccine and Cancer Fields of Application: Biomedical Aspects of Human Health

2009/2	Post-doctoral travel award - 1,500 (Canadian dollar) 5th International Meeting on Replicating Oncolytic Virus Therapeutics Prize / Award Travel award to attend the 5th International Meeting on Replicating Oncolytic Virus Therapeutics. Research Disciplines: Virology Areas of Research: Vaccine and Cancer Fields of Application: Biomedical Aspects of Human Health
2008/3	Poster award - 100 (Canadian dollar) Ontario Institute for Cancer Research Prize / Award Award for poster presented at the OICR annual scientific meeting. Research Disciplines: Immunology Areas of Research: Vaccine and Cancer Fields of Application: Biomedical Aspects of Human Health
2005/3	Poster award - 250 (Canadian dollar) Canadian Society for Immunology Prize / Award Canadian Society for Immunology Poster Award for scientific presentation at annual scientific meeting. Research Disciplines: Immunology
2005/3	D.G. Ingram Travel Award - 400 (Canadian dollar) University of Guelph Prize / Award Travel award to attend the Canadian Society for Immunology annual scientific meeting. Research Disciplines: Immunology Areas of Research: Transplantation and Graft Rejection Fields of Application: Biomedical Aspects of Human Health
2005/3	Poster award - 250 (Canadian dollar) Canadian Society for Immunology Prize / Award Canadian Society for Immunology poster award for presentation at annual scientific meeting. Research Disciplines: Immunology Areas of Research: Transplantation and Graft Rejection Fields of Application: Biomedical Aspects of Human Health
2005/3	Dr. J. Sherman Travel Award - 150 (Canadian dollar) University of Guelph Prize / Award Travel award to attend the Canadian Society for Immunology annual scientific meeting. Research Disciplines: Immunology Areas of Research: Transplantation and Graft Rejection Fields of Application: Biomedical Aspects of Human Health

2004/7	American Association of Veterinary Immunologists Travel Award - 1,000 (United States dollar) American Association of Veterinary Immunologists Prize / Award American Association of Veterinary Immunologists travel award to attend the International Congress on Immunology. Research Disciplines: Immunology Areas of Research: Transplantation and Graft Rejection Fields of Application: Biomedical Aspects of Human Health
2004/1	Graduate Student Recognition Award University of Guelph Distinction Elected by peers to receive the Ontario Veterinary College Graduate Student Recognition Award for outstanding leadership and contributions. Research Disciplines: Immunology
2004/1	Ontario Veterinary College Travel Award - 500 (Canadian dollar) University of Guelph Prize / Award Ontario Veterinary College travel award to attend the International Congress of Immunology. Research Disciplines: Immunology Areas of Research: Transplantation and Graft Rejection Fields of Application: Biomedical Aspects of Human Health
2003/1	Graduate Student Recognition Award University of Guelph Prize / Award Elected by peers to receive the Ontario Veterinary College Graduate Student Recognition Award for leadership and contributions. Research Disciplines: Immunology
2003/1	Dr. F. Schofield Korean-Canadian Scholarship - 2,000 (Canadian dollar) Korean-Canadian Scholarship Association Prize / Award Established by the Dr. Schofield Memorial Association of Korean-Canadian, in partnership with the Korean-Canadian Scholarship Association. The scholarship honours Dr. Frank Schofield's active role in the Korean independence movement, as well as his academic and medical contributions in the early 20th century. It is awarded annually to a student who demonstrates scholarship and contributions to academic life. Research Disciplines: Immunology
2002/9 - 2002/12	University Graduate Scholarship - 500 (Canadian dollar) University of Guelph Prize / Award To recognize academic excellence. Research Disciplines: Immunology

2002/1 - 2002/4	University Graduate Scholarship - 500 (Canadian dollar) University of Guelph Prize / Award To recognize academic excellence. Research Disciplines: Immunology
2001/1	Ontario Veterinary College Travel Award - 500 (Canadian dollar) University of Guelph Prize / Award Travel award to attend the annual scientific meeting of the Canadian Society for Immunology. Research Disciplines: Immunology
1995/9 - 1995/12	University Graduate Scholarship - 500 (Canadian dollar) University of Guelph Prize / Award To recognize academic excellence. Research Disciplines: Immunology
1995/1 - 1995/4	University Graduate Scholarship - 500 (Canadian dollar) University of Guelph Prize / Award To recognize academic excellence. Research Disciplines: Immunology
1990/9	University of Guelph Entrance Scholarship - 1,000 (Canadian dollar) University of Guelph Prize / Award Scholarship awarded for students entering their undergraduate program with an academic average of >90% in secondary school.
1990/9 - 1994/4	Canada Scholarship - 8,000 (Canadian dollar) Government of Canada Prize / Award Scholarship to support undergraduate-level university education. Only 1,250 of these scholarships were awarded to men across Canada in 1990. Awarded based on academic merit with semesterly renewal dependent on maintaining high academic standards.
1990/9	Wellington County Scholarship - 500 (Canadian dollar) County of Wellington Prize / Award Awarded in recognition of academic excellence.
1990/9	Ontario Scholar Ontario Government Prize / Award Awarded to students who maintained an academic average >80% throughout secondary school.

User Profile

Researcher Status: Researcher
Research Career Start Date: 1994/09/06
Engaged in Clinical Research?: No

Key Theory / Methodology: My research crosses the disciplines of immunology and virology. There are two areas of emphasis within my research program: one focuses on human health, the other on basic science. My health-

related research is both pre-clinical and translational and aims to develop novel biotherapies for the treatment of cancers. My basic program studies fundamental mechanisms of initiation and regulation of innate anti-viral immunity, with an emphasis on identifying causes of aberrant cytokine storms.

Research Interests: In an effort to destroy malignant cells with minimal bystander damage to normal tissues, I combine two approaches: 1. cancer immunotherapy, which directs the power of the immune system against tumours and, 2. oncolytic virotherapy that utilizes viruses that replicate in and kill only cancerous cells. The exquisite specificity and systemic targeting capability of these two approaches holds promise that some day cancer patients might be effectively treated without the toxicities associated with many conventional therapies. My extensive work with oncolytic viruses has also led to the discovery of a novel mechanism for the negative regulation of complex cytokine networks. This has led to a keen interest in basic aspects of innate antiviral immunity. In summary, my specific interests include: vaccines, oncolytic viruses, immunological tolerance, autoimmunity (to kill cancerous but not normal self), tumour biology, host anti-viral response and antigen presentation.

Research Experience Summary: I am an early-career faculty member, appointed Jan. 3, 2012, in the department of Pathobiology, University of Guelph. Key milestones achieved to date include: 1. Establishing a new viral immunology research program to develop effective new cancer biotherapies and to understand the regulation of cytokine networks in response to viral infections. 2. Using my expertise to fuel local, provincial, national and international collaborations. Research highlights as a post-doctoral fellow at McMaster University inlcuded: 1. Discovering that histone deacetlyase inhibition can enhance an oncolytic booster vaccine while abrogating autoimmune pathology. 2. Developing a novel method to synergize oncolytic virotherapy with cancer immunotherapy. 3. Advancing the field of cancer vaccinology. As a PhD student I developed a strategy to use oral tolerance to modulate host immunity to facilitate xenotransplantation. I also have significant management experience from industry appointments.

Research Specialization Keywords: immunology, virology, treating cancers in the brain, type I interferon signaling, type I interferon, vaccines, cancer, cytokines, regulation of cytokines, immunotherapy, viruses, flow cytometry

Disciplines Trained In: Immunology, Virology

Research Disciplines: Immunology, Virology

Areas of Research: Immunotherapy, Vaccine and Cancer, Cerebral Tumors, Immune System, Vaccination, Virus

Fields of Application: Pathogenesis and Treatment of Diseases, Biomedical Aspects of Human Health

Employment

2018/1	Associate Professor Pathobiology, Ontario Veterinary College, University of Guelph Full-time, Associate Professor Tenure Status: Tenure I received tenure in December 2017 and was promoted to the position of Associate Professor, effective July 1, 2018. I specialize in viral immunology and am responsible for training highly qualified personnel, managing a research program, teaching undergraduate, Doctor of Veterinary Medicine and graduate students, and providing community service.
2017/10	Goalie Coach Guelph Giants Special Needs Hockey Club (affil. with Special Hockey International and Hockey Canada) I am a volunteer coach. I teach children with special needs on the Guelph Giants junior team how to play the goaltending position for ice hockey.

2012/1 - 2017/12 Assistant Professor
Pathobiology, Ontario Veterinary College, University of Guelph
Full-time, Assistant Professor
Tenure Status: Tenure Track
A tenure-track early career faculty position, specializing in viral immunology. Responsible for training highly qualified personnel, managing a research program, teaching undergraduate, Doctor of Veterinary Medicine and graduate students, and providing community service.

Research Disciplines: Immunology, Virology

Areas of Research: Vaccine and Cancer, Immunotherapy, Vaccination, Virus, Immune Mediators: Cytokines and Chemokines, Auto-Immune Diseases, Cerebral Tumors, Leukemia

Fields of Application: Biomedical Aspects of Human Health

2005/9 - 2011/12 Post-doctoral fellow
Pathology and Molecular Medicine, Medicine, McMaster University
Full-time
Tenure Status: Non Tenure Track
McMaster Immunology Research Centre, McMaster University Advisor: Dr. Yonghong Wan Research: Developed expertise in the areas of cancer immunotherapy and oncolytic viruses for the purpose of rationally designing novel vaccine strategies for treating cancers and infectious diseases. Emphases: brain cancer, neuroimmunology, T and B cell biology and a diverse array of research techniques and analytical methods. Strategic collaborations: virologists, immunologists, nuclear imaging scientists who were interested in using brain cancer models as imaging tools, mathematics department (to model biological findings), McMaster Industry Liason Office (intellectual property interests), University of Ottawa, Ontario Institute for Cancer Research. I also gained some experience co-supervising graduate and undergraduate students.

Research Disciplines: Immunology, Virology

Areas of Research: Vaccine and Cancer, Immunotherapy, Virus, Cerebral Tumors

Fields of Application: Biomedical Aspects of Human Health

2000/1 - 2005/10 Research Assistant
Pathobiology, Ontario Veterinary College, University of Guelph
Full-time
Tenure Status: Non Tenure Track
PhD research project. Advisor: Dr. Bonnie Mallard Collaboration between the University of Guelph and University of Western Ontario. Developed strategies to suppress and modulate rat immune responses against porcine cells in support of xenotransplantation research.

Research Disciplines: Immunology

Areas of Research: Transplantation and Graft Rejection

Fields of Application: Biomedical Aspects of Human Health

1999/7 - 2000/12	Research Project Manager Pathobiology, Ontario Veterinary College, University of Guelph Full-time Tenure Status: Non Tenure Track Managed a xenotransplantation research project that represented collaboration between the Universities of Guelph, Western Ontario and Toronto and Imutran (former subsidiary of Novartis) for the purpose of breeding transgenic pigs to be used as organ/tissue donors. Research Disciplines: Immunology Areas of Research: Transplantation and Graft Rejection Fields of Application: Biomedical Aspects of Human Health
1999/1 - 1999/6	Quality Control Laboratory Technician Microbiology Quality Control Laboratory, Schneider's Meats, Ltd., Kitchener Full-time Quality control testing in a microbiology laboratory to monitor safety of meat products. Research Disciplines: Microbiology
1997/5 - 1998/12	Research Project Manager International Bio-Institute, Fergus, Ontario Full-time Obtained GLP (good laboratory practices) certification for research division. Managed veterinary drug efficacy and safety pre-clinical trials for submissions to the Canadian Bureau of Veterinary Drugs and the U.S.A. Food and Drug Administration. Also established a small ELISA (enzyme-linked immunosorbent assay)-based diagnostic laboratory. Research Disciplines: Veterinary Sciences Areas of Research: Infectious Diseases Fields of Application: Pathogenesis and Treatment of Diseases
1994/9 - 1997/4	Research Assistant Pathobiology, Ontario Veterinary College, University of Guelph Full-time Tenure Status: Non Tenure Track MSc research project. Advisor: Dr. Azad Kaushik Characterized the influence of age and strain on the peripheral blood lymphocytes of commercially raised chickens. Research Disciplines: Immunology Areas of Research: Animal Fields of Application: Pathogenesis and Treatment of Diseases
1994/5 - 1994/8	Undergraduate Research Assistant Pathobiology, Ontario Veterinary College, University of Guelph Full-time Tenure Status: Non Tenure Track Cloned and sequenced antibody variable region genes from lupus-prone mice in support of an autoimmunity research project. Sequences were subsequently published. Advisor: Dr. Azad Kaushik Research Disciplines: Immunology Areas of Research: Antibodies, Auto-Immune Diseases Fields of Application: Biomedical Aspects of Human Health

1993/5 - 1993/8 Undergraduate Research Assistant
Food Science, Ontario Veterinary College, University of Guelph
Full-time
Tenure Status: Non Tenure Track
Studying the viscoelastic properties of acid milk gels using a nametre. Supervisor: Dr. Arthur Hill

Research Disciplines: Biology and Related Sciences

Areas of Research: Nutriceuticals and Functional Foods

Fields of Application: Industrial Manufacturing and Production

Affiliations

The primary affiliation is denoted by (*)

(*) 2018/1 Associate Professor, Pathobiology, University of Guelph

2012/1 - 2017/12 Assistant Professor, Pathobiology, University of Guelph
A tenure-track early career faculty specializing in viral immunology. Responsible for educating students, managing a research program that results in publishing independent academic work in scholarly peer-reviewed journals and providing community service.

2021/1 - 2021/12 Sabbatical, University of Guelph
I was granted a research leave. This is standard practice for an academic faculty member. We are entitled to request a research leave following every six years of service. The purpose is to facilitate re-training in state-of-the-art research and teaching methods. This particular research leave allowed me to focus on research-related activities, including service to the research community during the declared COVID-19 pandemic. To accomplish this, I was relieved of all teaching and local service activities for a period of one year.

Research Funding History

Awarded [n=43]

2019/3 - 2024/2
Co-applicant Combined Anti-Angiogenic, Metronomic Chemotherapy, and Immunotherapy in the Treatment of Advanced Stage Ovarian Cancer, Grant

Funding Sources:

2019/4 - 2024/3 Canadian Institutes of Health Research (CIHR)
Project Grant
Total Funding - 725,000 (Canadian dollar)
Portion of Funding Received - 100,000
Funding Competitive?: Yes

Co-applicant : Jack Lawler; Sarah K. Wootton;

Principal Applicant : James J. Petrik

2021/9 - 2023/8
Principal Investigator Oxidative Stress as a Mechanism Causing Off-Target Infections of T Cells with Oncolytic Viruses (student stipend support), Scholarship

Funding Sources:

2021/9 - 2023/8 Ontario Veterinary College (OVC)
Master's Scholarship
Total Funding - 30,000 (Canadian dollar)

Principal Applicant : Sierra Vanderkamp

2021/9 - 2023/8
Principal Applicant
Heat- and Cold-Adaptation of Oncolytic Rhabdoviruses to Improve Their Clinical Utility, Grant, Operating

2020/7 - 2023/6
Co-applicant
Characterization of Innate Lymphoid Cells in Canine Blood, Grant

Funding Sources:

OVC Pet Trust
Operating Grant
Total Funding - 16,100
Portion of Funding Received - 0
Funding Competitive?: Yes

Co-applicant : Dr. Samuel Hocker;

Principal Investigator : Dr. Khalil Karimi

2020/7 - 2023/6
Co-applicant
The use of SPECTRA OPTIA, Apheresis System from TERUMO, in Veterinary Medicine, Grant

Funding Sources:

OVC Pet Trust
Equipment Grant
Total Funding - 40,000
Portion of Funding Received - 0
Funding Competitive?: Yes

Principal Investigator : Dr. Alice Defarges

2022/5 - 2023/4
Principal Investigator
Ontario Graduate Scholarship (awarded to MSc student but declined due to receipt of a scholarship of greater monetary value), Scholarship
Project Description: Studying off-target infection of activated T cells by oncolytic rhabdoviruses

Funding Sources:

Government of Ontario
Ontario Graduate Scholarship
Total Funding - 15,000 (Canadian dollar)

2022/5 - 2023/4
Principal Investigator
Canadian Institutes of Health Research Canada Graduate Scholarship (awarded to MSc student), Scholarship
Project Description: Studying off-target infection of activated T cells by oncolytic rhabdoviruses

Funding Sources:

2022/5 - 2023/4 Canadian Institutes of Health Research (CIHR)
Canada Graduate Scholarship
Total Funding - 17,500 (Canadian dollar) (Canadian dollar)

2020/9 - 2022/8
Principal Investigator
OVC MSc Scholarship, Scholarship

Funding Sources:

2020/9 - 2022/8 Ontario Veterinary College (OVC)
MSc Graduate Scholarship
Total Funding - 30,000 (Canadian dollar)

Principal Applicant : Lily Chan

2020/9 - 2022/8
Principal Applicant

Advancing a Promising Infected Cancer Cell Vaccine Platform into the Translational Research Pipeline, Grant

Funding Sources:

Cancer Research Society (The)
Operating Grant
Total Funding - 120,000
Portion of Funding Received - 120,000
Funding Competitive?: Yes

Co-applicant : Dr. Sarah K. Wootton

2017/7 - 2022/6
Co-applicant

Vascular Normalization as a Mechanism to Increase Oncolytic Virus Spread and Efficacy (a sub-project within a Program Project Grant that was awarded by the Terry Fox Research Institute to the Canadian Oncolytic Virus Consortium [$7,396,160]), Grant

Funding Sources:

2017/7 - 2022/3 Terry Fox Research Institute (TFRI)
Program Project Grant
Total Funding - 314,460 (Canadian dollar)
Portion of Funding Received - 314,460
Funding Competitive?: Yes

2020/3 - 2022/3
Principal Applicant

Developing Prophylactic Virus-Vectored Vaccines for COVID-19, Grant

Funding Sources:

Ontario Ministry of Colleges and Universities
COVID-19 Rapid Research Fund
Total Funding - 231,888
Portion of Funding Received - 231,888
Funding Competitive?: Yes

Co-investigator : Dr. Leonardo Susta; Dr. Sarah K. Wootton

2021/1 - 2022/3
Principal Investigator

Translational Development of an Avian Orthoavulavirus-1-Vectored Vaccine for COVID-19, Grant

Funding Sources:

National Research Council Canada (NRC) (Ottawa, ON)
Pandemic Response Challenge Program
Total Funding - 444,000
Portion of Funding Received - 319,000
Funding Competitive?: Yes

Co-investigator : Leonardo Susta; Sarah K. Wootton

2019/3 - 2022/2
Co-applicant

AAV Gene Therapy for the Treatment of Surfactant Protein B Deficiency, Grant

Funding Sources:

2019/3 - 2024/2 Canadian Institutes of Health Research (CIHR)
Project Grant
Total Funding - 620,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes

Co-applicant : Bernard Thébaud; Martin Kang;

Collaborator : Jeffrey Whitsett; Laura van Lieshout; Lawrence Nogee;

Principal Applicant : Sarah K. Wootton

2019/9 - 2021/8
Principal Investigator

Nora Cebotarev Memorial Graduate Scholarship (student stipend funding), Scholarship

Funding Sources:

2019/9 - 2021/8 University of Guelph
Nora Cebotarev Memorial Graduate Scholarship
Total Funding - 25,000 (Canadian dollar)

Principal Applicant : Jessica Minott

2020/9 - 2021/8
Principal Investigator

Ontario Graduate Scholarship (student stipend funding), Scholarship

Funding Sources:

2020/9 - 2021/8 Ontario Ministry of Colleges and Universities
Total Funding - 15,000 (Canadian dollar)

Principal Applicant : Jessica Minott

2021/5 - 2021/8
Principal Investigator

Andrea Leger Dunbar Summer Studentship (student salary funding), Scholarship

Funding Sources:

2021/5 - 2021/8 Ontario Veterinary College (OVC)
Andrea Leger Dunbar Summer Studentship
Total Funding - 9,000 (Canadian dollar)

Principal Applicant : Christina Napoleoni

2018/7 - 2021/6
Principal Investigator

Developing Biotherapies for the Treatment of Canine Cancers, Grant

Funding Sources:

2018/1 - 2022/12 Private Donation
private donation
Total Funding - 1,500 (Canadian dollar)
Portion of Funding Received - 1,500
Funding Competitive?: No

2018/6 - 2021/5
Co-applicant

PD-1 Expression on Blood Leukocytes in Dogs with Bladder Cancer, Grant

Funding Sources:

2018/4 - 2021/3 Pet Trust Fund (The)
Operating Grant
Total Funding - 27,584 (Canadian dollar)
Portion of Funding Received - 6,896
Funding Competitive?: Yes

Co-applicant : Anthony Mutsaers;

Principal Applicant : Samuel Hocker

2018/1 - 2021/1

Oncolytic Viral Vaccine Therapy of Feline Mammary Carcinoma, Grant

Co-investigator

Funding Sources:

2018/1 - 2021/1 Pet Trust Fund (The)
Operating Grant
Total Funding - 7,668 (Canadian dollar)
Portion of Funding Received - 1,534
Funding Competitive?: Yes

Co-applicant : Michelle Oblak; Robert Foster;

Co-investigator : Geoffrey Wood;

Principal Applicant : J. Paul Woods

2020/3 - 2021/1
Co-investigator

Developing Prophylactic Virus-Vectored Vaccines for COVID-19, Grant

Funding Sources:

University of Guelph, Ontario Veterinary College and Department of Pathobiology
Seed funding for COVID-19 research
Total Funding - 20,000
Portion of Funding Received - 20,000
Funding Competitive?: Yes

Co-investigator : Dr. Sarah K. Wootton;

Principal Applicant : Dr. Leonardo Susta

2020/5 - 2020/8
Principal Investigator

NSERC Undergraduate Student Research Assistantship (student salary funding), Scholarship

Funding Sources:

2020/5 - 2020/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Research Assistantship
Total Funding - 4,500 (Canadian dollar)

Principal Applicant : Lily Chan

2018/9 - 2020/8
Principal Applicant

Treatment of Osteosarcoma Lung Metastases with an Infected Cancer Cell Vaccine, Grant

Funding Sources:

2018/9 - 2021/8 Cancer Research Society (The)
Operating Grant
Total Funding - 60,000 (Canadian dollar)
Portion of Funding Received - 60,000
Funding Competitive?: Yes

2018/9 - 2021/8 Canadian Institutes of Health Research (CIHR)
CRS Operating Grant (jointly funded)
Total Funding - 62,086 (Canadian dollar)
Portion of Funding Received - 62,086
Funding Competitive?: Yes

Co-applicant : Sarah K. Wootton

2018/9 - 2020/8
Principal Applicant

Combining Oncolytic Virotherapy and Epigenetic Modifiers to Treat Acute Leukemias, Grant

Funding Sources:

2019/8 - 2021/7 Canadian Institutes of Health Research (CIHR)
CCS-RI Innovation Grant (jointly funded)
Total Funding - 100,000 (Canadian dollar)
Portion of Funding Received - 100,000
Funding Competitive?: Yes

2018/8 - 2021/7 Canadian Cancer Society Research Institute (CCSRI)
Innovation Grant
Total Funding - 105,215 (Canadian dollar)
Portion of Funding Received - 105,215
Funding Competitive?: Yes

2017/9 - 2020/8
Principal Investigator

Enhancing Immunogenic Cancer Cell Death Through the Novel Combination of Oncolytic Viruses and Photodynamic Therapy (student stipend support), Scholarship

Funding Sources:

2017/9 - 2020/8 Canadian Institutes of Health Research (CIHR)
Vanier Scholarship
Total Funding - 150,000 (Canadian dollar)
Portion of Funding Received - 33,000
Funding Competitive?: Yes

Principal Applicant : Ashley Ross;

Principal Investigator : Sarah Wootton

2020/5 - 2020/8
Principal Investigator

Andrea Leger Dunbar Summer Studentship (student salary funding), Scholarship

Funding Sources:

2020/5 - 2020/8 University of Guelph
Andrea Leger Dunbar Summer Studentship
Total Funding - 9,000 (Canadian dollar)

Principal Applicant : Kiersten Hanada

2019/9 - 2020/8
Principal Investigator

Ellen Nilsen Memorial Graduate Scholarship (student stipend funding), Scholarship

Funding Sources:

2019/9 - 2020/8 University of Guelph
Ellen Nilsen Memorial Graduate Scholarship
Total Funding - 1,500 (Canadian dollar)

Principal Applicant : Jessica Minott

2018/9 - 2020/8
Principal Investigator

Combining Oncolytic Viruses with Epigenetic Modifiers to Treat Acute Myeloid Leukemias (student stipend support), Scholarship

Funding Sources:

2018/9 - 2020/12 Ontario Veterinary College (OVC)
Graduate Scholarship
Total Funding - 37,000 (Canadian dollar)
Portion of Funding Received - 37,000
Funding Competitive?: Yes

Principal Applicant : Elaine Klafuric

2020/5 - 2020/8
Principal Investigator

BioCanRx Summer Studentship (student salary funding), Scholarship

Funding Sources:

2020/5 - 2020/8 National Centre of Excellence in Biotherapeutics for Cancer Treatment
Summer Studentship
Total Funding - 8,000 (Canadian dollar)

Principal Applicant : Lily Chan

2017/7 - 2020/6
Principal Investigator

Developing Biotherapies for the Treatment of Canine Cancers, Grant

Funding Sources:

2017/7 - 2020/6 Private Donation
private donation
Total Funding - 1,000 (Canadian dollar)
Portion of Funding Received - 1,000
Funding Competitive?: No

2017/7 - 2020/6
Co-applicant

Synthesis of a Novel Oncolytic Newcastle Disease Virus to Support the Treatment of Companion Animal Cancer Patients, Grant

Funding Sources:

2017/6 - 2020/6 Pet Trust Fund (The)
Operating Grant
Total Funding - 25,000 (Canadian dollar)
Portion of Funding Received - 5,000
Funding Competitive?: Yes

Co-applicant : Sarah Wootton;

Principal Applicant : Leonardo Susta

2018/1 - 2019/12
Co-investigator

The Role of Interleukin-17-Producing Cells in the Pathophysiology of Canine Immune Mediated Hemolytic Anemia, Grant

Funding Sources:

2018/1 - 2021/1 Pet Trust Fund (The)
Operating Grant
Total Funding - 10,583 (Canadian dollar)
Portion of Funding Received - 1,764
Funding Competitive?: Yes

Co-investigator : Anthony Abrams-Ogg; Darren Wood; Dorothee Bienzle; Geoffrey Wood;

Principal Applicant : Shauna Blois

2019/5 - 2019/8
Principal Investigator

Undergraduate Research Assistantship (student salary funding), Scholarship

Funding Sources:

2019/5 - 2019/8 University of Guelph
Undergraduate Research Assistantship
Total Funding - 8,000 (Canadian dollar)

Principal Applicant : Lily Chan

2017/9 - 2019/8
Co-applicant

Vascular Normalization as a Mechanism to Increase Uptake and Efficacy of Oncolytic Viruses and Vaccine-Induced Effector Cells for the Treatment of Advanced Stage Ovarian Cancer, Grant

Funding Sources:

2017/9 - 2019/8 Cancer Research Society (The)
Operating Grant
Total Funding - 120,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes

Co-applicant : Sarah Wootton;

Principal Applicant : James Petrik

2018/9 - 2019/4
Principal Investigator

The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy (student stipend support), Scholarship

Funding Sources:

2018/9 - 2019/4 Ontario Graduate Scholarship
Graduate Scholarship
Total Funding - 10,000 (Canadian dollar)
Portion of Funding Received - 5
Funding Competitive?: Yes

Principal Applicant : Jacob van Vloten;

Principal Investigator : Sarah K. Wootton

2014/4 - 2019/3
Principal Applicant

Developing Novel Cancer Biotherapies: Infrastructure to Support Translational Research in Companion Animals, Grant

Funding Sources:

2014/4 - 2019/3 Ministry of Research and Innovation (MRI) (Ontario)
Ontario Research Fund - Research Infrastructure Program
Total Funding - 124,886 (Canadian dollar)
Portion of Funding Received - 124,886
Funding Competitive?: Yes

2013/4 - 2019/3
Principal Applicant

Type I Interferon Receptor Signalling as a Master Switch for the Negative Regulation of Cytokine Networks, Grant

Funding by Year:

2013/7 - 2018/6 Total Funding - 175,000
Portion of Funding Received - 175,000
Time Commitment: 16

2015/4 - 2019/3
Principal Applicant

Development of Cutting-Edge Biotherapies for the Treatment of Cancers, Grant

Funding Sources:

2015/4 - 2018/3 Terry Fox Research Institute (TFRI)
New Investigator Award
Total Funding - 449,587 (Canadian dollar)
Portion of Funding Received - 449,587
Funding Competitive?: Yes

2016/3 - 2019/2
Principal Investigator

Developing Biotherapies for the Treatment of Canine Cancers, Grant

Funding Sources:

2016/3 - 2019/2 Private Donation
private donation
Total Funding - 400 (Canadian dollar)
Portion of Funding Received - 400
Funding Competitive?: No

2016/1 - 2019/1
Principal Applicant

Construction and Validation of Viral-Vectored Vaccines to Induce Robust Tumour-Specific T Cell Responses in Dogs with Oral Melanomas, Grant

Funding Sources:

2016/1 - 2019/1 Pet Trust Foundation
Operating Grant
Total Funding - 12,265 (Canadian dollar)
Portion of Funding Received - 12,265
Funding Competitive?: Yes

2016/7 - 2018/12
Co-applicant

Accelerated Clinical Development of Synthetic Antibody Immuno-Modulators Through Companion Animal Trials (the "total funding" represents the amount awarded to B. Bridle; the award for both applicants was $708,893), Grant

Funding Sources:

2016/7 - 2018/6 National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx)
Enabling Grant
Total Funding - 351,361 (Canadian dollar)
Portion of Funding Received - 319,261
Funding Competitive?: Yes

Principal Applicant : Jason Moffat

2016/9 - 2018/12
Principal Investigator

The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy (student stipend support), Scholarship

Funding Sources:

2016/9 - 2018/12 Ontario Veterinary College (OVC)
Graduate Scholarship
Total Funding - 21,000 (Canadian dollar)
Portion of Funding Received - 21,000
Funding Competitive?: Yes

Principal Applicant : Jacob van Vloten;

Principal Investigator : Sarah K. Wootton

2015/9 - 2018/8
Principal Investigator

Art Rouse Cancer Biology Graduate Stipend (student stipend support), Scholarship

Funding Sources:

2015/9 - 2018/8 Ontario Veterinary College (OVC)
Art Rouse Cancer Biology Graduate Stipend
Total Funding - 60,000 (Canadian dollar)
Portion of Funding Received - 60,000
Funding Competitive?: Yes

Principal Applicant : Robert Mould (PhD student)

2016/9 - 2018/8
Principal Investigator

Sex Disparity in Innate Immune Responses to Viral Infection: the Role of Type I Interferon (student stipend support), Scholarship

Funding Sources:

2016/9 - 2018/8 University of Guelph
Graduate Tuition Scholarship
Total Funding - 32,000 (Canadian dollar)
Portion of Funding Received - 5,333
Funding Competitive?: Yes

Principal Applicant : Katrina Allison (MSc student)

Completed [n=40]

2021/1 - 2022/1
Principal Investigator
Translational Development of an Avian Orthoavulavirus-1-Vectored Vaccine for COVID-19, Grant, Operating
Clinical Research Project?: No

Funding by Year:

2021/1 - 2022/1 Total Funding - 303,341 (Canadian dollar) (Canadian dollar)

2018/5 - 2018/8
Principal Investigator
Assessing the Impact of Sex Hormones on the Efficacy of Oncolytic Viruses ($8,000 for student salary support; $1,000 for operating funds), Scholarship

Funding Sources:

Ontario Veterinary College (OVC)
Andrea Leger Dunbar Summer Research Studentship
Total Funding - 9,000
Portion of Funding Received - 9,000
Funding Competitive?: Yes

Co-investigator : Jessica Minott

2018/5 - 2018/8
Principal Investigator
Type I Interferon-Mediated Regulation of IL-17 Production by Mast Cells (student salary support), Scholarship

Funding Sources:

Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Student Research Assistantship
Total Funding - 4,400
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Principal Applicant : Elaine Klafuric

2018/5 - 2018/8
Principal Investigator
Combining Oncolytic Virotherapy with Epigenetic Modifiers to Treat Lymphomas (student salary support), Scholarship

Funding Sources:

National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx)
Summer Studentship
Total Funding - 6,000
Portion of Funding Received - 6,000
Funding Competitive?: Yes

Principal Applicant : Samantha Holtz

2015/6 - 2018/4
Co-applicant
Development of a Vaccine to Protect Against Toxoplasma gondii Infection in Sheep, Grant

Funding Sources:

2015/6 - 2018/4 Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
Tier I Operating Grant (Production Animal Systems)
Total Funding - 59,250 (Canadian dollar)
Portion of Funding Received - 14,813
Funding Competitive?: Yes

Co-applicant : John Barta; Paula Menzies;

Principal Applicant : Sarah K. Wootton

2017/5 - 2017/8
Principal Investigator
Assessing the Impact of an Acidic Tumour Microenvironment on the Efficacy of Oncolytic Viruses (student salary support), Scholarship

Funding Sources:

Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Student Research Assistantship
Total Funding - 4,400
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Principal Applicant : Julia Saturno

2016/9 - 2017/8
Principal Investigator
The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy (student stipend support), Scholarship

Funding Sources:

2016/9 - 2017/8 Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
Highly Qualified Personnel PhD Scholarship
Total Funding - 21,000 (Canadian dollar)
Portion of Funding Received - 10,500
Funding Competitive?: Yes

Principal Applicant : Jacob van Vloten (PhD student; co-advised);

Principal Investigator : Sarah K. Wootton

2017/5 - 2017/8
Principal Investigator
Enhancing Dendritic Cell-Based Anti-Cancer Vaccines Through Adaptation to a Hypoxic Microenvironment (student salary support), Scholarship

Funding Sources:

National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx)
Summer Studentship
Total Funding - 6,000
Portion of Funding Received - 6,000
Funding Competitive?: Yes

Principal Applicant : Mankerat Singh;

Principal Investigator : Khalil Karimi

2014/9 - 2017/8
Principal Investigator
Using Oncolytic Viruses to Potentiate Histone Deacetylase Inhibitor-Mediated Killing of Acute Lymphoblastic Leukemia B Bells (student stipend support), Scholarship

Funding Sources:

2014/9 - 2017/8 Ontario Veterinary College
PhD Scholarship
Total Funding - 42,000 (Canadian dollar)
Portion of Funding Received - 42,000
Funding Competitive?: Yes

Principal Applicant : Megan Whaley (PhD student)

2016/9 - 2017/8
Principal Investigator

Augmentation of a Canine Melanoma Vaccine with Immunomodulatory Antibodies (student stipend support), Scholarship

Funding Sources:

2016/9 - 2017/8 Canadian Institutes of Health Research (CIHR)
Canada Graduate Scholarship - Master's
Total Funding - 17,500 (Canadian dollar)
Portion of Funding Received - 17,500
Funding Competitive?: Yes

Principal Applicant : Wing Ka "Amanda" AuYeung (MSc student)

2016/9 - 2017/8
Co-applicant

Support for Development of Novel Cancer Biotherapies, Grant

Funding Sources:

2016/9 - 2016/12 Private donation
Private donation
Total Funding - 25,000 (Canadian dollar)
Portion of Funding Received - 8,333
Funding Competitive?: No

Co-applicant : James Petrik;

Principal Applicant : Sarah Wootton

2014/6 - 2017/6
Principal Applicant

Assessment of Canine Melanoma Samples from the Ontario Veterinary College-Companion Animal Tumour Bank for Expression of Antigens that can be Targeted with an Oncolytic Cancer Vaccine, Grant

Funding Sources:

2014/6 - 2015/5 Pet Trust Fund (The)
Operating Grant
Total Funding - 11,593 (Canadian dollar)
Portion of Funding Received - 11,593
Funding Competitive?: Yes

2016/1 - 2016/12
Co-applicant

Support for Development of Novel Cancer Biotherapies, Grant

Funding Sources:

2016/1 - 2016/12 Private donation
Private donation
Total Funding - 50,000 (Canadian dollar)
Portion of Funding Received - 16,667
Funding Competitive?: No

Co-applicant : James Petrik;

Principal Applicant : Sarah Wootton

2015/9 - 2016/8
Principal Investigator

Augmentation of a Canine Melanoma Vaccine with Immunomodulatory Antibodies (student stipend support), Scholarship

Funding Sources:

2015/9 - 2016/8 Pet Trust Foundation
OVC Pet Trust Scholar Program
Total Funding - 35,000 (Canadian dollar)
Portion of Funding Received - 18,500
Funding Competitive?: Yes

Principal Applicant : Wing Ka "Amanda" Au Yeung (MSc student)

2016/5 - 2016/8
Principal Applicant

Evaluating the Impact of Oxygen Level, Temperature and pH on the Oncolytic Potential of Viruses and Epigenetic Modifiers in Canine Osteosarcoma Cells (student salary support), Scholarship

Funding Sources:

2016/5 - 2016/8 Zoetis Canada
Summer Student Research Fund
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 8,000
Funding Competitive?: Yes

Co-applicant : Manali Desai (summer research assistant)

2016/5 - 2016/8
Principal Investigator

Type I Interferon Signalling as a Master Switch for the Negative Regulation of a Broad Array of Cytokines (student salary support), Scholarship

Funding Sources:

2016/5 - 2016/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Student Research Award
Total Funding - 4,400 (Canadian dollar)
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Principal Applicant : Katrina Allison (summer research assistant)

2016/5 - 2016/8
Principal Applicant

Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas (student salary support), Scholarship

Funding Sources:

2016/5 - 2016/8 Merial
Summer Research Assistantship
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 8,000
Funding Competitive?: Yes

Co-applicant : Julia Saturno (summer research assistant)

2015/9 - 2016/8
Principal Investigator

The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy (student stipend support), Scholarship

Funding Sources:

2015/9 - 2016/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Graduate Scholarship
Total Funding - 21,000 (Canadian dollar)
Portion of Funding Received - 10,500
Funding Competitive?: Yes

Principal Applicant : Jacob van Vloten (PhD student; co-advised);

Principal Investigator : Sarah K. Wootton

2014/9 - 2016/8
Principal Applicant

Evaluation of Adjunct Oncolytic Immunotherapy in a Canine Lymphoma Clinical Trial, Grant

Funding Sources:

2014/6 - 2016/5 Cancer Research Society (The)
Operating Grant
Total Funding - 120,000 (Canadian dollar)
Portion of Funding Received - 120,000
Funding Competitive?: Yes

Co-applicant : J. Paul Woods

2014/8 - 2016/6
Co-applicant

Oncolytic Viral Vaccine Therapy of Breast Carcinoma, Grant

Funding Sources:

2014/6 - 2016/5 Canadian Breast Cancer Foundation (CBCF)
Research Project Grant Program
Total Funding - 298,416 (Canadian dollar)
Portion of Funding Received - 59,472
Funding Competitive?: Yes

Co-applicant : J. Paul Woods;

Principal Applicant : Brian D. Lichty

2015/7 - 2016/6
Co-applicant

Accelerated Clinical Development of Synthetic Antibody Immuno-Modulators Through Companion Animal Trials, Grant

Funding Sources:

2015/7 - 2016/6 National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx)
Enabling Grant
Total Funding - 143,716 (Canadian dollar)
Portion of Funding Received - 32,100
Funding Competitive?: Yes

Principal Applicant : Jason Moffat

2014/9 - 2015/8
Principal Investigator

The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy (student stipend support), Scholarship

Funding Sources:

2014/9 - 2015/8 Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
Highly Qualified Personnel PhD Scholarship
Total Funding - 21,000 (Canadian dollar)
Portion of Funding Received - 10,500
Funding Competitive?: Yes

Principal Applicant : Jacob van Vloten (PhD student; co-advised);

Principal Investigator : Sarah K. Wootton

2013/9 - 2015/8
Principal Investigator

The Role of Type I Interferon Receptor-Mediated Signaling in the Regulation of Cytokines Produced by Dendritic Cells (student stipend support), Scholarship

Funding Sources:

2013/9 - 2015/8 University of Guelph
Ontario Veterinary College MSc Fellowship
Total Funding - 30,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes

Funding by Year:

2013/9 - 2015/8 Total Funding - 30,000
Portion of Funding Received - 30,000
Time Commitment: 0

Principal Applicant : Alexandra Rasiuk (MSc student)

2015/5 - 2015/8
Principal Applicant

Transient Lymphopenia as a Mechanism to Allow an Oncolytic Virus to Replicate Inside a Tumour Despite Vaccination Against a Virus-Encoded Antigen (student salary support), Scholarship

Funding Sources:

2015/5 - 2015/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Student Research Assistantship
Total Funding - 4,400 (Canadian dollar)
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Co-applicant : Wing Ka "Amanda" Au Yeung (summer student)

2014/9 - 2015/8
Principal Investigator

Using Virus-Infected Dendritic Cells as Cancer Vaccines (student stipend support), Scholarship

Funding Sources:

2014/9 - 2016/8 University of Guelph
Graduate Research Assistant Tuition Supplement
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 8,000
Funding Competitive?: No

Principal Applicant : Robert Mould (MSc student)

2015/5 - 2015/8
Principal Applicant

Assessment of the Potential to Treat Canine Cancers with an Oncolytic Vaccine (student salary support), Scholarship

Funding Sources:

2015/5 - 2015/8 Zoetis Canada
Zoetis Summer Student Research Fund
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 8,000
Funding Competitive?: Yes

Co-applicant : Julia Kim (summer student)

2014/8 - 2015/7
Principal Applicant

Replacement of a Core Facility's Heavily-Used, 22-Year-Old Analytical Flow Cytometer for Which Parts and Service are no Longer Guaranteed, Grant

Funding Sources:

2014/8 - 2015/7 Natural Sciences and Engineering Research Council of Canada (NSERC)
Research Tools and Infrastructure
Total Funding - 103,249 (Canadian dollar)
Portion of Funding Received - 34,417
Funding Competitive?: Yes

Co-applicant : Brandon Plattner; Dorothee Bienzle

2013/7 - 2015/6
Principal Applicant

In Vitro Efficacy Testing of Oncolytic Viruses, Grant

Funding Sources:

2013/7 - 2015/6 Private donation
Private donation
Total Funding - 15,000 (Canadian dollar)
Portion of Funding Received - 15,000
Funding Competitive?: No

2012/6 - 2015/5
Principal Investigator

Assessment of the Potential to Treat Canine Lymphoma with an Oncolytic Vaccine, Grant, Operating
Clinical Research Project?: No
Project Description: We have published a strategy to synergize immunotherapy and oncolytic virotherapy, leading to durable cures in mouse models of cancer. To translate our success into a future canine lymphoma clinical trial, we must conduct preliminary studies to demonstrate safety and efficacy. This proposal has four aims: 1. prove that oncolytic immunotherapy is safe in dogs, 2. show that robust tumour-specific immune responses can be induced, 3. confirm expression of the targeted tumour antigen on canine lymphomas, and 4. show that effector mechanisms mediated by the treatment can kill lymphoma cells. This will provide the scientific rationale for a future clinical dog lymphoma trial. It will also allow us to get a permit for field testing from the Canadian Food Inspection Agency (CFIA), which is required before clinical testing of oncolytic viruses in pets.
Research Uptake: The goal of this research is to translate the findings into a clinical veterinary trial in which dogs with lymphoma will be treated. This will serve two purposes. It will provide a direct, practical benefit to pet owners and will serve as an intermediate animal model in support of a broad collaborative effort to test oncolytic vaccines in human clinical trials. Findings from these studies will also be disseminated via submission for publication in peer-reviewed journals.

Research Uptake Stakeholders: Academic Personnel

Research Settings: Canada (Urban)

Funding Sources:

2012/6 - 2015/5 Pet Trust Fund (The)
Operating Grant
Total Funding - 45,016 (Canadian dollar)
Portion of Funding Received - 100 (Canadian dollar)
Funding Renewable?: No
Funding Competitive?: Yes

Funding by Year:

2012/9 - 2013/8 Total Funding - 45,016 (Canadian dollar)
Portion of Funding Received - 100 (Canadian dollar)
Time Commitment: 6

Research Disciplines: Immunology, Virology

Areas of Research: Vaccine and Cancer, Immunotherapy

Fields of Application: Biomedical Aspects of Human Health

Co-investigator : Dr. J. Paul Woods

2014/9 - 2015/4
Principal Applicant

Testing the Efficacy of Cancer Therapeutics in Ovarian and Mammary Carcinoma Cells (student salary support), Scholarship

Funding Sources:

2014/9 - 2015/4 University of Guelph
Work-Study
Total Funding - 2,210 (Canadian dollar)
Portion of Funding Received - 2,210
Funding Competitive?: No

Co-applicant : Wing Ka "Amanda" Au Yeung (undergraduate student)

2012/9 - 2014/8
Principal Investigator

Characterizing a Novel Immunoevasion Strategy for Brain Cancer and How to Circumvent It (student stipend support), Scholarship

Funding Sources:

2012/9 - 2014/8 University of Guelph
Ontario Veterinary College MSc Scholarship
Total Funding - 30,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes

Funding by Year:

2012/9 - 2014/8 Total Funding - 30,000
Portion of Funding Received - 30,000
Time Commitment: 0

Principal Applicant : Zafir Syed (MSc student)

2014/5 - 2014/8
Principal Applicant

Evaluation of an Oncolytic Vaccine in Dogs (student salary support), Scholarship

Funding Sources:

2014/5 - 2014/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Student Research Assistantship
Total Funding - 4,400 (Canadian dollar)
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Co-applicant : Larissa Hattin (summer student)

2012/9 - 2014/8
Principal Applicant

Combining Histone Deacetylase Inhibition and Transient, Virus-Induced Lymphopenia to Treat Leukemia (student stipend support), Scholarship

Funding Sources:

2012/9 - 2014/8 University of Guelph
Ontario Veterinary College MSc Scholarship
Total Funding - 30,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes

Funding by Year:

2012/9 - 2014/8 Total Funding - 30,000
Portion of Funding Received - 30,000
Time Commitment: 0

Principal Applicant : Christian Ternamian (MSc student)

2013/6 - 2014/5
Co-applicant

Upgrade to State-of-the-Art Flow Cytometric Equipment, Grant

Funding Sources:

2013/6 - 2015/5 Natural Sciences and Engineering Research Council of Canada (NSERC)
Research Tools and Instruments Grant
Total Funding - 148,230 (Canadian dollar)
Portion of Funding Received - 49,410
Funding Competitive?: Yes

Funding by Year:

2013/6 - 2015/5 Total Funding - 148,230
Portion of Funding Received - 49,410
Time Commitment: 7

Co-applicant : Dr. Dorothee Bienzle;

Principal Applicant : Dr. Brandon Plattner

2013/5 - 2014/4
Principal Applicant

Development of an Immune Response Monitoring Facility to Support Clinical Testing of Novel Cancer Biotherapies in Companion Animals, Grant

Funding Sources:

2013/5 - 2014/4 The Smiling Blue Skies Cancer Fund
Donation
Total Funding - 14,554 (Canadian dollar)
Portion of Funding Received - 14,554
Funding Competitive?: No

Funding by Year:

2013/5 - 2014/4 Total Funding - 14,554
Portion of Funding Received - 14,554
Time Commitment: 3

2013/9 - 2014/4
Principal Applicant

Evaluating the Role of Akt Isoforms in the Sensitivity of Lung Cancer Cells to Oncolytic Viruses (student salary support), Scholarship

Funding Sources:

2013/9 - 2014/4 University of Guelph
Work-Study
Total Funding - 2,210 (Canadian dollar)
Portion of Funding Received - 2,210
Funding Competitive?: No

Co-applicant : Wing Ka "Amanda" Au Yeung (undergraduate student)

2012/5 - 2013/8
Principal Applicant

Using an Innate Anti-Viral Immune Response in the Presence of a Histone Deactylase Inhibitor to Treat Leukemias (student salary support), Scholarship

Funding Sources:

2012/5 - 2012/8 Canadian Society for Immunology
Summer Internship in Immunology
Total Funding - 2,400 (Canadian dollar)
Portion of Funding Received - 2,400
Funding Competitive?: Yes

Funding by Year:

2012/5 - 2012/8 Total Funding - 2,400
Portion of Funding Received - 2,400
Time Commitment: 0

Co-applicant : Evan Lusty (summer student)

2013/5 - 2013/8
Principal Applicant

Development of Flow Cytometry-Based Immunological Assays to Support Pre-Clinical and Clinical Companion Animal Cancer Trials (student salary support), Scholarship

Funding Sources:

2013/5 - 2013/8 University of Guelph
Undergraduate Research Assistant
Total Funding - 4,400 (Canadian dollar)
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Funding by Year:

2013/5 - 2013/8 Total Funding - 6,600
Portion of Funding Received - 6,600
Time Commitment: 0

Co-applicant : Wing Ka "Amanda" Au Yeung (summer student)

2012/9 - 2013/4
Principal Applicant

Testing the Efficacy of Cancer Therapeutics in Prostate Cancer Cell Lines (student salary support), Scholarship

Funding Sources:

2012/9 - 2013/4 University of Guelph
Work-Study
Total Funding - 2,210 (Canadian dollar)
Portion of Funding Received - 2,210
Funding Competitive?: No

Co-applicant : Jason Morgenstern (undergraduate student)

2012/5 - 2012/8
Principal Applicant

Establishment of Leukemia/Lymphoma Cell Lines from Clinical Specimens and Evaluation of Their Susceptibility to Oncolytic Viruses (student salary support), Scholarship

Funding Sources:

2012/5 - 2012/8 University of Guelph
Undergraduate Research Assistantship
Total Funding - 6,000 (Canadian dollar)
Portion of Funding Received - 6,000
Funding Competitive?: Yes

Funding by Year:

2012/5 - 2012/8 Total Funding - 6,000
Portion of Funding Received - 6,000
Time Commitment: 0

Co-applicant : Jason Morgenstern (summer student)

Declined [n=6]

2017/9 - 2021/8
Principal Investigator

Enhancing Immunogenic Cancer Cell Death Through the Novel Combination of Oncolytic Viruses and Photodynamic Therapy (student stipend support), Scholarship

Funding Sources:

2017/9 - 2020/8 Ontario Government
Ontario Graduate Scholarship
Total Funding - 60,000 (Canadian dollar)
Portion of Funding Received - 0
Funding Competitive?: Yes

Principal Applicant : Ashley Ross;

Principal Investigator : Sarah Wootton

2017/9 - 2020/8
Co-applicant

Enhancing Immunogenic Cancer Cell Death Through the Novel Combination of Oncolytic Viruses and Photodynamic Therapy (student stipend support), Scholarship

Funding Sources:

2017/9 - 2020/8 Ontario Veterinary College (OVC)
Doctoral Scholarship
Total Funding - 60,000 (Canadian dollar)
Portion of Funding Received - 0
Funding Competitive?: Yes

Principal Applicant : Ashley Ross;

Principal Investigator : Sarah Wootton

2016/9 - 2018/12
Co-applicant

The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy (student stipend support; declined due to receipt of external scholarships), Scholarship

Funding Sources:

Ontario Veterinary College (OVC)
Graduate Scholarship
Total Funding - 17,000
Portion of Funding Received - 17,000
Funding Competitive?: Yes

Co-applicant : Sarah K. Wootton;

Principal Applicant : Jacob van Vloten

2016/9 - 2017/8
Co-applicant

Augmentation of a Canine Melanoma Vaccine with Immunomodulatory Antibodies (student stipend support), Scholarship

Funding Sources:

2016/9 - 2017/8 Pet Trust Foundation
OVC Pet Trust Scholar Program
Total Funding - 17,500 (Canadian dollar)
Portion of Funding Received - 17,500
Funding Competitive?: Yes

Principal Applicant : Wing Ka "Amanda" AuYeung (MSc student)

2015/9 - 2016/8
Principal Investigator

The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy (student stipend support), Scholarship

Funding Sources:

2015/9 - 2016/8 Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
Highly Qualified Personnel PhD Scholarship
Total Funding - 21,000 (Canadian dollar)
Portion of Funding Received - 0
Funding Competitive?: Yes

Principal Applicant : Jacob van Vloten (PhD student; co-advised);

Principal Investigator : Sarah K. Wootton

2015/9 - 2016/8
Principal Investigator
Using Virus-Infected Dendritic Cells as Cancer Vaccines (student stipend support), Scholarship

Funding Sources:

2015/9 - 2016/8 University of Guelph
Graduate Research Assistant Tuition Supplement
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 0
Funding Competitive?: No

Principal Applicant : Robert Mould (MSc student; transferred to PhD)

Student/Postdoctoral Supervision

Bachelor's [n=1]

2020/9 - 2021/4
Principal Supervisor
Julia Kakish, University of Guelph
Thesis/Project Title: Cold-Adaptation of Viruses for Use as Vaccine Vectors (undergraduate research project student)
Present Position: Currently a member of my research team

Bachelor's Equivalent [n=10]

2020/5 - 2020/8
Principal Supervisor
Lily Chan, University of Guelph
Thesis/Project Title: Calming the Storm: Dissecting the Roles of Innate Lymphoid Cells in Cytokine-Mediated Pulmonary Inflammation Induced by Oncolytic Vesicular Stomatitis Virus (undergraduate summer research assistant)
Present Position: Currently a MSc student in my laboratory, University of Guelph

2020/5 - 2020/8
Principal Supervisor
Kiersten Hanada (In Progress) , University of Guelph
Thesis/Project Title: Calming the Cytokine Storm: Developing a Model to Study Toxic Cytokine Responses to Viruses (undergraduate summer research assistant)
Present Position: Completing the DVM program, University of Guelph

2018/5 - 2018/8
Principal Supervisor
Samantha Holtz (Completed) , University of Guelph
Student Degree Start Date: 2018/5
Student Degree Received Date: 2018/8
Thesis/Project Title: Combining Oncolytic Virotherapy with Epigenetic Modifiers to Treat Lymphomas (undergraduate summer research assistant)
Present Position: Completed a post-graduate diploma program., Queen's University

2017/5 - 2017/8 Principal Supervisor	Julia Saturno (Completed) , University of Guelph Student Degree Start Date: 2017/5 Student Degree Received Date: 2017/8 Thesis/Project Title: Pyrexia Can Impair Oncolytic Virotherapy (summer research assistantship) Project Description: This student conducted research in my laboratory for the summer of 2017, while enrolled in the doctor of veterinary medicine program, University of Guelph. Project title: Temperature as a confounding variable in oncolytic virotherapy for canine melanomas. Present Position: veterinary practice
2016/5 - 2016/8 Principal Supervisor	Manali Desai (Completed) , University of Guelph Student Degree Start Date: 2016/5 Student Degree Received Date: 2016/8 Thesis/Project Title: Evaluating the Impact of Temperature on the Oncolytic Potential of Viruses in Canine and Murine Osteosarcoma Cells (summer research assistantship) Project Description: Studied the efficacy of oncolytic viruses in a panel of canine and murine osteosarcoma cell lines. Present Position: veterinary practice
2016/5 - 2016/8 Principal Supervisor	Julia De Carvalho Nakamura (Completed) , University of Sao Paulo, Brazil Student Degree Start Date: 2016/5 Student Degree Received Date: 2016/8 Thesis/Project Title: The Impact of Temperature on the Oncolytic Activity of Viruses (summer research assistantship) Project Description: Participated in Students Without Borders Program, May-September 2016; conducted research in my laboratory stydying the effect of high and low temperatures on oncolytic viruses. Present Position: Veterinary practice, Sao Paulo, Brazil
2016/5 - 2016/8 Principal Supervisor	Julia Saturno (Completed) , University of Guelph Student Degree Start Date: 2016/5 Student Degree Received Date: 2016/8 Thesis/Project Title: Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas (summer research assistantship) Project Description: Studied the efficacy of oncolytic viruses in a panel of canine melanoma cell lines. Present Position: veterinary practice
2015/5 - 2015/8 Principal Supervisor	Haley Spangler-Forgione (Completed) , University of Guelph Student Degree Start Date: 2015/5 Student Degree Received Date: 2015/8 Thesis/Project Title: Par6 Influences the Susceptibility of Mammary Carcinoma Cells to Oncolytic Viruses (summer research assistantship) Project Description: Title of project: Par6 influences the susceptibility of mammary carcinoma cells to oncolytic viruses Present Position: Veterinary practice

2015/5 - 2015/8 Principal Supervisor	Julia Kim (Completed) , University of Guelph Student Degree Start Date: 2015/5 Student Degree Received Date: 2015/8 Thesis/Project Title: Assessment of the Potential to Treat Canine Cancers with an Oncolytic Vaccine (summer research assistantship) Project Description: Undergraduate summer research assistant, May - August 2014. Project: Used western blotting to assess canine osteosarcoma, melanoma and lymphoma specimens for the expression of various tumour-associated antigens. The results will guide the development of novel viral vectors to be used in a future canine cancer trial. Present Position: Graduate student, Department of Population Medicine, University of Guelph
2014/5 - 2014/8 Principal Supervisor	Julia Kim (Completed) , University of Guelph Student Degree Start Date: 2013/9 Student Degree Received Date: 2014/8 Thesis/Project Title: Assessment of Canine Melanoma Samples from the Ontario Veterinary College-Companion Animal Tumour Bank for Expression of Antigens that can be Targeted with an Oncolytic Cancer Vaccine (summer research assistantship) Project Description: Undergraduate summer research assistant, May - August 2015. Project: Assessment of the potential to treat canine cancers with an oncolytic vaccine. Present Position: Graduate student, Department of Population Medicine, University of Guelph

Bachelor's Honours [n=22]

2020/9 - 2021/4 Principal Supervisor	Sierra Vanderkamp, University of Guelph Thesis/Project Title: Evaluating the Role of Oxidative Stress in Off-Target Infections of T Cells by Oncolytic Rhabdoviruses (undergraduate research project student) Present Position: Currently a member of my research team
2018/9 - 2019/4 Principal Supervisor	Jessica Minott (Completed) , University of Guelph Thesis/Project Title: Assessing the Impact of Sex Hormones on the Efficacy of Oncolytic Viruses (4th year undergraduate research project student) Present Position: Currently a MSc student in my laboratory, University of Guelph
2018/5 - 2018/8 Principal Supervisor	Jessica Minott (Completed) , University of Guelph Thesis/Project Title: Assessing the Impact of Sex Hormones on the Efficacy of Oncolytic Viruses (undergraduate summer research assistant) Present Position: Currently a MSc student in my laboratory, University of Guelph
2018/5 - 2018/8 Principal Supervisor	Elaine Klafuric (Completed) , University of Guelph Thesis/Project Title: Type I Interferon-Mediated Regulation of IL-17 Production by Mast Cells (undergraduate summer research assistant) Present Position: Currently a MSc student in my laboratory
2017/5 - 2017/8 Principal Supervisor	Mankerat Singh (Completed) , University of Guelph Student Degree Start Date: 2017/5 Student Degree Received Date: 2017/8 Thesis/Project Title: Optimizing the Antigen Presentation Potential of Cultured Dendritic Cells Through the Use of Interleukin-4 (summer research assistantship) Project Description: Mankerat complete his Honour's BSc program in April 2017 and then conducted a research project under my supervision for the summer 2017. Project title: Enhancing dendritic cell-based anti-cancer vaccines through adaptation to a hypoxic microenvironment. Present Position: unknown

2016/9 - 2017/4 Principal Supervisor	Mankerat Singh (Completed) , University of Guelph Student Degree Start Date: 2016/9 Student Degree Received Date: 2017/4 Thesis/Project Title: Optimizing a Dendritic Cell-Based Vaccine for Induction of Immunological Memory (4th year undergraduate research project) Project Description: Mankerat conducted research in my laboratory for two semesters as an undergraduate student enrolled in the course HK*4371/2 (Research in Human Biology and Nutritional Sciences). His project was entitled: Differentiating dendritic cells in the presence of interleukin-4 to enhance their potential as vaccines. He subsequently presented this work at the Summit for Cancer Immunotherapy, Gatineau, QC, in June 2017, where he received the only undergraduate award for best poster. Present Position: unknown
2016/5 - 2016/9 Principal Supervisor	Katrina Allison (Completed) , University of Guelph Student Degree Start Date: 2012/9 Student Degree Received Date: 2016/8 Thesis/Project Title: Sex Disparity in Innate Immune Responses to Viral Infection: the Role of Type I Interferon Project Description: Undergraduate summer research assistant in my laboratory; May-August 2016. Studied gender bias in the role of type I interferon signalling on the cytokine response to viral infection. Present Position: Naturopathic Medicine College Training Program (Toronto, Ontario)
2015/5 - 2015/8 Principal Supervisor	Wing Ka "Amanda" AuYeung (Completed) , University of Guelph Student Degree Start Date: 2011/9 Student Degree Received Date: 2015/8 Thesis/Project Title: Transient Lymphopeniaas a Mechanism to Allow an Oncolytic Virus to Replicate Inside a Tumour Despite Vaccination Against a Virus-Encoded Antigen (NSERC Undergraduate Student Research Assistantship) Project Description: Undergraduate summer research assistant, May-August 2015. Project: Transient lymphopenia as a mechanism to allow an oncolytic virus to replicate inside a tumour despite vaccination against a virus-encoded antigen Present Position: Flow Cytometry Technician, The Hospital for Sick Children, Toronto, Ontario, Canada
2014/5 - 2014/9 Principal Supervisor	Larissa Hattin (Completed) , University of Guelph Student Degree Start Date: 2010/9 Student Degree Received Date: 2014/8 Thesis/Project Title: Evaluation of an Oncolytic Vaccine in Dogs (NSERC Undergraduate Student Research Assistantship) Project Description: Assessed the oncolytic potential of a recombinant Newcastle disease virus in human prostate cancer cell lines. Present Position: Emergency medicine residency program, University of British Columbia
2014/5 - 2014/8 Principal Supervisor	Robert Mould (Completed) , University of Guelph Student Degree Start Date: 2010/9 Student Degree Received Date: 2014/4 Thesis/Project Title: Combining Antigen-Presenting Cell-Based Vaccination with Oncolytic Viruses for the Treatment of Prostate Cancers (summer research assistantship) Project Description: Undergraduate summer research assistant, May-August 2014. Project: The potential to use Orf virus and Newcastle disease virus-infected dendritic cells and/or macrophages as cancer vaccines. Present Position: Postdoctoral fellow in my laboratory, University of Guelph

2013/9 - 2014/4 Principal Supervisor	Larissa Hattin (Completed) , University of Guelph Student Degree Start Date: 2013/9 Student Degree Received Date: 2014/8 Thesis/Project Title: Testing the Oncolytic Potential of Two Recombinant Newcastle Disease Viruses in Human Prostate Cancer Cell Lines (summer research assistantship) Project Description: Sept. 2013-April 2014: Larissa conducted her 4th-year undergraduate research project (Course codes: BIOM*4521 [Fall semester] and BIOM*4522 [Spring semester]) in my laboratory. Project title: Testing the oncolytic potential of a novel recombinant Newcastle Disease Virus in human prostate cancer cell lines. She continued this project as a summer undergraduate research assistant, May-August 2014 Present Position: Emergency medicine residency program, University of British Columbia
2013/9 - 2014/4 Principal Supervisor	Wing Ka "Amanda" AuYeung (Completed) , University of Guelph Student Degree Start Date: 2011/9 Student Degree Received Date: 2015/4 Thesis/Project Title: Evaluating the Role ofAkt Isoforms in the Sensitivity of Lung Cancer Cells to Oncolytic Viruses (Work-Study Program; part-time research while pursuing full-time undergraduate studies) Project Description: Undergraduate summer research assistant, May-August 2013. Project: Development of flow cytometry-based immunological assays to support pre-clinical and clinical companion animal cancer trials. Present Position: Flow Cytometry Technician, The Hospital for Sick Children, Toronto, Ontario, Canada
2013/9 - 2014/4 Principal Supervisor	Sofia Oke (Completed) , University of Guelph Student Degree Start Date: 2010/9 Student Degree Received Date: 2014/4 Thesis/Project Title: Determining Whether TLR3 and/or TLR7 Ligation Causes Dysregulation of Cytokine Signaling in Macrophages Lacking the Type I Interferon Receptor (summer research assistantship) Project Description: Sofia conducted her 4th-year undergraduate research project (Course codes: BIOM*4521 [Fall semester] and BIOM*4522 [Spring semester]) in my laboratory, September 2013-April 2014. Project: Determining whether TLR3 and/or TLR7 ligation causes dysregulation of cytokine signaling in dendritic cells lacking the type I interferon receptor. Present Position: Research technician (Dr. Sachdev Sidhu's lab, University of Toronto)
2013/9 - 2015/8 Principal Supervisor	Alexandra Rasiuk (Completed) , University of Guelph Student Degree Start Date: 2009/9 Student Degree Received Date: 2013/8 Thesis/Project Title: The Role of Type I Interferon Signalling in the Regulation of Cytokines Produced by Antigen-Presenting Cells (4th year undergraduate research project) Project Description: Undergraduate research project course (BIOM*4521 and BIOM*4522), Sept. 2012 - August 2013. Project: Studying the role of type I interferon receptor-mediated signaling in the regulation of cytokines produced by dendritic cells. Present Position: Research associate in industry

2013/5 - 2013/8 Principal Supervisor	Wing Ka "Amanda" AuYeung (Completed) , University of Guelph Student Degree Start Date: 2013/9 Student Degree Received Date: 2014/4 Thesis/Project Title: Development of Flow Cytometry-Based Immunological Assays to Support Pre-Clinical and Clinical Companion Animal Cancer Trials (NSERC Undergraduate Student Research Assistantship) Project Description: Part-time undergraduate research assistant (work-study program, September 2013 - April 2014. Project: The role of Akt isoforms in the rate of proliferation of cancer cell lines and their susceptibility to oncolytic viruses. Present Position: Flow Cytometry Technician, The Hospital for Sick Children, Toronto, Ontario, Canada
2013/5 - 2013/7 Principal Supervisor	Jason Morgenstern (Completed) , University of Guelph Student Degree Start Date: 2009/9 Student Degree Received Date: 2013/4 Thesis/Project Title: Testing the Efficacy of Oncolytic Viruses, Histone Deacetylase Inhibitors and Toll-Like Receptor Ligands in Cancer Cell Lines (summer research assistantship) Project Description: Undergraduate summer research assistant, May -August 2012. Project: Establishment of leukemia/lymphoma cell lines from clinical specimens and evaluation of their susceptibility to oncolytic viruses. Present Position: Medical residency program in public health + Master's of Public Health program, McMaster University
2012/9 - 2013/4 Principal Supervisor	Evan Lusty (Completed) , University of Guelph Student Degree Start Date: 2009/9 Student Degree Received Date: 2013/4 Thesis/Project Title: Characterizing Oncolytic Viruses and Toll Like Receptor Ligands in the In Vitro Treatment of Human Prostate Cancer (4th year undergraduate research project) Project Description: Evan conducted his 4th-year undergraduate research project (Course codes: BIOM*4521 [Fall semester] and BIOM*4522 [Spring semester]) in my laboratory. Project: Testing oncolytic viruses in human prostate cancer cell lines. Present Position: MD program, Queen's University (Kingston, Ontario)
2012/9 - 2013/4 Principal Supervisor	Jason Morgenstern (Completed) , University of Guelph Student Degree Start Date: 2009/9 Student Degree Received Date: 2013/4 Thesis/Project Title: Investigating the Potential to use Recombinant Newcastle Disease Viruses as Oncolytic Virotherapies for Prostate and Cervical Cancers (Work-Study Program; part-time research while pursuing full-time undergraduate studies) Project Description: Undergraduate summer research assistant, May - July 2013. Project: Characterizing the oncolytic potential of a novel fowl reovirus in established cancer cell lines. Present Position: Medical residency program in public health + Master's of Public Health program, McMaster University

2012/9 - 2013/4 Principal Supervisor	Alexandra Rasiuk (Completed) , University of Guelph Student Degree Start Date: 2009/9 Student Degree Received Date: 2013/4 Thesis/Project Title: Optimization of a Protocol for Harvesting and Differentiating Murine Bone Marrow-Derived Dendritic Cells for use as a Cancer Vaccine (4th year undergraduate research project) Project Description: Alexandra conducted her 4th-year undergraduate research project (Course codes: BIOM*4521 [Fall semester] and BIOM*4522 [Spring semester]) in my laboratory. Research project: Optimization of a protocol for harvesting and differentiating murine bone marrow-derived dendritic cells for use as a cancer vaccine. Present Position: Post-graduate diploma program in clinical research at Seneca College, Toronto
2012/5 - 2012/8 Principal Supervisor	Jason Morgenstern (Completed) , University of Guelph Student Degree Start Date: 2009/9 Student Degree Received Date: 2013/4 Thesis/Project Title: Evaluation of the Susceptibility of Cancer Cell Lines to Oncolytic Viruses (summer research assistantship) Project Description: Part-time undergraduate research assistant (work-study program), September 2012-April 2013. Project: Testing oncolytic viruses in human prostate and cervical cancer cell lines. Present Position: Medical residency program in public health + Master's of Public Health program, McMaster University
2012/5 - 2013/7 Principal Supervisor	Evan Lusty (Completed) , University of Guelph Student Degree Start Date: 2009/9 Student Degree Received Date: 2013/4 Thesis/Project Title: Testing Various Oncolytic Viruses, Histone Deacetylase Inhibitors and Toll-Like Receptor Ligands as Monotherapies in Human Prostate and Cervical Cancer Cells (summer research assistantship) Project Description: Undergraduate summer research assistant, May - August 2012. Was awarded a Canadian Society for Immunology - Summer Internship in Immunology for this work. Project: Using an innate anti-viral immune response in the presence of a histone deactylase inhibitor to treat leukemias. Present Position: MD program, Queen's University (Kingston, Ontario)
2012/5 - 2012/8 Principal Supervisor	Evan Lusty (Completed) , University of Guelph Student Degree Start Date: 2009/9 Student Degree Received Date: 2013/4 Thesis/Project Title: Using an Innate Anti-Viral Immune Response in the Presence of a Histone Deacetylase Inhibitor to Treat Leukemias (summer research assistantship) Project Description: Undergraduate summer research assistant May - June 2013. Project: Testing oncolytic viruses in human prostate cancer cell lines. Present Position: MD program, Queen's University (Kingston, Ontario)

Master's Equivalent [n=1]

2020/2 Principal Supervisor	Yeganeh Mehrani (In Progress) , Ferdowsi University of Mashhad, Iran Student Degree Start Date: 2020/2 Student Degree Expected Date: 2022/10 Thesis/Project Title: Development of Flow Cytometric Methods to Evaluate Canine Innate Lymphocyte Subsets Present Position: Visiting scientist in my laboratory

Master's Thesis [n=12]

2021/9 Academic Advisor	Sierra Vanderkamp (In Progress) , University of Guelph Student Degree Start Date: 2021/9 Student Degree Expected Date: 2023/8 Thesis/Project Title: Mechanisms Governing Off-Target Infection and Killing of T Cells by Oncolytic Viruses
2021/9 Academic Advisor	Julia Kakish (In Progress) , University of Guelph Student Degree Start Date: 2021/9 Student Degree Expected Date: 2023/8 Thesis/Project Title: Sensitization of Decitabine-Treated Leukemias to Oncolytic Virotherapy
2021/4 - 2022/8 Academic Advisor	Fatemeh Darya Fazel (In Progress) , University of Guelph Student Degree Start Date: 2020/9 Student Degree Expected Date: 2022/8 Thesis/Project Title: mRNA-Based Vaccines for Preventing the Infection of Poultry with Influenza Viruses
2020/9 Principal Supervisor	Lily Chan (In Progress) , University of Guelph Student Degree Start Date: 2020/9 Student Degree Expected Date: 2022/8 Thesis/Project Title: The Roles of Innate Leukocytes in Dendritic Cell-Based Vaccinations Present Position: Currently a member of my research team
2018/9 Principal Supervisor	Elaine Klafuric (In Progress) , University of Guelph Student Degree Start Date: 2018/9 Student Degree Expected Date: 2021/12 Thesis/Project Title: Combining Oncolytic Viruses with Epigenetic Modifiers to Treat Acute Myeloid Leukemias Present Position: Currently a member of my research team, University of Guelph
2017/9 - 2019/12 Academic Advisor	Adriana Bianco (Completed) , University of Guelph Student Degree Start Date: 2017/9 Student Degree Received Date: 2019/12 Thesis/Project Title: Anti-Cancer Effects of Beta Glucans Present Position: unknown
2016/9 - 2016/12 Principal Supervisor	Katrina Allison (Withdrawn) , University of Guelph Student Degree Start Date: 2016/9 Thesis/Project Title: Sex Disparity in Innate Immune Responses to Viral Infection: the Role of Type I Interferon Project Description: Studying gender bias in the role of type I interferon signalling on the cytokine response to viral infection. Present Position: Naturopathic Medicine College Training Program (Toronto, Ontario)
2015/9 - 2017/8 Principal Supervisor	Wing Ka "Amanda" AuYeung (Completed) , University of Guelph Student Degree Start Date: 2015/9 Student Degree Received Date: 2017/8 Thesis/Project Title: Developing Novel Biotherapies for the Treatment of Melanomas Project Description: Amanda is studying the mechanisms underlying biotherapies for melanomas. Present Position: Research Associate, Notch Therapeutics, Toronto, Ontario, Canada, The Hospital for Sick Children, Toronto, Ontario, Canada

2015/1 - 2016/8 Academic Advisor	Nahla El Skhawy (Completed) , University of Guelph Student Degree Start Date: 2014/9 Student Degree Received Date: 2016/8 Thesis/Project Title: The Role of the Immune System in Johne's Disease in Cattle Project Description: Immunological aspects of Johne's disease in cattle. Present Position: unknown
2013/9 - 2015/8 Principal Supervisor	Alexandra Rasiuk (Completed) , University of Guelph Student Degree Start Date: 2013/9 Student Degree Received Date: 2015/8 Thesis/Project Title: Role of Type I Interferon Signalling in Regulating Survival, Proliferation, and Cytokine Production in Antigen-Presenting Cells Project Description: Thesis title: Role of Type I Interferon Signalling in Regulating Survival, Proliferation, and Cytokine Production in Antigen-Presenting Cells Present Position: Research associate in industry
2012/9 - 2014/8 Principal Supervisor	Christian Ternamian (Completed) , University of Guelph Student Degree Start Date: 2012/9 Student Degree Received Date: 2014/8 Thesis/Project Title: Targeting Acute Lymphoblastic Leukemia with Oncolytic Virotherapy and Immunotherapy Project Description: Combining histone deacetylase inhibition and transient, virus-induced lymphopenia to treat leukemia. Present Position: Completed Medical Doctorate program at Queen's University
2012/9 - 2014/8 Principal Supervisor	Zafir Syed (Completed) , University of Guelph Student Degree Start Date: 2012/9 Student Degree Received Date: 2014/8 Thesis/Project Title: Oncolytic Immunotherapy for the Treatment of High-Grade Gliomas Project Description: Synergizing immuno- and oncolytic viro-therapies for the treatment of primary brain cancer. Present Position: Radiology residency program, University of Western Ontario

Doctorate [n=19]

2021/3 Academic Advisor	Ben Muselius (In Progress) , University of Guelph Degree Name: PhD Student Degree Start Date: 2021/1 Student Degree Expected Date: 2024/5 Thesis/Project Title: Proteomics Analysis of Infections with the Fungal Pathogen Cryptococcus neoformans Present Position: graduate student
2020/11 Academic Advisor	Brenna Stevens (In Progress) , University of Guelph Student Degree Start Date: 2020/9 Student Degree Expected Date: 2024/8 Thesis/Project Title: Gene Therapy for Cystic Fibrosis Project Description: Transferred from MSc program. Present Position: graduate student
2019/9 Academic Advisor	Sylvia Thomas (In Progress) , University of Guelph Student Degree Start Date: 2019/9 Student Degree Expected Date: 2023/8 Thesis/Project Title: Adeno-Associated Virus-Vectored Gene Editing Platform for the Correction of Monogenic Lung Diseases Project Description: Transferred from the MSc program. Present Position: Graduate student in Wootton lab

2019/9 - 2023/8 Principal Supervisor	Jason Knapp (In Progress) , University of Guelph Student Degree Start Date: 2019/9 Student Degree Expected Date: 2023/8 Thesis/Project Title: Heat-Adaptation of Oncolytic Rhabdoviruses to Improve Their Clinical Utility Present Position: Graduate student in my laboratory
2019/9 - 2024/8 Principal Supervisor	Jessica Minott (In Progress) , University of Guelph Student Degree Start Date: 2019/9 Student Degree Expected Date: 2022/8 Thesis/Project Title: Development of an Oncolytic Orf Virus-Infected Cell Vaccine for the Treatment of Spontaneous Mammary Carcinoma Metastases (transferred from MSc program) Present Position: Graduate student in my laboratory
2018/9 - 2022/8 Academic Advisor	Amira Rghei (In Progress) , University of Guelph Student Degree Start Date: 2018/9 Thesis/Project Title: Adeno-Associated Virus-Vectored Immunoprophylaxis for Filovirus Infections Present Position: Graduate student in Wootton lab
2017/9 - 2021/8 Principal Supervisor	Ashley Stegelmeier (Completed) , University of Guelph Student Degree Start Date: 2017/9 Student Degree Received Date: 2021/8 Student Canadian Residency Status: Canadian Citizen Thesis/Project Title: Vectorizing Immunomodulatory Antibodies for the Treatment of Canine Melanomas Project Description: The objective of this research is to enable tumour-bearing dogs to synthesize anti-canine PDL-1 in vivo using AAV with an inducibleTet-on promoter, which will allow fine control of expression of the antibody.This novel administration of an immunomodulatory canine antibody with aninducible promoter has the potential to improve efficacy of immunotherapies inmelanoma-bearing dogs while minimizing risk of off-target autoimmunity. Present Position: Research Manager, Kitchener, Ontario, Canada
2017/1 - 2020/1 Principal Supervisor	Maedeh "Mahi Azizi" Darzianiazizi (Completed) , University of Guelph Student Degree Start Date: 2017/1 Student Degree Received Date: 2020/1 Thesis/Project Title: Elucidating the Roles of Sex, Neutrophils and Mast Cells in Type I Interferon-Regulated Cytokine Responses to Viruses Present Position: Working in industry
2017/1 - 2020/12 Academic Advisor	Nadiyah Alqazlan (Completed) , University of Guelph Student Degree Start Date: 2016/9 Student Degree Received Date: 2020/12 Thesis/Project Title: Low Pathogenic Avian Influenza Virus H9N2 in Chickens: Transmission Routes, Effects of Environmental Factors on Transmission and Means to Disrupt Transmission Project Description: LowPathogenic Avian Influenza Virus H9N2 in Chickens: Transmission Routes, Effectsof Environmental Factors on Transmission and Means to Disrupt Transmission Present Position: PhD student (Sharif Lab, University of Guelph)

2014/9 - 2020/4 Co-Supervisor	Jacob van Vloten (Completed) , University of Guelph Student Degree Start Date: 2014/9 Student Degree Received Date: 2020/4 Thesis/Project Title: The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy Project Description: Direct entry from the BSc program into the PhD program. Project: Development of a novel Orf virus natural isolate into a cancer biotherapy. Present Position: Postdoctoral fellow in the lab of Dr. Richard Vile, Mayo Clinic, Rochester, Minnesota
2014/9 - 2017/8 Principal Supervisor	Megan Strachan-Whaley (Completed) , University of Guelph Student Degree Start Date: 2014/9 Student Degree Received Date: 2017/8 Thesis/Project Title: Combination of Epigenetic Modifier Drugs with Oncolytic Viral Therapy as a Novel Treatment for Leukemias Project Description: Using oncolytic viruses to potentiate histone deacetylase inhibitor-mediated killing of acute lymphoblastic leukemia B cells. Present Position: Postdoctoral fellow in industry
2014/2 - 2016/8 Academic Advisor	Marianne Wilcox (Completed) , University of Guelph Student Degree Start Date: 2013/9 Student Degree Received Date: 2016/8 Thesis/Project Title: Mathematical Modeling of Cytokine Storms in Rhabdovirus-Infected Mice Lacking Type I Interferon Signaling in Hematopoietic Cells Project Description: Mathematical modeling of cytokine storms in rhabdovirus-infected mice lacking type I interferon signaling in hematopoietic cells. Present Position: unknown
2013/8 - 2018/9 Academic Advisor	Lisa Santry (Completed) , University of Guelph Student Degree Start Date: 2011/9 Student Degree Received Date: 2018/9 Thesis/Project Title: Functional Role of AKT Isoforms in Jaagsiekte Sheep Retrovirus Envelope Protein-Induced Lung Tumourigenesis and the Susceptibility of the Resulting Tumours to Viral Oncolysis Project Description: Project #1: Functional role of AKT isoforms in Jaagsiekte Sheep Retrovirus envelope protein-induced lung tumorigenesis and the susceptibility of the resulting tumours to viral oncolysis. Project #2: Using a derivative of thrombospondin-1 to normalize tumour vasculature for enhanced delivery of oncolytic viruses. Project #3: Development of a Newcastle disease virus vector expressing an immunomodulatory antibody. Present Position: Research associate in industry

Doctorate Equivalent [n=1]

2018/1 - 2022/4 Academic Advisor	Karen Carlton (In Progress) , University of Guelph Student Degree Start Date: 2018/1 Student Degree Expected Date: 2022/4 Thesis/Project Title: Crimean-Congo Hemorrhagic Fever DNA Vaccine trial: Pilot Safety and Toxicity Study in Cattle and Goats Present Position: DVSc student in the Arroyo and Lillie labs, University of Guelph

Post-doctorate [n=6]

2020/5 - 2021/4 Principal Supervisor	Robert Mould (Completed) , University of Guelph Student Degree Start Date: 2020/5 Student Degree Received Date: 2021/4 Thesis/Project Title: Development of Vaccines for COVID-19 Present Position: Still part of my research team
2020/3 - 2020/7 Co-Supervisor	Jacob van Vloten (Completed) , University of Guelph Student Degree Start Date: 2020/3 Student Degree Received Date: 2020/7 Thesis/Project Title: Development of Vaccines for COVID-19 Present Position: Postdoctoral fellow in the lab of Dr. Richard Vile, Rochester, MN, USA, Mayo Clinic, Rochester, Minnesota
2018/9 - 2019/8 Principal Supervisor	Megan Strachan-Whaley (Completed) , University of Guelph Student Degree Start Date: 2018/9 Student Degree Received Date: 2019/8 Thesis/Project Title: Combining Oncolytic Viruses and Epigenetic Modifiers to Treat Acute Leukemias Present Position: Enrolled in medical school (Dalhousie University)
2015/5 - 2017/12 Co-Supervisor	Dr. Li Deng (Completed) , University of Guelph Student Degree Start Date: 2015/4 Student Degree Received Date: 2017/12 Thesis/Project Title: Engineering Virus-Vectored Cancer Vaccines for Clinical Canine Cancer Trials Project Description: Development of novel virus vectors for use in oncolytic and immunotherapies. Present Position: Postdoctoral fellow (Wan lab, McMaster University)
2013/9 - 2014/4 Principal Supervisor	Dr. Scott Walsh (Completed) , University of Guelph Student Degree Start Date: 2013/9 Student Degree Received Date: 2014/8 Thesis/Project Title: Type I Interferon Receptor Signalling as a Master Switch for the Negative Regulation of Cytokine Networks Project Description: Type I interferon receptor signalling as a master switch for the negative regulation of cytokine networks. Present Position: Postdoctoral fellow in the laboratory of Dr. Yonghong Wan, McMaster University, Hamilton, ON, Canada
2013/2 - 2013/8 Principal Supervisor	Dr. Jondavid de Jong (Completed) , University of Guelph Student Degree Start Date: 2013/2 Student Degree Received Date: 2013/8 Thesis/Project Title: Construction of Human Adenovirus Serotype 48 and Maraba Virus Vectors Project Description: Construction of recombinant Maraba virus and human adenovirus serotype 48 vectors for use in cancer immune- and oncolytic viro-therapy. Present Position: Research Associate, Mirexus (Guelph, Ontario; biotechnology company)

Diploma [n=4]

2015/10 - 2016/3 Principal Supervisor	Katrina Geronimo (Completed) , St. Joan of Arc Catholic Secondary School, Mississauga, Ontario Student Degree Start Date: 2012/9 Student Degree Received Date: 2016/6 Thesis/Project Title: Hypoxia Variably Affects Oncolytic Virus Efficacy While Potentiating the Growth of Human Cervical Cancer Cells Project Description: September 2015 - May 2016: Participated in the Sanofi BioGENEius Challenge Canada. This is a national research competition for secondary school students (http://biogenius.ca/). Over a 6-month period she averaged 2-3 bus trips to the University of Guelph per week to work approximately half-days in my laboratory. Her project title was "Hypoxia variably affects oncolytic virus efficacy while potentiating the growth of human cervical cancer cells". Present Position: BSc program, University of Guelph, University of Guelph
2015/10 - 2016/3 Principal Supervisor	Arthane Kodeeswaran (Completed) , St. Joan of Arc Catholic Secondary School, Mississauga, Ontario Student Degree Start Date: 2012/9 Student Degree Received Date: 2016/6 Thesis/Project Title: The Effect of Temperature on the Efficacy of Oncolytic Viruses in Human Cervical Cancer Cells Project Description: September 2015 - May 2016: Participated in the Sanofi BioGENEius Challenge Canada. This is a national research competition for secondary school students (http://biogenius.ca/). Over a 6-month period she averaged 2-3 bus trips to the University of Guelph per week to work approximately half-days in my laboratory. Her project title was "The effect of temperature on the efficacy of oncolytic viruses in human cervical cancer cells". Notably, Arthane was one of the award winners for the Greater Toronto Area regional competition. Present Position: BSc program, University of Guelph, University of Guelph
2013/12 - 2014/4 Principal Supervisor	Micaella Talan (Completed) , St. Joan of Arc Catholic Secondary School, Mississauga, Ontario Student Degree Start Date: 2010/9 Student Degree Received Date: 2014/6 Thesis/Project Title: High School Research Project: The Effects of Quercetin and Kaempferol on the Cytotoxicity of Carboplatin and Entinostat on Cancer Cell Lines Project Description: I am serving as a mentor for this secondary school student as she competes in the Sanofi BioGENEius challenge (see: http://sanofibiogeneiuschallenge.ca/). Project title: Using plant flavonoids quercetin and kaempferol in combination with the chemotherapeutic agent, carboplatin, to treat cancer cell lines. Present Position: BSc program, McMaster University
2013/12 - 2014/4 Principal Supervisor	Brittney Tin (Completed) , St. Joan of Arc Catholic Secondary School, Mississauga, Ontario Student Degree Start Date: 2010/9 Student Degree Received Date: 2014/6 Thesis/Project Title: High School Research Project: The Effects of Quercetin and Kaempferol on the Cytotoxicity of Carboplatin and Entinostat on Cancer Cell Lines Project Description: I am serving as a mentor for this secondary school student as she competes in the Sanofi BioGENEius challenge (see: http://sanofibiogeneiuschallenge.ca/). Project title: Using plant flavonoids quercetin and kaempferol in combination with the chemotherapeutic agent, carboplatin, to treat cancer cell lines. Present Position: BSc program, McMaster University

Research Associate [n=2]

2021/10 - 2022/4 Principal Supervisor	David Speicher (In Progress) , University of Guelph Student Degree Start Date: 2021/10 Thesis/Project Title: Virus Vectors for the Prevention of Infectious Diseases and Treatment of Cancers
2016/5 - 2023/4 Principal Supervisor	Dr. Khalil Karimi (In Progress) , University of Guelph Student Degree Start Date: 2016/5 Thesis/Project Title: Role of Type I Interferon Signalling on the Responses of Innate Lymphoid Cell Subsets to Viral Infection Project Description: Assists with co-management of my research program, with an emphasis on studying the role of innate lymphoid cell subsets in response to viral infection. Present Position: Research Associate/Associated Faculty Member in my laboratory, University of Guelph

Technician [n=1]

2019/12 - 2024/12 Co-Supervisor	David Marom (In Progress) , University of Guelph Student Degree Start Date: 2019/9 Thesis/Project Title: General research support. Present Position: A part-time member of my research team

Staff Supervision

Event Administration

2019/9 - 2020/1	Local Organizing Committee Member, Canadian Society for Virology 2020 Annual Scientific Meeting (Note: this meeting was cancelled due to COVID-19), Conference, 2020/6 - 2020/6

2020/7 - 2025/12	Reviewer, Viral Immunology, Journal
2019/11 - 2025/12	Reviewer, Clinical Cancer Research, Journal
2018/6 - 2025/12	Reviewer, Canadian Journal of Veterinary Medicine, Journal
2018/5 - 2025/12	Reviewer, Reviews in Medical Virology, Journal
2017/9 - 2025/12	Reviewer, Science Translational Medicine, Journal
2017/5 - 2025/12	Reviewer, Veterinary Immunology and Immunopathology, Journal
2015/5 - 2025/12	Reviewer, Canadian Journal of Veterinary Research, Journal
2015/5 - 2025/12	Reviewer, Viruses, Journal
2014/5 - 2025/12	Reviewer, Journal of Visualized Experimentation, Journal
2013/12 - 2025/12	Reviewer, PLOS ONE, Journal
2020/9 - 2025/8	Guest Editor, Viruses, Journal
2018/5 - 2018/5	Reviewer, Reviews in Medical Virology (reviewed the second of a linked pair of manuscripts), Journal
2017/12 - 2018/1	Reviewer, PLOS ONE (reviewed a manuscript), Journal

2016/11 - 2016/12	Reviewer, Canadian Journal of Veterinary Research (reviewed a manuscript), Journal
2015/10 - 2015/10	Reviewer, Viruses (reviewed a manuscript), Journal
2015/5 - 2015/5	Reviewer, Viruses (reviewed a manuscript), Journal
2014/1 - 2014/2	Reviewer, PLOS ONE (reviewed a manuscript), Journal
2013/10 - 2013/10	Reviewer, Canadian Journal of Veterinary Research (reviewed a manuscript), Journal
2013/9 - 2013/10	Reviewer, PLOS ONE (reviewed a manuscript), Journal
2013/7 - 2013/8	Reviewer, Molecular Therapy (reviewed a manuscript), Journal
2013/4 - 2013/4	Reviewer, PLOS ONE (reviewed a manuscript), Journal
2013/1 - 2013/3	Reviewer, Journal of Vaccines and Immunization (reviewed a manuscript), Journal
2012/8 - 2012/8	Reviewer, Canadian Veterinary Journal (reviewed a manuscript), Journal
2011/10 - 2011/11	Reviewer, Clinical Medicine Insights Oncology (reviewed a manuscript), Journal

Mentoring Activities

2021/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 Mentorees: Jason Knapp April 30, 2021; Jason Knapp's PhD qualifying examination
2021/4	Chair of MSc final examination committee, University of Guelph Number of Mentorees: 1 Mentorees: Christine Yanta April 27, 2021; Christine Yanta's MSc thesis defence.
2020/12	Chair of PhD final examination committee, University of Guelph Number of Mentorees: 1 December 21, 2020; Ryan Snyder's PhD thesis defence
2020/7	Chair of PhD Qualifying Examination Committee, University of Guelph Number of Mentorees: 1 July 28, 2020; Melanie Iverson's PhD qualifying examination
2020/6	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 June 12, 2020; Ran Xu's PhD qualifying examination
2020/5	PhD final examination committee member, University of Guelph Number of Mentorees: 1 May 27, 2020; Robert Mould's PhD thesis defence
2020/5	MSc final examination committee member, University of Guelph Number of Mentorees: 1 May 15, 2020; Elana Raaphorst's MSc thesis defence
2020/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 April 16, 2020; Heng Kang's PhD qualifying examination
2020/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 April 20, 2020; Sugandha Raj's PhD qualifying examination

2020/1	PhD final examination committee member, University of Guelph Number of Mentorees: 1 January 3, 2020; Maedeh Darzianiazizi's PhD thesis defence
2019/12	Chair of PhD Qualifying Examination Committee, University of Guelph Number of Mentorees: 1 December 6, 2019; Ayumi Matsuyama's PhD qualifying examination
2019/5	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 May 3, 2019; Seyed Hossein's PhD qualifying examination
2019/4	Chair of MSc final examination committee, University of Guelph Number of Mentorees: 1 April 15, 2019; Megan Neely's MSc thesis defence
2019/4	MSc final examination committee member, University of Guelph Number of Mentorees: 1 April 26, 2019; Kristen Lamers's MSc thesis defence
2019/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 April 18, 2019; Gary Lee's PhD qualifying examination
2019/2	DMin final examination committee member, Tyndale University Number of Mentorees: 1 February 3, 2019; Jeffrey Roy's DMin thesis defence
2019/1	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 January 29, 2019; Karen Carlton's PhD qualifying examination
2018/12	PhD final examination committee member, University of Western Ontario Number of Mentorees: 1 December 6, 2018; Corby Fink's PhD thesis defence
2018/12	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 December 17, 2018; Thomas McAusland's PhD qualifying examination
2018/11	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 November 26, 2018; Ashley Stegelmeier's PhD qualifying examination
2018/9	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 September 4, 2018; Maedeh Darzianiazizi's PhD qualifying examination
2018/6	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 June 22, 2018; Laura van Lieshout's PhD qualifying examination
2018/4	PhD final examination committee member, University of Guelph Number of Mentorees: 1 April 27, 2018; Jegarubee Bavananthasivam's PhD thesis defence
2018/1	PhD final examination committee member, University of Guelph Number of Mentorees: 1 January 15, 2018; Lisa Santry's PhD thesis defence

2018/1	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 January 19, 2018; Nadiyah Alqazlan's PhD qualifying examination
2018/1	PhD final examination committee member, University of Guelph Number of Mentorees: 1 January 9, 2018; Megan Strachan-Whaley's PhD thesis defence
2017/12	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 December 1, 2017; Benoit Cuq's PhD Qualifying Examination
2017/9	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 September 25, 2017: Carina Cooper's PhD qualifying examination
2017/8	MSc final examination committee member, University of Guelph Number of Mentorees: 1 August 21, 2017; Amanda AuYeung's MSc thesis defence
2017/3	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 March 27, 2017: Jacob van Vloten's PhD qualifying examination
2017/1	PhD final examination committee member, University of Guelph Number of Mentorees: 1 January 25, 2017; Neda Barjesteh's PhD thesis defence
2017/1	MSc final examination committee member, University of Toronto Number of Mentorees: 1 January 16, 2017; Tiffany Ho's MSc thesis defence
2016/9	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 December 19, 2016: Peyman Asadian's PhD qualifying examination
2016/8	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 August 24, 2016: Kathy Matuszewska's PhD qualifying examination
2016/6	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 June 14, 2016: Megan Strachan-whaley's PhD qualifying examination
2016/6	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 June 6, 2016: Seyedmehdi Emam's PhD qualifying examination
2016/5	PhD final examination committee member, University of Guelph Number of Mentorees: 1 May 3, 2016: Served on the examination committee for Shirene Singh's PhD defence
2016/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 April 27, 2016: Alexander Bekele-Yitbarek's PhD qualifying examination
2015/9	MSc examination committee member, University of Guelph Number of Mentorees: 1 September 2, 2015: Alexandra Rasiuk's MSc thesis defense

2015/8	Chair of MSc examination committee, University of Guelph Number of Mentorees: 1 August 18, 2015: Chaired James Ackford's MSc thesis defense
2015/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 April 27, 2015: Jegarubee Bavananthasivam's PhD qualifying examination
2015/2	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 February 18, 2015: Marianne Wilcox's PhD qualifying examination
2014/8	MSc examination committee member, University of Guelph Number of Mentorees: 1 August 13, 2014: Served on the examination committee for Zafir Syed's MSc thesis defence
2014/8	MSc examination committee member, University of Guelph Number of Mentorees: 1 August 12, 2014: Served on the examination committee for Christian Ternamian's MSc thesis defence
2014/6	Chair of MSc examination committee, University of Guelph Number of Mentorees: 1 June 10, 2014: Chaired Kelly Fleming's MSc thesis defence
2014/1	PhD final examination committee member, University of Guelph Number of Mentorees: 1 January 3, 2014: Scott Walsh's PhD defense
2013/12	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 December 16, 2013: Lisa Santry's PhD qualifying examination
2013/12	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 December 11, 2013: Shirene Singh's PhD qualifying examination
2013/11	Chair of MSc examination committee, University of Guelph Number of Mentorees: 1 November 19, 2013: Chaired Shaun Kernaghan's MSc thesis defense
2013/6	MSc examination committee member, University of Guelph Number of Mentorees: 1 June 14, 2013: Ian Villanueva's MSc thesis defense
2012/9	MSc examination committee member, University of Guelph Number of Mentorees: 1 September 5, 2012: Sonja Zours' MSc thesis defense
2012/7	Chair of MSc examination committee, University of Guelph Number of Mentorees: 1 July 20, 2012: Chaired Inas Elawadli's MSc thesis defense
2012/5	PhD qualification examination committee member, University of Guelph Number of Mentorees: 1 May 7, 2012: Li Deng's PhD qualification examination
2012/4	Chair of MSc examination committee, University of Guelph Number of Mentorees: 1 April 19, 2012: Chaired Iman Mehdizadeh Gohari's MSc thesis defense

Expert Witness Activities

2022/1	Expert Witness, ONTARIO SUPERIOR COURT OF JUSTICE BETWEEN SARAH HARJEE, EVAN KRAAYENBRINK, HIBAH AOUN, SARAH LAMB, SAM SABOURIN, JACKIE RAMNAUTH, MARK MCDONOUGH and LINDA MCDONOUGH -and- HER MAJESTY THE QUEEN IN RIGHT OF THE PROVINCE OF ONTARIO, Canada, Toronto
2022/1	Expert Witness, A family court case. A former wife who does not want her 12-year-old son to receive a COVID-19 jab vs The former husband who does want his son to receive a COVID-19 jab, Canada
2022/2 - 2022/4	Expert Witness, COURT OF QUEEN'S BENCH OF ALBERTA ANNETTE LEWIS vs ALBERTA HEALTH SERVICES; UNIVERSITY OF ALBERTA HOSPITAL, AND VARIOUS DOCTORS (granted anonymity), Canada, Wetaskiwin
2022/2 - 2022/2	Expert Witness, ONTARIO SUPERIOR COURT OF JUSTICE B E T W E E N: NATIONAL ORGANIZED WORKERS UNION Applicant/Moving Party - and - SINAI HEALTH NETWORK, Canada, Toronto
2021/12 - 2022/2	Expert Witness, IN THE HIGH COURT OF NEW ZEALAND WELLINGTON REGISTRY BETWEEN NZDSOS INC; NZTSOS INC AND THE MINISTER FOR COVID-19 RESPONSE; THE DIRECTOR-GENERAL OF HEALTH; ATTORNEY-GENERAL, New Zealand, Wellington
2022/1 - 2022/1	Expert Witness, IN THE HIGH COURT OF NEW ZEALAND BETWEEN DCB AND THE MINISTER OF HEALTH; THE GROUP MANAGER OF THE NEW ZEALAND MEDICAL DEVICES SAFETY AUTHORITY (MEDSAFE); THE COVID-19 RESPONSE MINISTER, New Zealand, Wellington
2021/12 - 2022/1	Expert Witness, DR. MIKLOS MATYA VS CHILDREN'S HOSPITAL OF EASTERN ONTARIO, Canada, Ottawa
2021/4 - 2022/1	Expert Witness, Hearing Tribunal of the Alberta College and Association of Chiropractors (ACAC) into the conduct of Dr. Curtis Wall, a regulated member of ACAC, Canada, Calgary
2021/4 - 2021/6	Expert Witness, ONTARIO SUPERIOR COURT OF JUSTICE BETWEEN: HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO AND ADAMSON BARBECUE LIMITED AND WILLIAM ADAMSON SKELLY, Canada, Toronto
2021/4 - 2021/4	Expert Witness, COURT OF QUEEN'S BENCH OF ALBERTA GRACELIFE CHURCH OF EDMONTON, JAMES COATES, DONNA KLAY, ALLAN NEILL, and ACHNES SMITH vs THE PROVINCE OF ALBERTA AS REPRESENTED BY THE MINISTER OF HEALTH, THE CHIEF MEDICAL OFFICER OF HEALTH, and ALBERTA, Canada, Edmonton

Organizational Review Activities

2020/8	Reviewer, Canadian Institutes of Health Research Served on the Cancer Biology and Therapeutics grant review panel
2020/5	Reviewer, Cancer Research Society Served on grant review panel C2 - Tumour suppressor genes, oncogenes and DNA repair
2019/10	Reviewer, Canadian Foundation for Innovation Served on an expert committee to review an application to the John R. Evans Leaders Fund

2018/10	Reviewer, Canadian Institutes of Health Research Started a three-year term serving on the Virology and Viral Pathogenesis grant review panel
2014/6	Reviewer, Canadian Cancer Society Research Institute Served on grant review panel I3 - Immunology Signalling and Stem Cells
2020/6 - 2020/7	Reviewer, Swiss National Science Foundation Spark Grant
2019/12 - 2020/1	Reviewer, Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant
2019/12 - 2019/12	Reviewer, New Foundations in Research Fund Reviewed an Exploration Grant
2019/9 - 2019/10	Reviewer, Prostate Cancer UK Reviewed a grant application.
2018/8 - 2018/9	Reviewer, Mitacs Accelerate Reviewed one grant application.
2017/12 - 2018/1	Reviewer, Student Scinapse Competition Reviewed 7 applications.
2017/9 - 2017/10	Reviewer, Breast Cancer Now_UK Reviewed a grant application.
2017/3 - 2017/4	Reviewer, Graduate Women in Science Fellowship Reviewed one application.
2016/12 - 2017/1	Reviewer, Student Scinapse Competition Reviewed 10 applications.
2016/11 - 2016/12	Reviewer, Mitacs Accelerate Reviewed one grant application.
2015/11 - 2015/11	Reviewer, Natural Sciences and Engineering Research Council of Canada (NSERC) Collaborative Health Research Program
2014/12 - 2015/1	Reviewer, Natural Sciences and Engineering Research Council of Canada (NSERC) Served as an external reviewer for a NSERC Discovery Grant application
2014/4 - 2014/5	Reviewer, Croatian Science Foundation Reviewed a grant application.

Community and Volunteer Activities

2015/1	Member of the Animal Isolation Unit Advisory Committee, University of Guelph To provide advice from the perspective of a researcher to Campus Animal Facilities in an effort to balance the needs of technicians, the administration and those conducting animal research at biosafety level 2.
2014/12	Volunteer Fundraiser, University of Guelph Assisting fundraising efforts for the Global Vets program by auctioning an immunology review session (2014) and a faculty-student hockey game (2015).
2014/5	Volunteer Interviewer, University of Guelph Conducting annual entrance interviews for the Doctor of Veterinary Medicine program.

2014/2	Member of the Dept. of Pathobiology Research Committee, University of Guelph Deliberate on departmental research-related issues and provide recommendations to the department. Keep track of departmental equipment. Coordinate equipment grant applications.
2013/2	Member of the Dept. of Pathobiology Seminar Committee, University of Guelph Organize and run the Dept. of Pathobiology's annual seminar series, which runs from September to April. Host visiting speakers. Also organize and run an annual 3-minute thesis competition for trainees. I chaired this committee Sept. 2015-Aug. 2016
2013/2	Member of the Dept. of Pathobiology Awards Committee, University of Guelph Review and rank all award applications submitted in the Department of Pathobiology.
2013/1	Scientific Reviewer of Animal Utilization Protocols, University of Guelph Review the scientific content of applications for animal utilization protocols for the Animal Care Committee.
2012/11	Volunteer Judge, University of Guelph Annual poster judging for the Graduate Student Research Symposium (showcases graduate student research projects).
2012/8	volunteer judge, University of Guelph Annual poster judging for the Career Opportunites and Research Experience Program (formerly called "Summer Leadership and Research Program"; showcases summer student research projects).
2012/2	Co-Manager of the University of Guelph Core Flow Cytometry Facility, University of Guelph Manage the core flow cytometry facility at the University of Guelph in conjunction with one other faculty member.
2011/10	Scientific Reviewer, Various scientific journals Review manuscripts submitted to the following journals: Molecular Therapy PLOS ONE Journal of Vaccines and Immunization Canadian Veterinary Journal Clinical Medicine Insights Oncology Canadian Journal of Veterinary Research Journal of Visualized Experimentation Reviews in Medical Virology Viruses
1997/1	Member, Canadian Society for Immunology A registered member of the Canadian Society for Immunology
2016/3 - 2016/3	volunteer judge, University of Guelph Judged student-run exhibits that are open to the public at the Ontario Veterinary College.
2014/4 - 2016/1	Grant Review Panel Member, Prostate Cancer Canada I served on Panel C "Experimental Therapeutics"
2015/2 - 2015/3	Scientific Reviewer, Oxford University Press Reviewed Chapter 12: Tumor Immunology and Immunotherapy from the textbook "Molecular Biology of Cancer, fourth edition" by Pecorino.
2015/1 - 2015/2	Scientific Reviewer, Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant review
2014/5 - 2014/6	Scientific Reviewer, Croatian Science Foundation Grant review
2010/9 - 2014/5	Assistant Coach, Stanley Stick Hockey Association, Guelph, Ontario Serve as a volunteer for this not-for-profit hockey association. Assist with coaching a boys hockey team. Learn to skate program: 2010-11 Novice division: 2011-2014

2003/9 - 2012/4	Organizer, Men's recreational hockey group, Guelph, Ontario Managed a men's recreational hockey group.

Knowledge and Technology Translation

2014/1	Co-Investigator, Technology Transfer and Commercialization Group/Organization/Business Serviced: University of Guelph Target Stakeholder: General Public Outcome / Deliverable: Submitted an invention disclosure form:Avianorthoreovirus (ARV) strain PB1: a potential oncolytic, vaccine and adjuvant Activity Description: Invention disclosure to the University of Guelph Catalyst Centre: "Avian orthoreovirus (ARV) strain PB1: a potential oncolytic, vaccine and adjuvant"
2011/3	Co-investigator, Technology Transfer and Commercialization Group/Organization/Business Serviced: McMaster University, Hamilton, Ontario Target Stakeholder: General Public Outcome / Deliverable: Patent Evidence of Uptake/Impact: Used as part of the intellectual property to establish a new biotechnology company called "Turnstone Biologics" References / Citations / Web Sites: http://www.turnstonebio.com/ http://www.google.com/patents/WO2012122629A1?cl=en Activity Description: Bridle BW, Bell JC, Diallo JS, Lemay C, Lichty BD, Wan Y "Vaccination and HDAC inhibition" Provisional Patent 61/451,794 filed March 11, 2011, PCT Patent Application No. PCT/CA2012/000212 national phase filings in Europe, North America, China, and Japan underway
2011/2	Co-Investigator, Technology Transfer and Commercialization Group/Organization/Business Serviced: McMaster University, Hamilton, Ontario Target Stakeholder: General Public Outcome / Deliverable: Patent Evidence of Uptake/Impact: Used as part of the intellectual property to establish a new biotechnology company called "Turnstone Biologics" References / Citations / Web Sites: http://www.turnstonebio.com/ Activity Description: Bridle BQ, Lichty BD, Wan Y "Vaccination method utilizing follicular B cells" Provisional patent 61/446,248 (filed February 24, 2011)
2009/3	Co-Investigator, Technology Transfer and Commercialization Group/Organization/Business Serviced: McMaster University, Hamilton, Ontario Target Stakeholder: General Public Outcome / Deliverable: Patent Evidence of Uptake/Impact: Used as part of the intellectual property to establish a new biotechnology company called "Turnstone Biologics" References / Citations / Web Sites: http://www.turnstonebio.com/ http://www.google.com/patents/WO2010105347A1?cl=en Activity Description: Bridle BW, Bramson J, Lichty BD, Wan Y "Vaccination Methods" PCT Patent application No. PCT/CA2010/000379 (PCT filed March 16, 2010) national phase filings in Europe, North America, and China underway
2019/9 - 2030/7	Co-Founder, Involvement in/Creation of Start-up Group/Organization/Business Serviced: IHN Pharma, Inc. Target Stakeholder: Patients Outcome / Deliverable: Novel biotherapies for the treatment of cancers. Evidence of Uptake/Impact: This company is in the start-up phase. Activity Description: Along with six collaborators, we are establishing a start-up biotechnology company called "INH Pharma, Inc." to leverage intellectual properties related to proprietary oncolytic viruses.

Committee Memberships

2019/8	Committee Member, Chair search committee, University of Guelph To recruit and hire a new Chair for the Department of Pathobiology
2019/6	Committee Member, Faculty Search Committee, University of Guelph To hire a new virologist for a tenure-track faculty position in the Department of Pathobiology
2018/9	Committee Member, Virology and Viral Pathogenesis Grant Review Panel, Canadian Institutes of Health Research Review and rank grant proposals.
2017/12	Chair, Department of Pathobiology Awards Committee, University of Guelph Review and rank applications for academic awards.
2017/12	Committee Member, Ontario Veterinary College Graduate Awards Committee, University of Guelph Review and rank award applications from graduate students at the college level.
2017/12	Committee Member, Scientific Review Committee for the Pet Trust Foundation, University of Guelph Review and rank applications to the Pet Trust Foundation's bi-annual operating grant competitions.
2017/12	Committee Member, Ontario Veterinary College Undergraduate Awards Committee, University of Guelph Review and rank award applications from students in the Doctor of Veterinary Medicine and other undergraduate programs within the Ontario Veterinary College.
2016/7	Committee Member, Department of Pathobiology Seminar Series Committee, University of Guelph Help schedule a weekly seminar series that spans the Fall and Winter semesters. Host external speakers.
2014/12	Co-chair, Ad hoc committee to manage the University of Guelph's flow cytometry facility., University of Guelph Co-management of institutional core flow cytometry facility (two high-throughput analytical flow cytometers, plus one flow sorter). Other co-managers: Dorothee Bienzle and Brandon Plattner.
2014/9	Ex-Officio, Scientific Reviewer for Animal Care Committee, University of Guelph Provide expert scientific reviews of animal utilization protocols that have been submitted to the institutional animal care committee.
2014/1	Committee Member, Department of Pathobiology Research Committee, University of Guelph Identify, review and make recommendations related to departmental research issues.
2020/7 - 2020/8	Committee Member, Cancer Biology and Therapeutics Grant Review Panel, Canadian Institutes of Health Research Review and rank grant applications.
2020/6 - 2020/7	Chair, PhD Qualifying Examination Committee, University of Guelph Examinee: Melanie Iverson
2020/5 - 2020/6	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Ran Xu
2020/4 - 2020/5	Committee Member, PhD Thesis Examination Committee, University of Guelph Examinee: Robert Mould

2020/4 - 2020/5	Committee Member, MSc Thesis Examination Committee, University of Guelph Examinee: Elana Raaphorst
2020/3 - 2020/5	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Sugandha Raj
2019/12 - 2020/1	Committee Member, PhD Thesis Examination Committee, University of Guelph Examinee: Maedeh Darzianiazizi
2019/11 - 2019/12	Chair, PhD Qualifying Examination Committee, University of Guelph Examinee: Ayumi Matsuyama
2019/7 - 2019/8	Committee Member, Expert Review Committee, Canadian Foundation for Innovation To review a grant application for funding from the John R. Evans Leaders Fund
2019/6 - 2019/7	Committee Member, Technician search committee., University of Guelph To recruit and hire a new technician for the Department of Pathobiology
2019/3 - 2019/5	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Seyed Hossein Karimi
2019/3 - 2019/4	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Kristen Lamers (MSc)
2019/3 - 2019/4	Chair, Thesis Examination Committee, University of Guelph Examinee: Megan Neely (MSc)
2019/3 - 2019/4	Committee Member, MSc Thesis Examination Committee, University of Guelph Examinee: Kristen Lamers
2019/2 - 2019/4	Chair, PhD Qualifying Examination Committee, University of Guelph Examinee: Gary Lee
2019/1 - 2019/2	Committee Member, Thesis Examination, Tyndale College and Theological Seminary Examinee: Jeffrey Roy (DMin)
2018/11 - 2019/1	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Karen Carlton
2018/11 - 2018/12	Committee Member, Thesis Examination Committee, University of Western Ontario Examinee: Corby Fink (PhD)
2018/10 - 2018/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Thomas McAusland
2018/9 - 2018/11	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Ashley Ross
2018/7 - 2018/9	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Maedeh Darzianiazizi
2018/4 - 2018/6	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Laura van Lieshout
2018/3 - 2018/4	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Jegarubee Bavananthasivam (PhD)
2017/12 - 2018/1	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Megan Strachan-Whaley (PhD)
2017/12 - 2018/1	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Lisa Santry (PhD)
2017/11 - 2018/1	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Nadiyah Alqazlan

2017/10 - 2017/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Benoit Cuq
2012/5 - 2017/11	Committee Member, Department of Pathobiology Awards Committee, University of Guelph Review and rank applications for academic awards.
2017/7 - 2017/9	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Carina Cooper
2017/6 - 2017/8	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Amanda AuYeung (MSc)
2016/4 - 2017/4	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Megan Stachan-Whaley (written and oral portions of exam were separated due to a maternity leave).
2017/1 - 2017/3	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Jacob van Vloten
2016/12 - 2017/1	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Neda Barjesteh (PhD)
2016/12 - 2017/1	Committee Member, Thesis Examination Committee, University of Toronto Examinee: Tiffany Ho (MSc)
2016/10 - 2016/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Peyman Asadian
2014/1 - 2016/12	Committee Member, Prostate Cancer Canada - Panel C - Experimental Therapeutics Grant Review Panel, Prostate Cancer Canada Review grants submitted to the "Experimental Therapeutics" panel and make recommendations for funding.
2016/6 - 2016/8	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Kathy Matuszewska
2016/4 - 2016/6	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Seyedmehdi Emam
2015/8 - 2016/6	Chair, Department of Pathobiology Seminar Series Committee, University of Guelph Help schedule a weekly seminar series that spans the Fall and Winter semesters. Host external speakers.
2016/4 - 2016/5	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Shirene Singh (PhD)
2016/2 - 2016/4	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Alexander Bekele-Yitbarek
2015/8 - 2015/9	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Alexandra Rasiuk (MSc)
2015/6 - 2015/8	Chair, Thesis Examination Committee, University of Guelph Examinee: James Ackford (MSc)
2013/6 - 2015/8	Committee Member, Department of Pathobiology Seminar Series Committee, University of Guelph Help schedule a weekly seminar series that spans the Fall and Winter semesters. Host external speakers.
2015/5 - 2015/5	Committee Member, Doctor of Veterinary Medicine Admissions Interview Committee, University of Guelph Interviewed and ranked applicants to the Doctor of Veterinary Medicine program.

2015/2 - 2015/4	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Jegarubee Bavananthasivam
2014/12 - 2015/2	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Marianne Wilcox
2014/7 - 2014/8	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Christian Ternamian (MSc)
2014/7 - 2014/8	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Zafir Syed (MSc)
2014/5 - 2014/6	Chair, Thesis Examination Committee, University of Guelph Examinee: Kelly Fleming (MSc)
2013/12 - 2014/1	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Scott Walsh (PhD)
2013/12 - 2013/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Shirene Singh
2013/10 - 2013/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Lisa Santry
2013/10 - 2013/11	Chair, Thesis Examination Committee, University of Guelph Examinee: Shaun Kernaghan (MSc)
2013/5 - 2013/6	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Ian Villanueva (MSc)
2012/8 - 2012/9	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Sonja Zours (MSc)
2012/6 - 2012/7	Chair, Thesis Examination Committee, University of Guelph Examinee: Inas Elawadli (MSc)
2012/3 - 2012/5	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Li Deng
2012/3 - 2012/4	Chair, Thesis Examination Committee, University of Guelph Examinee: Iman Mehdizadeh Gohari (MSc)

Other Memberships

2020/6	Member, One Health Institute University of Guelph Within One Health, University of Guelph researchers work across disciplines and sectors to interrogate the biological and social factors that impinge on the health of organisms, from the level of molecules to that of ecosystems, with unique strengths in comparative medicine. This research also explores how these factors are shaped by environmental parameters, such as climate change, ultimately informing public health and environmental health practice and policy.
2017/6	Member Scientist, Dog Osteosarcoma Group: Biomarkers Of Neoplasia (DOG BONe) This groups consists of eight faculty members from the Ontario Veterinary College, University of Guelph, who share a vision for collaborative research to advance our understanding of canine osteosarcomas, how to predict clinical outcomes and to develop novel therapies. The group includes two veterinary oncologists, two veterinary surgical oncologists, a statitician, a veterinary pathologist, an immunologist and a cancer biologist.

2016/9	Member, European Academy for Tumor Immunology I was invited to be a member of this international organization that is based in Europe. The purpose is to promote international collaborations and unify research in the area of immunotherapies for cancers.
2015/4	Member Scientist, Canadian Oncolytic Virus Consortium (COVCo) COVCo is a pan-Canadian network of fifteen clinical and basic scientists dedicated to developing and advancing the oncolytic virus platform as a targeted and revolutionary approach to cancer therapeutics. Our common vision is that an iterative cycle of discovery and clinical testing is the fastest and most effective way to develop new biological therapeutics. We are funded by the Terry Fox Research Institute (Program Project Grant).
2014/12	Member scientist, National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx) Total funding: $60 million ($25 million from the federal government + $35 million from partners) over 5 years. Total # of researchers across Canada: 42 (representing 17academic institutions). Also supported by: 8 private sector and 19 community partners. Scientific Director: Dr. John Bell, Ottawa Hospital Research Institute. I am one of the 42 founding members.
2012/1	Member, Institute for Comparative Cancer Investigation, University of Guelph The Institute for Comparative Cancer Investigation at the University of Guelph facilitates translational oncology research in companion animals at the OVC Mona Campbell Centre for Animal Cancer by managing clinical trials and the Companion Animal Tumour Sample Bank. Our goals: to advance the understanding of cancer and improve treatment options to benefit both companion animal and human cancer patients.
2001/3	Member, Canadian Society for Immunology The mandate of the Canadian Society for Immunology is to foster and support Immunology research and education throughout Canada

Most Significant Contributions

Using epigenetic modification to enhance anoncolytic booster vaccine while abrogating autoimmune pathology

I discovered that an immunosuppressive histone deacetylase inhibitor (entinostat) could enhance oncolytic booster vaccines (Bridle BW et al. Molecular Therapy 2013 Apr;21(4):887-94). Regulatory T cells could be transiently suppressed with simultaneous up-regulation of major histocompatibility complex expression on tumour cells (making them more visible targets) and concomitant prolongation of viral oncolysis, resulting in more efficacious tumour-specific T cell responses. Importantly, the vitiligo normally associated with melanoma immunotherapy was abrogated. This was a novel strategy for separating anti-tumour autoimmunity from autoimmune pathology and was the first time anyone demonstrated the ability to dramatically improve anti-melanoma efficacy while simultaneously suppressing vitiligo; something the literature suggested could not be done. This garnered a patent and receipt of substantial research funding. This research is now being applied to leukemias.

Knowledge translation during the COVID-19 pandemic:Providing fact-based answers to the lay public, policy makers and courts of law
Beginning in May 2019 I began disseminating information about immunological concepts relevant to COVID-19. I have authored nine lay articles, served on two discussion panels, was a keynote speaker at five events (two were international conferences), I gave seven television interviews (three were for national news, including W5 and Global National News), I was interviewed for 35 newspaper/magazine articles (including National Geographic, The Globe and Mail, Toronto Star and Toronto Sun), I conducted 55 radio interviews spanning almost every province and one territory and included international interviews in New Zealand and Scotland, and I was asked to serve as an expert witness for two lawsuits related to COVID-19 (one in Calgary and one in the Ontario Superior Court of Justice).

From bench to bedside in five years: Synergizing oncolytic virotherapy with cancer immunotherapy
In 2010 I led a team that described a unique approach to synergize cancer immunotherapy with oncolytic virotherapy (Bridle BW, et al. Molecular Therapy 2010 Aug; 18(8):1430-9). This was accomplished using an oncolytic virus to boost pre-existing tumour-specific immune responses. The prevailing wisdom in the field was that immunotherapy and oncolytic virotherapy could not be effectively combined. However, I was able to prove this wrong and an optimized version of this therapy entered a phase I/II human clinical trial in January 2015, followed by three more clinical trials. This rapid progression from bench to bedside was facilitated by extensive collaborations, including the Terry Fox Foundation-funded Canadian Oncolytic Virus Consortium, of which I am a member. This also resulted in a patent application (I have 40% inventorship) that formed foundational intellectual property used to establish a biotechnology company (Turnstone Biologics).

Presentations

1. (2023). I gave a presentation entitled "The COVID-19 Vaccine Trials" in the European Parliament on May 3, 2023. International COVID Summit 3 May 2-4, 2023, Brussels, Belgium
   Main Audience: Decision Maker
   Invited?: Yes
   Description / Contribution Value: I presented in a one-day conference held for medical professionals only on May 2, 2023. I then presented in the European Parliament on May 3, 2023. I also attended press conferences on May 4, 2023.
2. SIERRA VANDERKAMP, ASHLEY A. STEGELMEIER, Byram W. Bridle (Dr. Bridle's trainees capitalized). (2021). In Vitro Analysis of Oxidative Stress on Off-Target Infection of Activated T Cells by Oncolytic Vesicular Stomatitis Virus. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
   Main Audience: Researcher
   Invited?: No, Keynote?: No, Competitive?: No
3. LILY CHAN, Sarah K. Wootton, Byram W. Bridle* and KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's HQP capitalized). (2021). Following Administration of Dendritic Cell-Based Vaccines There is an Increase in Type 2 Innate Lymphoid Cells in the Local Draining Lymph Node and Spleen. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
   Main Audience: Researcher
   Invited?: No, Keynote?: No, Competitive?: No

4. J Yates, R MOULD, L CHAN, J KNAPP, Y MEHRANI, Y Pei, P Pham, A Leacy, L Santry, BA McBey, P Major, Byram W. Bridle*, L Susta*, S Wootton* (*equal senior authors) (Dr. Bridle's HQP capitalized). (2021). Recombinant avian orthoavulavirus-1 engineered to express variants of the SARS-CoV-2 Spike Protein induces mucosal and systemic immune responses. American Society for Gene and Cell Therapy Annual Meeting 2021 (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

5. JASON P. KNAPP, JACOB P. VAN VLOTEN, Lisa A. Santry, Jacob Yates, JESSICA A. MINOTT, Sarah K. Wootton, and Byram W. Bridle (Dr. Bridle's trainees capitalized). (2021). Differential Susceptibility of Viral-Vectored Vaccines to Temperatures Over 37oC. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

6. JULIA E. KAKISH, JASON P. KNAPP, ARTHANE KODEESWARAN, KATRINA GERONIMO, MARY ELLEN CLARK, and Byram W. Bridle (Dr. Bridle's trainees capitalized). (2021). Investigating the Effect of Low Anatomical Temperatures on Rhabdoviruses. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

7. YEGANEH MEHRANI, LILY CHAN, ASHLEY A. STEGELMEIER, Byram W. Bridle*, KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's HQP capitalized). (2021). Antiviral Cytokine Responses in Murine Bone-Marrow-Derived Mast Cells: Disruption of Type I Interferon Signaling and Elevation of Inflammatory Cytokines. American Society for Virology Annual Scientific Meeting (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

8. ASHLEY A. STEGELMEIER, Kevin Stinson, Sarah K. Wootton, Byram W. Bridle (Dr. Bridle's trainee capitalized). (2021). Characterizing Cytokine, Chemokine, and Acute-Phase Protein Profiles of Plasma Samples Derived from Patients that Tested Positive for COVID-19. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

9. Kathy Matuszewska, Simone Ten Kortenaar, Madison Pereira, Duncan Petrik, Leslie Ogilvie, Pierre P. Major, Jack Lawler, Sarah K. Wootton, Byram W. Bridle, Jeremy Simpson, Jim Petrik. (2021). Fc3TSR Normalizes the Tumor Microenvironment and Improves Treatment Delivery in an Orthotopic, Syngeneic Mouse Model of Epithelial Ovarian Cancer. Canadian Conference on Ovarian Cancer Research (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

10. (2021). Answers to Outstanding Questions About COVID-19 Vaccines Will Dictate the Success or Failure of the Rollout. Second International COVID-19 Symposium, New Zealand
Main Audience: General Public
Invited?: Yes, Keynote?: Yes

11. ASHLEY STEGELMEIER, KIERSTEN HANADA, KHALIL KARIMI, Sarah Wootton, Byram Bridle (Dr. Bridle's HQP capitalized). (2021). Developing a Murine Cytokine Storm Model with IFNAR-Knockout Mice to Rapidly Test SARS-CoV-2 Immunotherapies. American Society for Virology Annual Scientific Meeting (virtual) (oral presentation),
Invited?: Yes, Keynote?: No, Competitive?: Yes

12. Amira Rghei, Laura van Lieshout, Benjamin McLeod, Yanlong Pei, Hugues Faust, Gary Kobinger, Brad Thompson, KHALIL KARIMI, Byram W. Bridle, Leonardo Susta, Sarah Wootton (Dr. Bridle's HQP capitalized). (2021). Vectorized Expression of SARS-CoV-2-Specific Human Antibodies in Mice and Sheep is Feasible and Well-Tolerated. American Society for Gene and Cell Therapy Annual Meeting 2021 (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

13. YEGANEH MEHRANI, LILY CHAN, ASHLEY A. STEGELMEIER, Byram W. Bridle*, KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's trainees capitalized). (2021). Excessive Antiviral Cytokine Responses in Adoptively Transferred Mast Cells: Disruption of Type I Interferon Signaling Elevates Inflammatory Cytokines. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

14. JESSICA A. MINOTT, JACOB P. VAN VLOTEN, LILY CHAN, YEGANEH MEHRANI, Sarah K. Wootton*, Byram W. Bridle* and KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's trainees capitalized). (2021). Investigating the Role of Neutrophils in Oncolytic Orf Virus-Activated Anti-Tumour Immunity in a Pre-Clinical Murine Model of Melanoma. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Invited?: No, Keynote?: No, Competitive?: No

15. LILY CHAN, ASHLEY STEGELMEIER, Sarah K. Wootton, Byram W. Bridle* and KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's HQP capitalized). (2021). The Tolerogenic Potential of Dendritic Cells Infected with an Adeno-Associated Virus Gene Therapy Vector. American Society for Virology Annual Scientific Meeting (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

16. (2021). Answers to Outstanding Questions About COVID-19 Vaccines Will Dictate the Success or Failure of the Rollout. COVID-19 Panel Discussion: A Vaccine Recovery Hosted by the Infectious Disease Working Group, University of Toronto, Canada
Main Audience: General Public
Invited?: Yes, Keynote?: Yes

17. (2020). Tumour Microenvironmental Barriers to Successful Oncolytic Virotherapy. McMaster Immunology Research Centre Seminar Series, McMaster University, Hamilton, Ontario, January 15, 2020, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: Yes

18. (2020). COVID-19: Realistic Timelines for Vaccine Development. Kitchener Public Library: Science Literacy Week (Webinar), Canada
Main Audience: General Public
Invited?: Yes, Keynote?: Yes

19. (2020). Kitchener Public Library: Science Literacy Week. Biology and Control of SARS-CoV-2 (Webinar), Canada
Main Audience: General Public
Invited?: Yes, Keynote?: No

20. Cristine J. Reitz, Faisal J. Alibhai, Tarak N. Khatua, Mina Rasouli, Byram W. Bridle, Thomas P. Burris, Tami A. Martino. (2020). Circadian Medicine to Treat Myocardial Infarction (Heart Attack): Targeting the Cardiac NLRP3 Inflammasome (poster). Society for Research on Biological Rhythms (SRBR) 2020 Virtual Conference, United States of America
Main Audience: Researcher
Invited?: Yes, Keynote?: No

21. (2020). COVID-19 Vaccines: Facts to Inform Policies. New Zealand COVID-19 Science and Policy Symposium Webinar, New Zealand
Main Audience: Decision Maker
Invited?: Yes, Keynote?: Yes

22. Kiersten Hanada, Ashley Stegelmeier, Lily Chan, Yeganeh Mehrani & Byram Bridle. (2020). Calming the COVID-19 Storm: Developing a Model to Study Toxic Cytokine Responses to Viruses (poster; won 1st place). Ontario Veterinary College Summer Career Opportunities and Research Exploration Program, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

23. Ashley Stegelmeier, Kiersten Hanada, Khalil Karimi, Sarah Wootton, Byram Bridle. (2020). Developing a Murine Cytokine Storm Model with IFNAR-Knockout Mice to Rapidly Test SARS-CoV-2 Immunotherapies (oral presentation; won 1st place out of 40 presentations). University of Guelph Graduate Association On-Line Research Conference, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

24. Ashley A. Stegelmeier, Amanda W.K. AuYeung, Robert Mould, Thomas McAusland, Lisa Santry, Jacob van Vloten, Megan Strachan-Whaley, Elaine Klafuric, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). Off-Target Infection of Stimulated T Cells by Vesicular Stomatitis Virus has Implications for Single- Versus Multi-Dosing Oncolytic Virotherapy Protocols (poster and 'speed-talk' oral presentation). Annual Scientific Meeting of the Canadian Cancer Immunotherapy Consortium, Toronto, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

25. (2019). Graduate Studies in the Department of Pathobiology (oral presentation as part of a panel discussion). Career Opportunities and Research Experience Summer Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No

26. Lily Chan, Robert Mould, Sarah K. Wootton, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2019). Dendritic Cell Vaccines Provoke an Increase in the Number of Interleukin-22-Producing Type 3 Innate Lymphoid Cells in the Local Draining Lymph Nodes and in The Spleen (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

27. Jacob van Vloten, Sarah K. Wootton* and Byram W. Bridle* (*co-equal senior authors). (2019). Quantifying T-Cell and Antibody Responses Induced by Antigen-Agnostic Immunotherapies (oral presenation). Ontario Veterinary College Graduate Student Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

28. (2019). Developing Novel Cancer Biotherapies (oral presentation). Canadian Cancer Society Relay for Life, Guelph, Canada
Main Audience: General Public
Invited?: Yes, Keynote?: Yes

29. Ashley A. Ross, Amanda W.K. AuYeung, Robert Mould, Thomas McAusland, Lisa Santry, Jacob van Vloten, Megan Whaley, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). Off-Target Infection of Stimulated T Cells by Vesicular Stomatitis Virus Has Implications for Single- Versus Multi-Dosing Oncolytic Virotherapy Protocols (oral presentation). Ontario Veterinary College Graduate Student Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

30. Jacob P. van Vloten, Joelle C. Ingrao, Robert C. Mould, Lisa A. Santry, Khalil Karimi, D. Grant McFadden, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). An OrfV-Infected Cell Vaccine Induces Innate and Adaptive Immune Responses Against Osteosarcoma Metastases Resulting in Long-Term Survival. Annual Scientific Meeting of the Canadian Cancer Immunotherapy Consortium (poster and 'speed talk' oral presentation), Toronto, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

31. E Klafuric, M Strachan-Whaley, L Santry, A AuYeung, J van Vloten, R Mould, T McAusland, ME Clark, J Minott, S Holtz, J Saturno, K Karimi, A Mutsaers, S Wootton and Byram W. Bridle. (2019). Combining Decitabine with Oncolytic Virotherapy Preferentially Kills Acute Leukemia Cells Via Lethal Oxidative Stress (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

32. Maedeh Darzianiazizi (Mahi Azizi), Jacob Van Vloten, Shayan Sharif, Ravi Kulkarni, Byram W. Bridle*, Khalil Karimi* (*co-equal senior authors). (2019). Differential Sex-Mediated Hepatotoxicity Caused by a Viral Infection with a Concomitant Defect in Type I Interferon Signaling (oral presentation). Ontario Veterinary College Graduate Student Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

33. Robert Mould, Jacob van Vloten, Ashley Ross, Mankerat Singh, Anthony Mutsaers, James Petrik, Leonardo Susta, Geoffrey Wood, Sarah Wootton, Byram W. Bridle*, Khalil Karimi* (*co-equal senior authors). (2019). The Functional Utility Of A Unique Subset Of Bone Marrow-Derived Dendritic Cells For Cancer Vaccines (poster presentation). Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

34. Robert Mould, J. van Vloten, C. Fink, A. Ross, M. Singh, L. Susta, A. Mutsaers, J. Petrik, G. Wood, S. Wootton, G. Dekaban, Byram W. Bridle*, Khalil Karimi* (*co-equal senior authors). (2019). IL-12-secreting Dendritic Cells That Do Not Produce TNF-? Are A Minor Component Of 'Dendritic Cell Cultures' But The Dominant Antigen Presenters (poster presentation). Ontario Veterinary College Graduate Student Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

35. Elaine Klafuric, Megan Strachan-Whaley, Lisa Santry, Amanda AuYeung, Jacob van Vloten, Robert Mould, Thomas McAusland, Khalil Karimi, Anthony Mutsaers, Sarah Wootton and Byram W. Bridle. (2019). Combining Decitabine with Oncolytic Virotherapy Preferentially Kills Acute Myeloid Leukemia Cells Via Lethal Oxidative Stress (oral presentation). Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

36. Jacob P. van Vloten, Joelle C. Ingrao, Robert C. Mould, Lisa A. Santry, Khalil Karimi, D. Grant McFadden, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). An ORF Virus-Infected Cell Vaccine Induces Innate and Adaptive Immune Responses Against Osteosarcoma Metastases Resulting in Long-Term Survival (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

37. Rghei, AD, Lieshout, LV, Shihua, H, Soule, G, Bridle, BW, Qui, X, and Wootton, SK. (2019). AAV-Mediated Expression of Monoclonal Antibodies for the Prevention of Marburg Virus Infection (poster). Annual Meeting of the American Society of Gene and Cell Therapy, Washington DC, United States of America
Main Audience: Researcher
Invited?: Yes, Keynote?: No

38. Robert Mould, J van Vloten, C Fink, L Chan, A Stegelmeier, M Singh, L Susta, A Mutsaers, J Petrik, G Wood, S Wootton, G Dekaban, Byram W. Bridle* and Khalil Karimi* (*co-equal senior authors). (2019). IL-12-secreting Dendritic Cells That Do Not Produce TNF-α Are A Minor Component Of 'Dendritic Cell Cultures' But The Dominant Antigen Presenters. Annual Scientific Meeting of the Canadian Cancer Immunotherapy Consortium (poster and 'speed talk' oral presentation), Toronto, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

39. Jason P. Knapp, Megan R. Strachan-Whaley, Elaine M. Klafuric and Byram W. Bridle. (2019). Combining Epigenetic Modifiers and Oncolytic Viruses to Treat Acute Leukemias throughout the Central Nervous System (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

40. Cristine J. Reitz, Faisal J. Alibhai, Tarak N. Khatua, Mina Rasouli, Byram W. Bridle, Thomas P. Burris and Tami A. Martino. (2019). Circadian Medicine: Targeting the Cardiac Inflammasome to Prevent Heart Failure. 2nd Southern Ontario Cardiovascular Research Association Annual Conference, York University, October 18, 2019, Toronto, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

41. Ashley A. Stegelmeier and Byram W. Bridle. (2019). Off-Target Infection of Stimulated T Cells by Vesicular Stomatitis Virus has Implications for Single- Versus Multi-Dosing Oncolytic Virotherapy Protocols. Annual Inter-Lab Retreat for the Canadian Oncolytic Virus Consortium, Elgin, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

42. Thomas McAusland, Jacob van Vloten, Lisa Santry, Joelle Ingrao, Matthew Guilleman, Rozanne Arulanandam, Pierre Major, Jean-Simon Diallo, Leonardo Susta, Khalil Karimi, Byram W. Bridle, Sarah Wootton. (2019). Viral Sensitizer-Mediated Enhancement of Oncolytic NDV Leads to Rapid Clearance of Primary Tumours in a Mouse Model of Melanoma (poster and oral presentations). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

43. Alicia Viloria-Petit, Geoffrey Wood, Anthony Mutsaers, Michelle Oblak, Brigitte Brisson, Byram Bridle, Paul Woods and David Pearl. (2019). DOGBONe: A Canine Research Platform for the Discovery of Reliable Biomarkers of Osteosarcoma Progression. Canadian Society for Molecular Biosciences, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

44. J Vloten, K Matuszewska, A Stegelmeier, L Santry, J Minott, T McAusland, E Klafuric, R Mould, K Karimi, G McFadden, J. Petrik, Byram W. Bridle*, and Sarah K. Wootton* *equal senior authors. (2019). ORF Virus as an Immunotherapy for Advanced-Stage Ovarian Cancers (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

45. Ashley A. Stegelmeier, Amanda W.K. AuYeung, Robert Mould, Thomas McAusland, Lisa Santry, Jacob van Vloten, Megan Whaley, Elaine Klafuric, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). Off-Target Infection of Stimulated T Cells by Vesicular Stomatitis Virus has Implications for Single- Versus Multi-Dosing Oncolytic Virotherapy Protocols (poster and oral presentations). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

46. R Mould, J van Vloten, C Fink, L Chan, A Ross, M Singh, L Susta, A Mutsaers, J Petrik, G Wood, S Wootton, G Dekaban, Byram W. Bridle* and Khalil Karimi* *equal senior authors. (2019). IL-12-Secreting Dendritic Cells that do not Produce TNF-α are a Minor Component of 'Dendritic Cell Cultures' but the Dominant Antigen Presenters (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

47. Jacob P. van Vloten, Lisa A. Santry, Elaine M. Klafuric, Thomas M. McAusland, Khalil Karimi, Grant McFadden, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). Quantifying T-Cell and Antibody Responses Induced by Antigen-Agnostic Immunotherapies (poster presentation). Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

48. Ashley A. Ross, Wing Ka Amanda AuYeung, Jim J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2018). Elucidating Infection of Stimulated Leukocytes by Oncolytic Viruses (poster presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

49. Elaine Klafuric, M. Strachan-Whaley, L. Santry, A. AuYeung, J. van Vloten, R. Mould, T. McAusland, M.E. Clark, J. Minott, S. Holtz, J. Saturno, K. Karimi, A. Mutsaers, S. Wootton and Byram W. Bridle. (2018). Combining Decitabine with Oncolytic Virotherapy Preferentially Kills Acute Leukemia Cells Via Lethal Oxidative Stress (oral and poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

50. Robert Mould, Jacob P. Van Vloten, Anthony Mustaers, James J. Petrik, Leonardo Susta, Geoffrey Wood, Sarah K. Wootton, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2018). A Systematic Analysis of the Functional Utility of Bone Marrow-Derived Dendritic Cells as a Vaccine: Comparing Several Common Culturing Protocols (poster presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

51. Robert Mould, Jacob P. Van Vloten, Anthony Mustaers, James J. Petrik, Leonardo Susta, Geoffrey Wood, Sarah K. Wootton, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2018). A Systematic Analysis of the Functional Utility of Bone Marrow-Derived Dendritic Cells as a Vaccine: Comparing Several Common Culturing Protocols (poster presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

52. Maedeh Darzianiazizi (aka Mahi Azizi), Robert C. Mould, Jacob P. van Vloten, Ashley A. Ross, Shayan Sharif, Ravi Kulkarni, Byram W. Bridle* and Khalil Karimi* (*co-senior authors). (2018). Upregulation of Programmed Death Ligand-1 (PDL-1) on Neutrophils in Response to Recombinant Vesicular Stomatitis Virus (rVSV?m51) Infection (oral and poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

53. Jacob P van Vloten, Robert C Mould, Joelle C Ingrao, James J Petrik, Grant McFadden, Sarah K Wootton and Byram W Bridle. (2018). An Orf Virus-Infected Cell Vaccine Elicits Long-Term Survival in an Osteosarcoma Lung Metastasis Model Through NK Cell Activity (poster and oral presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

54. Jacob P. van Vloten, Robert Mould, Mary Ellen Clark, Arthane Kodeeswaran, Katrina Geronimo, Julia De Carvalho Nakamura, Julia Saturno, Grant McFadden, James Petrik, Sarah Wootton and Byram W. Bridle. (2018). Pyrexia Impedes Oncolytic Rhabdovirus-Mediated Therapy (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

55. Samantha Holtz, Megan Strachan-Whaley, Mary-Ellen Clark, Robert Mould, Lisa Santry, Thomas McAusland, Sarah K. Wootton, Khalil Karimi and Byram W. Bridle. (2018). Combining Oncolytic Virotherapy with Epigenetic Modifiers to Treat Lymphomas (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

56. Megan R. Strachan-Whaley, Julia Saturno, Wing Ka Amanda AuYeung, Jacob P. vanVloten, Anthony Mutsaers, Sarah K. Wootton and Byram W. Bridle. (2018). Combining Decitabine with Oncolytic Viruses to Kill Acute Leukemias by Oxidative Stress (poster and oral presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

57. Maedeh Darzianiazizi (aka Mahi Azizi), Robert C. Mould, Jacob Van Vloten, Ashley Ross, Shayan Sharif, Ravi Kulkarni, Byram W. Bridle and Khalil Karimi. (2018). Innate Immune Responses to Recombinant Vesicular Stomatitis Virus: the Role of Type I Interferon Signaling and Neutrophils (poster presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

58. Maedeh Darzianiazizi (Aka Mahi Azizi), Robert C. Mould, Jacob Van Volten, Ashley Ross, Shayan Sharif, Ravi Kulkarni, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2018). Innate Immune Responses to Recombinant Vesicular Stomatitis Virus: Immunosuppressive Neutrophils (poster presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

59. Robert Mould, Mankerat Singh, Jacob van Vloten, Ashley Ross, Leonardo Susta, Anthony Mutsaers, James Petrik, Geoffrey Wood, Sarah Wootton, Byram W. Bridle* and Khalil Karimi* (*co-senior authors). (2018). Analyzing The Functional Utility Of Bone Marrow-Derived Dendritic Cells As A Cancer Vaccine: Investigation Of A Unique IL-12-Producing DC Subset (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

60. Jacob P. van Vloten, Robert Mould, Mary Ellen Clark, Arthane Kodeeswaran, Katrina Geronimo, Julia De Carvalho Nakamura, Julia Saturno, Grant McFadden, James Petrik, Sarah Wootton and Byram W. Bridle. (2018). Pyrexia Impedes Oncolytic Rhabdovirus-Mediated Therapy (oral presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

61. J. Paul Woods, Byram Bridle, Michelle Oblak, Robert Foster, Geoffrey Wood, Victoria Sabine, Jeff Hummel and Brian Lichty. (2018). Novel Oncolytic Maraba virus for the Adjuvant Treatment of Feline Mammary Carcinoma (poster presentation). Veterinary Cancer Society: Immunotherapy Workshop, Anchorage, United States of America
Main Audience: Researcher
Invited?: Yes, Keynote?: No

62. Jacob P van Vloten, Robert C Mould, Joelle C Ingrao, James J Petrik, Grant McFadden, Sarah K Wootton and Byram W Bridle. (2018). An Orf Virus-Infected Cell Vaccine Elicits Long-Term Survival in an Osteosarcoma Lung Metastasis Model Through NK Cell Activity (oral presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

63. Ashley A. Ross, Amanda W.K. AuYeung, Robert Mould, Thomas McAusland, Lisa Santry, Jacob van Vloten, Megan Strachan-Whaley, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2018). Infection of Stimulated Leukocytes by Oncolytic Viruses: Implications for Single- Versus Multi-Dosing Protocols (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

64. Lisa A. Santry, Jacob P. van Vloten, Robert C. Mould, Amanda W.K. AuYeung, Thomas M. McAusland, Byram W. Bridle* and Sarah K. Wootton* (*co-senior authors). (2018). Recombinant Newcastle Disease Viruses Expressing Checkpoint Inhibitors Induce a Proinflammatory State and Enhance Tumor-Specific Immune Responses in Two Syngeneic Mouse Models of Cancer (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

65. Ashley Ross, Amanda AuYeung, Robert Mould, Thomas McAusland, Jim Petrik, Sarah Wootton and Byram Bridle. (2018). Infection of Stimulated Leukocytes by Oncolytic Viruses: Implications for Single- Versus Multi-Dosing Protocols (oral presentation). Graduate Student Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

66. Thomas M. McAusland, Jacob P. van Vloten, Lisa A. Santry, Joelle C. Ingrao, Matthew Guilleman, Rozanne Arulanandam, Jean-Simon Diallo, Leo Susta, Khalil Karimi, Byram W. Bridle and Sarah K. Wootton. (2018). Enhancement of NDV-Mediated Oncolysis and Tumor Regression Through the Addition of Small Molecule Viral Sensitizers (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

67. Jessica Minott, Robert Mould, Mary Ellen Clark, Khalil Karimi and Byram W. Bridle. (2018). Assessing the Impact of Estrogen Receptor Signaling on the Efficacy of Oncolytic Viruses (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

68. Megan R. Strachan-Whaley, Amanda W.K. AuYeung, Jacob P. vanVloten, Julia Saturno, Lisa A. Santry, Thomas M. McAusland, Robert C. Mould, Anthony J. Mutsaers, Sarah K. Wootton and Byram W. Bridle. (2018). Decitabine Increases the Sensitivity of Leukemias to Oncolytic Viruses Through the Induction of Oxidative Stress (poster presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

69. Ashley A. Ross, Wing Ka Amanda AuYeung, Thomas McAusland, Lisa Santry, Jim J. Petrik, Sarah K. Wootton, Byram W. Bridle. (2018). Elucidating Infection of Stimulated Leukocytes by Oncolytic Viruses (oral presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

70. Li Deng, Robert C. Mould, Julia Kim, Wing Ka Amanda AuYeung, Byram W. Bridle. (2017). Construction and Validation of a Novel Vaccine for the Treatment of Canine Melanomas (poster presentation). Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

71. Li Deng, Robert C. Mould, Julia Kim, Wing Ka Amanda AuYeung, Byram W. Bridle. (2017). Construction and Validation of a Novel Vaccine for the Treatment of Canine Melanomas (poster presentation). 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

72. Kathy Matuszewska, Lisa Santry, Byram Bridle, Sarah K. Wootton, Jack Lawler, Jim Petrik. (2017). Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

73. Julia Saturno, Jacob van Vloten, Lisa Santry, Robert Mould, Sarah Wootton, Byram Bridle. (2017). Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

74. Megan Strachan-Whaley and Byram W. Bridle. (2017). Combining Oncolytic Viruses With Epigenetic Modifiers in Leukemia. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

75. Mankerat Singh, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2017). Differentiating Dendritic Cells in the Presence of Interleukin-4 to Enhance their Potential as Vaccines (poster presentation; won first place in the undergraduate student category). Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

76. (2017). Cancer Biotherapies: Lessons Learned from Translational Research. RGE Murray Seminar Series, Western University, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: Yes

77. Megan Rae Strachan-Whaley, Amanda AuYeung, Julia Saturno, Lisa Santry, Byram W. Bridle. (2017). Decitabine Increases the Sensitivity of Acute Leukemic Cells to Oncolytic Viruses (poster and speed-talk presentations). 2017 Annual Scientific Meeting of the Terry Fox Research Institute November 4, 2017, Vancouver, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: Cancer Research Society (The) - PIN #19046; Terry Fox Research Institute (TFRI) - Project #1041

78. Megan Rae Strachan-Whaley, Amanda AuYeung, Julia Saturno, Lisa Santry, Byram W. Bridle. (2017). Decitabine Increases the Sensitivity of Acute Leukemic Cells to Oncolytic Viruses (poster presentation). Canadian Cancer Research Conference November 5-7, 2017, Vancouver, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: Cancer Research Society (The) - PIN #19046; Terry Fox Research Institute (TFRI) - Project #1041

79. Amanda WK AuYeung, Robert C. Mould, Jacob van Vloten, Mahi Azizi, Lisa Santry, Sarah K. Wootton, J. Paul Woods, Geoffrey Wood, James Petrik, Khalil Karimi and Byram W. Bridle. (2017). Virus-Induced Leukopenia: Challenging the Cell Trafficking Paradigm During Oncolytic Virotherapy. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

80. Anthony Mutsaers, Byram W. Bridle, Brigitte Brisson, Michelle Oblak, Alicia Viloria-Petit, Geoffrey Wood and Paul Woods. (2017). Naturally-Occurring Bone Cancers in Pet Dogs as a Model of Human Osteosarcomas (poster presentation). Cancer Bone Society Annual Scientific Meeting, Indianapolis, United States of America
Main Audience: Researcher
Invited?: Yes, Keynote?: No

81. Jacob van Vloten, Mary Ellen Clark, Arthane Kodeeswaran, Katrina Geronimo, Julia De Carvalho, Julia Saturno, Rob Mould, Grant McFadden, James Petrik, Sarah Wootton and Byram W. Bridle. (2017). Simulated Pyrexia Attenuates Rhabdovirus-Mediated Oncolysis of Cancer Cells. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

82. Maedeh Darzianiazizi, Katrina Allison, Byram Bridle* and Khalil Karimi* *co-senior authors. (2017). Sex Disparity in Innate Immune Responses to Recombinant Vesicular Stomatitis Virus: the Role of Type I Interferon Signaling and Neutrophils. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

83. Mankerat Singh, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2017). Differentiating Dendritic Cells in the Presence of Interleukin-4 to Enhance Their Potential as Vaccines. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

84. Megan Strachan-Whaley, Amanda AuYeung, Lisa Santry, Tony Mutsaers, Sarah Wootton, Byram Bridle. (2017). A Combination of Oncolytic Viruses and Epigenetic Modifiers as a Novel Therapy for Acute Leukemias. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

85. R. Mould, A. AuYeung, J. van Vloten, D. Yu, L. Zhang, A. Pelin, J. Bell, Y. Wan, K. Karimi, L. Susta, J. Petrik, A. Mutsaers, G. Wood, S. Wootton and Byram W. Bridle. (2017). Clodronate-Mediated Depletion of Marginal Zone Macrophages Potentiates Rapid Induction of Tumour-Specific T Cell Responses by Oncolytic Virus Booster Vaccines. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

86. Lisa A. Santry, Amanda AuYeung, Thomas M. McAusland, Jacob P. van Vloten, Rob C. Mould, Kathy Matuszewska, Byram W. Bridle , James J. Petrik, Sarah K. Wootton. (2017). Evaluating the Therapeutic Potential of Oncolytic Newcastle Disease Virus in Mouse Models of Melanoma and Colon Carcinoma. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

87. Amanda WK AuYeung, Robert C. Mould, Jacob van Vloten, Mahi Azizi, Lisa Santry, Sarah K. Wootton, J. Paul Woods, Geoffrey Wood, James Petrik, Khalil Karimi and Byram W. Bridle. (2017). Virus-Induced Leukopenia: Challenging the Cell Trafficking Paradigm During Oncolytic Virotherapy. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

88. Kathy Matuszewska, Lisa Santry, Byram Bridle, Sarah K. Wootton, Jack Lawler, Jim Petrik. (2017). Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

89. Maedeh Darzianiazizi, Katrina Allison, Khalil Karimi, Byram Bridle. (2017). Sex Disparity in Innate Immune Responses to Recombinant Vesicular Stomatitis Virus: The Role of Type I Interferon Signaling and Neutrophils. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

90. Presented by: Allison K Co-authors: Karimi K, Bridle BW. (2016). Gender Disparity in Innate Immune Responses to Viral Infection: The Role of Type I Interferon. Ontario Veterinary College - Career Opportunities and Research Experience Program (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

Funding Sources: Natural Sciences and Engineering Research Council of Canada (NSERC) - 436264-2013

91. Presenter: Strachan-Whaley M Co-authors: AuYeung WA, Santry L, Mutsaers A, Wootton SK, Bridle BW. (2016). Sensitization of Leukemic Cells to Oncolytic Viruses Using Epigenetic Modifiers. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: Cancer Research Society (The) - 19046

92. Presenter: AuYeung WA Co-authors: Mould R, Woods JPI, Wood G, Petrik J, Bridle BW. (2016). Mechanisms That Allow Oncolytic Viral Replication Inside a Tumour Despite Pre-Existing Immunity Against a Virus-Encoded Antigen. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3

93. Presenter: Matuszewska K Co-authors: Santry L, Bridle BW, Wootton S, Petrik JJ. (2016). Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer. Summit for Cancer Immunotherapy (podium and poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

94. Presenter: de Carvalho J Co-authors: van Vloten J, Bridle BW. (2016). The Impact of Temperature on the Oncolytic Activity of Viruses. Ontario Veterinary College - Career Opportunities and Research Experience Program (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

    Funding Sources: Cancer Research Society (The) - 19046

95. Presenter: Deng L Co-authors: Kim J, Mould RC, van Vloten J, AuYeung WA, Desai M, Bridle BW. (2016). From Mice to Humans Via Dogs: Development of a Novel Biotherapy for Osteosarcomas. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: Terry Fox Research Institute (TFRI) - 1041

96. Katrina Geronimo, Mary Ellen Clark, Arthane Kodeeswaran, Glen Kim and Byram Bridle. (2016). Hypoxia Variably Affects Oncolytic Virus Efficacy While Potentiating the Growth of Human Cervical Cancer Cells. Sanofi Biogenius Canada, Ontario - Greater Toronto Poster Competition, Toronto, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

97. (2016). Career Night (small group meetings with academic trainees to discuss aspects of a career as a faculty member). A career night hosted by the Faculty of Health Sciences PDF Association at McMaster University, Hamilton, ON. This was open to all trainees at McMaster University and other regional universities (there were attendees from U. of Waterloo and Guelph), Hamilton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

98. Presenter: AuYeung WA Co-authors: Mould R, Woods JP, Wood G, James P, Bridle BW. (2016). Mechanisms that Allow Oncolytic Viral Replication Inside a Tumour Despite Pre-Existing Immunity Against a Virus-Encoded Antigen (podium and poster presentation). Summit for Cancer Immunotherapy, Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3

99. Presenter: Desai M Co-authors: van Vloten J, Santry L, Bridle BW. (2016). Evaluating the Impact of Temperature on the Oncolytic Potential of Viruses In Canine and Murine Osteosarcoma Cells. Ontario Veterinary College - Career Opportunities and Research Experience Program (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

Funding Sources: Terry Fox Research Institute (TFRI) - 1041

100. Presenter: Woods JP Co-authors: Bridle BW, Oblak M, Foster R, Sabine V, Skowronski K, Hummel J, Lichty B. (2016). Novel Oncolytic Maraba Virus for the Adjuvant Treatment of Feline Mammary Carcinoma. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

101. (2016). Cancer Biotherapies: Lessons Learned from Translational Research. Department of Molecular and Cellular Biology Seminar Series, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: Yes

102. Presenter: Strachan-Whaley M Co-authors: AuYeung WA, Santry L, Mutsaers A, Bienzle D, Wootton SK, Bridle BW. (2016). Sensitization of Leukemic Cells to Oncolytic Viruses Using Epigenetic Modifiers. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Cancer Research Society (The) - 19046

103. Presenter: Woods JP Co-authors: Bridle BW, Bienzle D, Delay J, Morrison A, Cieplak M, Hummel J, Lichty B. (2016). A Safety Assessment of a Novel Oncolytic Maraba Virus in Cats. American College of Veterinary Internal Medicine Forum (poster presentation), Denver, United States of America
Main Audience: Researcher
Invited?: Yes, Keynote?: No

104. Presenter: Mould R Co-authors: AuYeung WA, Wood G, Wootton SK, Susta L, Petrik JJ, Mustaers A, Bridle BW. (2016). Increasing the Magnitude of Tumour-Specific T Cell Responses by Spreading a Vaccine Dose Across Multiple Injection Sites. Summit for Cancer Immunotherapy (podium and poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Terry Fox Research Institute (TFRI) - 1041

105. Presenter: Deng L Co-authors: Kim J, Mould RC, van Vloten J, AuYeung WA, Bridle BW. (2016). From Mice to Humans Via Dogs: Development of a Novel Biotherapy for Osteosarcomas. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Terry Fox Research Institute (TFRI) - 1041

106. Presenter: Santry L Co-authors: van Vloten JP, Matuszewska K, Bridle BW, Petrik JJ, Wootton SK. (2016). Recombinant Newcastle Diease Virus as an Oncolytic Therapy for Ovarian and Prostate Cancers. American Society of Gene and Cell Therapy Annual Meeting (poster presentation), Washington, United States of America
Main Audience: Researcher
Invited?: Yes, Keynote?: No

107. Presenter: Ingrao J Co-authors: Shapiro K, de Jong J, van Vloten J, Barta JR, Menzies PI, Bridle BW, Wootton SK. (2016). Development of a Vaccine Against Parasitic Abortion in Sheep. OMAFRA/Rural Policy Learning Commons 2016 Product Development Research Day, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

108. Arthane Kodeeswaran, Mary Ellen Clark, Katrina Geronimo, Glen Kim and Byram W. Bridle. (2016). The Effect of Temperature on the Efficacy of Oncolytic Viruses in Human Cervical Cancer Cells (awarded 3rd place). Sanofi Biogenius Canada, Ontario - Greater Toronto Poster Competition, Toronto, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

109. Presenter: van Vloten J Co-authors: Clark M, Geronimo K, Kodeeswaran A, Santry L, Mould RC, McFadden G, Petrik JJ, Wootton SK, Bridle BW. (2016). Fever-Grade Temperatures Attenuate Rhabdovirus-Mediated Oncolysis of Cancer Cells. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: Cancer Research Society (The) - 19046

110. Presenter: Saturno J Co-authors: van Vloten J, Santry L, Bridle BW. (2016). Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas. Ontario Veterinary College - Career Opportunities and Research Experience Program (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

    Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3

111. Presenter: Mould RC Co-authors: AuYeung WA, Wood G, Wootton SK, Susta L, Petrik JJ, Mustaers A, Bridle BW. (2016). Increasing the Magnitude of Tumour-Specific T Cell Responses by Spreading a Vaccine Dose Across Multiple Injection Sites. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: Terry Fox Research Institute (TFRI) - 1041

112. Presenter: Saturno J Co-authors: van Vloten J, Santry L, Bridle BW. (2016). Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas. 2016 Merial NIH National Veterinary Scholars Symposium (poster presentation), Columbus, United States of America
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3

113. Presenter: AuYeung WA Co-authors: Spangler-Forgione H, Woods JP, Petrik JJ, Wood G, Bridle BW. (2016). Suppression of Oxygen Reactive Species Decreases Melanogenesis Resulting in Melanomas with Reduced Immunogenicity. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3

114. Presenter: van Vloten J Co-author: Bridle BW. (2016). Fever-Grade Temperatures Attenuate Rhabdovirus-Mediated Oncolysis of Cancer Cells. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium (podium presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: Cancer Research Society (The) - 19046

115. Poster presented by: AuYeung WKA Co-authors: Mould RC, Kim J, Spangler H, Bridle BW. (2015). Mechanisms that Allow Oncolytic Viral Replication Inside a Tumour Despite Pre-Existing Immunity Against a Virus-Encoded Antigen. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

116. Presenter: Matuszewska K Co-authors: Santry L, Petrik J, Bridle BW, Wootton SK. (2015). Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

117. Presenter: AuYeung WA Co-authors: Mould RC, Spangler H, Kim J, Bridle BW. (2015). Mechanisms that Allow Oncolytic Viral Replication Inside a Tumor Despite Pre-Existing Immunity Against a Virus-Encoded Antigen. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3

118. Talk given by: Santry LA Co-authors: van Lieshout L, Au Yeung WKA, Bridle BW, Wootton SK. (2015). Manipulation of Akt Isoform Expression Levels and Their Effect on Transformation by the Jaagsiekte Sheep Retrovirus Envelope Protein. Workshop #22: Retroviruses II, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

119. Poster presented by: Spangler H* Co-authors: van Vloten J*, Wootton SK, Viloria-Petit A, Bridle BW. (2015). Par6 Influences the Susceptibility of Mammary Carcinoma Cells to Oncolytic Viruses. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

120. Poster presented by: Rasiuk A* Co-authors: Walsh S*, Bridle BW. (2015). The Necessity of the Type I Interferon Receptor in Regulating Cytokines Produced Upon Viral Infection. Poster Session #35: Viruses and Innate and Acquired Immunity, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

121. (2015). Companion Animal Cancer Biotherapies. The Hamilton Academy of Veterinary Medicine, Hamilton, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes

122. Presenter: Mould R Co-authors: Kim J, Walsh S, de Jong J, Wood G, Wootton S, Susta L, Petrik J, Mutsaers A, Bridle BW. (2015). Combining Virotherapy with Immunotherapy to Treat Osteosarcoma in a Preclinical and Clinical Model. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Terry Fox Research Institute (TFRI) - 1041

123. Poster presented by: van Vloten JP* Co-authors: Ingrao J, Mould RC*, Bridle BW, Wootton SK. (2015). Assessing the Oncolytic Potential of ORFV Strains In Vitro. Poster Session #12: Oncolytic Viruses and Gene Therapy, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

124. Presenter: van Vloten J Co-authors: Wootton S, Bridle BW. (2015). Harnessing Immunogenic Cell Death to Potentiate Anti-Cancer Efficacy During ORFV-Induced Oncolysis. Ontario Veterinary College Graduate Student Research Symposium (podium presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Cancer Research Society (The) - 19046

125. Poster presented by: Strachan-Whaley MR* Co-authors: AuYeung A*, Kim J*, Bienzle D, Wootton SK, Bride BW. (2015). Using Viruses to Potentiate Epigenetic Modifier-Mediated Killing of Leukemic Cells. Poster Session #12: Oncolytic Viruses and Gene Therapy, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

126. Presenter: Ingrao J Co-authors: van Vloten J, Shapiro K, Barta J, Menzies P, Bridle BW, Wootton S. (2015). Development of Orf Virus (Parapoxvirus ovis) as a Multivalent Viral Vector Platform Against Toxoplasma gondii. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

127. Talk given by: Kozak RA Co-authors: Hattin L*, Biondi MJ, Walsh S*, Morgenstern J*, Lusty E*, Chereponov V, McBey B-A, Leishman DP, Feld JJ, Bridle BW, Nagy É. (2015). In Vitro Oncolytic Activity of a Novel Orthoreovirus Against Hepatocellular Carcinoma. Workshop #43: Oncolytic Viruses, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

128. Poster presented by: Kim J Co-authors: AuYeung A, Deng L, Mould RC, Bridle BW. (2015). Assessment of the Potential to Treat Canine Cancers with an Oncolytic Vaccine. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

129. Presenter: Strachan-Whaley M Co-authors: AuYeung WA, Kim J, Bienzle D, Mutsaers A, Wootton S, Bridle BW. (2015). Combining Oncolytic Viruses with Epigenetic Modifiers as a Novel Therapy for Leukemia. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

    Funding Sources: Cancer Research Society (The) - 19046

130. (2015). Canine Osteosarcoma Biotherapy: Revolutionizing How Bone Cancers are Treated in Humans. Valérie's Flutter Foundation Gala Dinner, Ottawa, Canada
Main Audience: General Public
Invited?: Yes, Keynote?: Yes

131. Hattin, L.*, Kozak, R., & Bridle, B. W. (2014). Investigation of Recombinant NDV as an Oncolytic Therapy for Prostate Tumors. Poster presented by summer student Larissa Hattin. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

132. Mould, R.*, Walsh, S.*, van Vloten, J.*, Wootton, S., & Bridle, B. W. (2014). Combining Antigen Presenting Cell-Based Vaccination with Oncolytic Viruses for the Treatment of Prostate Cancer Poster presented by summer student Robert Mould (awarded 3rd place).Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

133. Kim, J.*, Walsh, S.*, & Bridle, B. W. (2014). Screening Canine Melanoma and Osteosarcoma Specimens for Putative Tumour-Associated Antigen Expression. Poster presented by summer student Julia Kim. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

134. van Vloten, J.*, de Jong, J.*, Rasiuk, A.*, Bridle, B. W., & Wootton, S. (2014). The Generation of Immune-Modulatory Gene-Knockout Orf Virus Recombinants for Use in Oncolytic Virotherapy Poster presented by Jacob Van Vloten. International Union of Microbiological Societies, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

135. Kozak, R., Hattin, L.*, Yeung, W. A., Lusty, E.*, Leishman, D., J. Feld, B. W. Bridle, E. Nagy. (2014). A Novel Orthoreovirus as a Potential Therapeutic for Hepatocellular Carcinoma Talk given by Robert Kozak. International Union of Microbiological Societies, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

136. Talan, M.*, Tin, B.*, Ternamian, C.*, Syed, Z.*, & Bridle, B. W. (2014). The Effects of Quercetin and Kaempferol on the Cytotoxicity of Carboplatin and Entinostat on Various Cancer Cell Lines Poster presented by Micaella Talan and Brittney Tin. Sanofi BioGENEius Challenge Canada, Toronto, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

137. Ternamian, C.* & Bridle, B. W. (2014). Oncolytic Rhabdoviruses in Combination with Histone Deacetylase Inhibition Synergistically Kill Murine B Lymphoblastic Leukemia Cells Talk given by Christian Ternamian. Institute for Comparative Cancer Investigation 7th Annual Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

138. Santry, L., Yeung, W. A.*, Bridle, B. W., & Wootton, S. (2014). Function of Akt Isoforms in Transformation by the Jaagsiekte Sheep Retrovirus Envelope Protein Talk given by Lisa Santry. International Union of Microbiological Societies, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

139. Kozak, R., Hattin, L.*, Feld, J., Ackford, J., Nagy, E., B. W. Bridle. (2014). Oncolytic Viruses as Therapy for Hepatocellular Carcinoma Poster presented by Robert Kozak. National CIHR Research Training Program in Hepatitis C, 3rd Canadian Symposium on HepC Virus, Toronto, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

140. Syed, Z.*, Walsh, S.*, & Bridle, B. W. (2014). Treating High-Grade Glioma with Oncolytic Virotherapy and Histone Deacetylase Inhibitors Poster presented by Zafir Syed. Institute for Comparative Cancer Investigation 7th Annual Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

141. Walsh, S.*, Rasiuk, A.*, & Bridle, B. W. (2014). Negative Regulation of Cytokine Expression by Type One Interferon Signaling in VSV Infection Poster presented by Scott Walsh. International Union of Microbiological Societies, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

142. Van Vloten, J.*, de Jong, J.*, Rasiuk, A.*, Bridle, B. W., & Wootton, S. (2014). The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy. Poster presented by summer student Jacob Van Vloten. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

143. (2014). Treating Feline Mammary Carcinoma With an Oncolytic Vaccine: Companion Animal Trials as a Stepping Stone Towards Successful Translation into Human Patients. Cancer Grand Rounds at Western University, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

144. (2013). A Novel Barrier to Cancer Immunotherapy in the Brain. Talk in the speed-poster session of the 6th annual meeting of the Canadian Cancer Immunotherapy Consortium; plus a poster presentation., Toronto, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

145. Poster presentation by my MSc student, Zafir Syed* Co-author: B. Bridle. (2013). Oncolytic Immunotherapy for the Treatment of High-Grade Glioma. Graduate Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

146. A poster presented by my MSc student, Christian Ternamian* Co-author: B. Bridle. (2013). Synergizing Oncolytic Virotherapy and HDAC Inhibition in a Murine Model of B-Cell Lymphoblastic Leukemia. Graduate Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

147. This was a talk given by my fourth-year research project student, Evan Lusty* Co-author: B. Bridle. (2013). Characterizing Oncolytic Viruses, Toll-Like Receptor Ligands and Histone Deacetylase Inhibitors in the In Vitro Treatment of Human Prostate Cancer. 6th Annual Cancer Research Symposium, Institute for Comparative Cancer Investigation, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

148. (2013). Tumour Immunology. Seminar presentation in the Cancer Biology rounds, Clinical Oncology Group, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

149. A poster presented by my undergraduate research assistant, Wing Ka Au Yeung* Co-author: B. Bridle. (2013). Development of a Flow Cytometry-Based Immunological Assay to Support Pre-Clinical and Clinical Companion Animal Cancer Trials. Ontario Veterinary College's Summer Leadership and Research Program, poster presentations., Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

150. Poster presentation by my undergraduate research associate, Evan Lusty* Co-presenter: Jason Morgenstern* Co-author: B. Bridle. (2012). Establishment of Leukemia/Lymphoma Cell Lines from Clinical Specimens and Evaluation of Their Susceptibility to Oncolytic Viruses.Summer Leadership and Research Program, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

151. (2012). Replication-Deficient Adenovirus and Oncolytic Rhabdoviruses as Cancer Vaccines. Keynote speaker at symposium entitled "Viral delivery and nanoparticle vectors" organized by students in Molecular Virology (MICR*4330) course, University of Guelph., Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: Yes, Competitive?: No

152. (2012). Paradoxically, Immunotherapy Might be More Efficacious When Tumours are Inside the Brain. Plenary talk at the "Modelling Cancer In Vivo, In Vitro and In Silico" session of the Institute for Comparative Cancer Investigation 4th Annual Cancer Research Symposium, University of Guelph., Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes

153. Poster presentation by my undergraduate research assistant, Jason Morgenstern* Co-presenter: Evan Lusty* Co-author: B. Bridle. (2012). Using an Innate Anti-Viral Immune Response in the Presence of a Histone Deacetylase Inhibitor to Treat Leukemias. Summer Leadership and Research Program, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

154. (2012). Using Oncolytic Viruses to Potentiate Immunotherapy for Childhood Cancers. Talk given at the Canadian Oncolytic Virus Consortium Annual Meeting, Lake Cecebe, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

155. Poster presentation by B. Bridle Co-authors: Chantal Lemay, Jean-Simon Diallo, Lan Chen, Jonathan Pol, Andrew Nguyen, Jonathan Bramson, John Bell, Brian Lichty and Yonghong Wan. (2011). A Histone Deacetylase Inhibitor Dramatically Improves the Therapeutic Index of an Oncolytic Vaccine by Augmenting Anti-Tumour Activity While Inhibiting Autoimmune Sequellae. CIHR New Principal Investigators Meeting, Toronto, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

156. Poster presentation by Jonathan Pol Co-authors: Byram Bridle, Liang Zhang, Stephen Hanson, Natasha Kazdhan, Jonathan Bramson, David Stojdl, Yonghong Wan, Brian Lichty. (2011). Maraba virus: a new vector for oncolytic viro-immunotherapy.6th International Conference on Oncolytic Viruses as Cancer Therapeutics, Las Vegas, United States of America
Main Audience: Researcher
Invited?: No, Keynote?: No

157. Poster presentation by Jonathan Pol Co-authors: Byram Bridle, Liang Zhang, Stephen Hanson, Natasha Kazdhan, Jonathan Bramson, David Stojdl, Yonghong Wan, Brian Lichty. (2011). Maraba virus: a new vector for oncolytic viro-immunotherapy.14th Annual Meeting of the Translational Research Cancer Centers Consortium, Seven Springs, United States of America
Main Audience: Researcher
Invited?: No, Keynote?: No

158. (2011). Oncolytic Vaccines: the Billion Dollar Idea. Seminar Series, Ottawa Hospital Research Institute, Ottawa, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

159. (2011). A Histone Deacetylase Inhibitor Dramatically Improves the Therapeutic Index of an Oncolytic Vaccine by Augmenting Anti-Tumour Activity While Inhibiting Autoimmune Sequella. Talk given in the concurrent symposium "Personalized Medicine: From Discovery and Validation to Implementation", 1st Annual Canadian Cancer Research Conference., Toronto, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes

160. (2011). Rapid and Massive Boosting of Tumour-Specific T Cells by Targeting Antigen Presentation to Follicular B Cells. Concurrent session, 14th Annual Meeting of the Translational Research Cancer Centers Consortium., Seven Springs, United States of America
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes

161. (2011). Immunoediting and Immunotherapy of Cancers. Seminar presentation in the Cancer Biology rounds, Clinical Oncology Group, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

162. (2010). Antigen Presentation by B Cells Maximizes Secondary T Cell Number and Quality: Implications for Booster Vaccines. 1st Annual McMaster University Faculty of Health Sciences Post-Doctoral Research Day (received award for best presentation), Hamilton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes

163. Poster presented by Liang Zhang. Co-authors: Byram Bridle, Jonathan Pol, Allison Rosen, Jonathan Bramson, Brian Lichty, Yonghong Wan. (2010). Virus infected B cells are potent antigen presenting cells.3rd Annual Cancer Immune Therapy Symposium, Niagara Falls, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

164. Poster presented by Stephen Hanson. Co-authors: Byram Bridle and Brian Lichty. (2010). The placenta specific gene Plac1 is a potential target for therapeutic cancer vaccines.Ontario Institute for Cancer Research Annual Meeting, Alliston, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

165. Additional co-chair: Tommy Alain, McGill University. (2010). Improving the Therapeutic Index of Cancer Immunotherapy With A Histone Deacetylase Inhibitor Also, was the session co-chair, leading a discussion on the viro- vs. immune-centric approach to oncolytic virotherapy.Ontario Regional Biotherapeutics Program, 2nd Annual Scientific Retreat, Haliburton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

166. (2010). Fine-Tuning Oncolytic Immunovirotherapy With A Histone Deacetylase Inhibitor. Meeting of the Canadian Oncolytic Virus Consortium, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

167. Oral presentation by Brian Lichty. Co-authors: Byram Bridle, K. Stephenson, J. Boudreau, S. Koshy, N. Kazdhan, E. Pullenayegum, J. Brunellière, J. Bramson and Y. Wan. (2010). Potentiating cancer immunotherapy using an oncolytic virus.4th European Congress of Virology, Cernobbio, Italy
Main Audience: Researcher
Invited?: Yes, Keynote?: No

168. Poster presented by Jonathan Pol. Co-authors: Byram Bridle, Natasha Kazdhan, Jonathan Bramson, David Stojdl, Yonghong Wan, Brian Lichty. (2010). Maraba virus: a new oncolytic vaccine vector.Ontario Institute for Cancer Research Annual Meeting, Alliston, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

169. (2010). Antigen Presentation by B Cells Maximizes Secondary T Cell Number and Quality: Implications for Booster Vaccines. 1st session, 3rd Annual Meeting of the Canadian Cancer Immunotherapy Consortium, Niagara Falls, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes

170. (2010). Fine-Tuning Oncolytic Immunovirotherapy with a Histone Deacetylase Inhibitor. Concurrent session, Annual Meeting, Ontario Institute for Cancer Research, Alliston, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes

171. Poster presented by Liang Zhang. Co-authors: Byram Bridle, Jonathan Pol, Allison Rosen, Jonathan Bramson, Brian Lichty, Yonghong Wan. (2010). Virus infected B cells are potent antigen presenting cells.23rd Annual Meeting of the Canadian Society for Immunology, Niagara Falls, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

172. (2009). Treating Brain Cancer with Immunotherapy and Oncolytic Viruses. Research Seminar Series, Central Animal Facility, McMaster University, Hamilton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

173. Poster Presentation by B. Bridle Co-authors: Kyle Stephenson, Jeanette Boudreau, Sandeep Koshy, Natasha Kazdhan, Jonathan Bramson, Brian Lichty and Yonghong Wan. (2009). Potentiating cancer immunotherapy using an oncolytic virus.McMaster Industry Liaison Office Innovation Showcase, Hamilton, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No

174. Jean-Simon Diallo, Ottawa Hospital Research Institute. (2009). Session Co-Chair; Led a discussion on: Combination Cancer Treatment Strategies. Ontario Regional Biotherapeutics Program, 1st Annual Scientific Retreat, Haliburton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

175. Poster presentation. Co-presenters: Kyle Stephenson, Jeanette Boudreau, Sandeep Koshy, Natasha Kazdhan, Jerome Brunellière, Jonathan Bramson, Brian Lichty B and Yonghong Wan. (2009). Embracing anti-viral immunity to make an oncolytic vector more effective.The 5th International Meeting on Replicating Oncolytic Virus Therapeutics, Banff, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

176. Poster Presentation by B. Bridle Co-authors: Ruby Chang, Brian Lichty, Shucui Jiang, jonathan Bramson and Yonghong Wan. (2009). Immunotherapy can reject intracranial tumour cells without overt damage to the brain despite sharing the target antigen.Ontario Institute for Cancer Research Annual Meeting, Alliston, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

177. Poster presentation given by Jeanette Boudrea. Co-authors: Kyle Stephenson, Patrick Palidino, Byram Bridle, Brian Lichty, Jonathan Bramson and Yonghong Wan. (2009). Activation of natural killer cells by dendritic cell vaccines is strongly influenced by maturation protocol and plays a key role in determining cancer therapeutic efficacy.Ontario Institute for Cancer Research Annual Meeting, Alliston, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

178. Oral presentation given by Brian Lichty. Co-authors: Byram Bridle, Kyle Stephenson, Jeanette Boudreau, Sandeep Koshy, Natasha Kazdhan, Jerome Brunellière, Jonathan Bramson and Yonghong Wan. (2009). Vaccinating against an oncolytic virus can enhance therapy.Plenary Session, The 5th International Meeting on Replicating Oncolytic Virus Therapeutics, Banff, AB, 2009, Banff, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

179. (2008). Combining Cancer Vaccination with Viral Oncolysis to Maximize Tumour Destruction. Ottawa Hospital Research Institute Seminar Series, Ottawa, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

180. (2008). Combining Immunological and Oncolytic Virotherapy to Treat Brain Cancer. Infection and Immunity Seminar Series, McMaster University, Hamilton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

Broadcast Interviews

2021/05/01	Since May 2021, I have engaged in ~150 additional media commitments related to COVID-19. (I have not had time to delineate the details of each of these service commitments but most are publicly available via internet searches)
2021/04/07	Decisions Made by the National Advisory Committee on Immunization Re: COVID-19 Vaccines, Interviewed by host Alex Pierson for the ON Point radio show, AM640 Toronto
2021/04/01	Transmission of SARS-CoV-2 Via Aerosols, Interviewed by host Arlene Bynaon for the ON Point radio show, AM640 Toronto
2021/03/25	COVID-19 Vaccine Hesitancy, Interviewed by host Alex Pierson for the ON Point radio show, AM640 Toronto
2021/03/23	Risk of Damage to Children's Immune Systems Due to Prolonged COVID-19 Policy-Mandated Isolation, Interviewed by host Alex Pierson for the ON Point radio show, AM640 Toronto

2021/03/16	Risk of Damage to Children's Immune Systems Due to Prolonged COVID-19 Policy-Mandated Isolation, Interviewed by host Mike Stubbs for Global News Radio London (980 CFPL).
2021/03/12	Risk of Damage to Children's Immune Systems Due to Prolonged COVID-19 Policy-Mandated Isolation, Interviewed by host Shayne Ganam for 770CHQR Global News, Calgary.
2021/03/12	Risk of Damage to Children's Immune Systems Due to Prolonged COVID-19 Policy-Mandated Isolation, Interviewed by host Alex South for Sputnik Radio in Edinburgh, Scotland
2021/03/11	A year of COVID-19 lockdown is putting kids at risk of allergies, asthma and autoimmune diseases, 570 News Talk Radio (Kitchener, Ontario, Canada) I was interviewed by host Brian Burke.
2021/03/11	A year of COVID-19 lockdown is putting kids at risk of allergies, asthma and autoimmune diseases, CTV National News Interviewed by Merella Fernandez for the national news show.
2021/03/11	A year of COVID-19 lockdown is putting kids at risk of allergies, asthma and autoimmune diseases, CTV News Kitchener I was interviewed by host Carmen Wong for the local news show.
2021/03/09	5 factors that could dictate the success or failure of the COVID-19 vaccine rollout, 106.5 ELMNT FM Toronto/95.7 ELMNT FM Ottawa I was interviewed by host David Moses for a show called "Moment of Truth".
2021/02/22	Byram Bridle, Associate Professor of Viral Immunology at the University of Guelph talks to Peter about the COVID vaccine, Magic Talk radio program, New Zealand, https://www.magic.co.nz/home/news/2021/02/byram-bridle--associate-professor-of-viral-immunology-at-the-uni.html, Peter Williams
2021/02/18	5 factors that could dictate the success or failure of the COVID-19 vaccine rollout, Magic Talk Radio, Mediaworks, New Zealand I was interviewed live on air by host Peter Williams
2021/02/12	5 factors that could dictate the success or failure of the COVID-19 vaccine rollout, 570 News Talk Radio (Kitchener, Ontario, Canada) Interviewed live on radio by host Mike Farwell
2020/12/14	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Windsor, Ontario I was interviewed on radio.
2020/12/14	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Peterborough/Kingston/Barrie, Ontario I was interviewed on the "Ontario Morning" radio show.
2020/12/14	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, ELMNT FM Radio, 106.5 FM in Toronto and 95.7 FM in Ottawa I was interviewed on the David Moses talk show.
2020/12/14	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Toronto, Ontario I was interviewed on radio.
2020/12/14	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, London, Ontario I was interviewed on radio.
2020/12/14	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Sudbury, Ontario I was interviewed on radio.
2020/12/14	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Sudbury, Ontario I was interviewed on radio.

2020/12/14	Article title: The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Kitchener, Ontario I was interviewed on radio.
2020/11/25	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Sudbury, Ontario I was interviewed by host Jonathan Pinto on the "Up North" program.
2020/11/25	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Montreal, Quebec I was interviewed by host Sabrina Marandola on the "Let's Go" program.
2020/11/25	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Vancouver, British Columbia I was interviewed by host Gloria Macarenko on the "On the Coast" program.
2020/11/25	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, London/Windsor, Ontario I was interviewed by host Chris dela Torre on the "Afternoon Drive" program.
2020/11/25	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Whitehorse, Yukon I was interviewed by host Dave White on the "Airplay" program.
2020/11/25	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, UK Radio, Radio Sputnik, Edinburgh, Scotland I was interviewed by host Alex South.
2020/11/25	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Saskatchewan I was interviewed by host Garth Materie on the "Afternoon Edition" program.
2020/11/25	The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Winnipeg, Manitoba I was interviewed on the "Up to Speed" program.
2020/10/12 - 2020/10/12	"U of G Covid Vaccine Research", https://www.facebook.com/uofguelph/videos/u-of-g-covid-vaccine-research/274022033801852/, Facebook video
2020/10/10 - 2020/10/10	"Training our immune systems: Why we should insist on a high-quality COVID-19 vaccine", Interviewed live on-air (two time slots) for 'Weekend Mornings on CKNW" by host Stirling Faux, CKNW Radio, Vancouver, BC
2020/10/08 - 2020/10/08	"Training our immune systems: Why we should insist on a high-quality COVID-19 vaccine", Interviewed live on-air by host Brian Bourke, 570 News Talk Radio (Kitchener, Ontario, Canada)
2020/08/16 - 2020/08/16	"Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk", Interviewed by Miriam Harris for a radio show, Newshub in Auckland, New Zealand
2020/08/16 - 2020/08/16	"COVID-19 Vaccines:<?>Facts to Inform Policies", https://www.youtube.com/watch?v=HndetYzK8gU, New Zealand's COVID-19 Science and Policy Symposium
2020/08/05 - 2020/08/05	"Why vaccines are less effective in the elderly, and what it means for COVID-19", Interviewed live on-air on the Mike Farwell show, 570 News Talk Radio (Kitchener, Ontario, Canada)
2020/07/29 - 2020/07/29	"Why vaccines are less effective in the elderly, and what it means for COVID-19", Interviewed live on-air by host Scott Radley, 900 CHML (radio station in Hamilton, Ontario, Canada)
2020/07/27 - 2020/07/27	"Why vaccines are less effective in the elderly, and what it means for COVID-19", Interviewed live on air by host Jill Bennett, NewsTalk 980 CKNW, Vancouver (radio)

2020/07/13 - 2020/07/13	"Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk", Interviewed by host David Moses for a second, follow-up talk show, ELMNT FM Radio; 106.5 FM in Toronto and 95.7 FM in Ottawa
2020/07/07 - 2020/07/07	"Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk", Interviewed by host David Moses for a talk show, ELMNT FM Radio; 106.5 FM in Toronto and 95.7 FM in Ottawa
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2020/06/22 - 2020/06/22	"Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk", Interviewed live on-air by host Devon Peacock, Global News Radio 980 CFPL (London, Ontario, Canada)
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   Conference Date: 2015/6
   Paper
   Co-Author
   Submitted
   Refereed?: Yes, Invited?: No

   Funding Sources: Natural Sciences and Engineering Research Council of Canada (NSERC) - 436264-2013

Intellectual Property

Patents

1. ONCOLYTIC VIRUSES WITH REPLICATIVE ABILITY AT TEMPERATURES HIGHER THAN WILDTYPE AND USES THEREOF. United States of America. Provisional Application No. 62/976,616. 2020/02/21.
   Patent Status: Pending
   Inventors: Byram W. Bridle Jacob P. van Vloten
   Describes two novel oncolytic rhabdoviruses with superior oncolytic activity at temperatures above 37oC as compared to the parental viruses. Also describes a method to generate these types of viruses. This will enhance efficacy of oncolytic rhabdoviruses in tumours that are at higher temperatures than ambient tissues and in human patients that develop fevers (a common response to this therapy) and in veterinary patients whose normal body temperatures are >37oC.
2. AVIAN ONCOLYTIC VIRUS HAVING MODIFIED SEQUENCES AND USES THEREOF. United States of America. 2018/12/14.
   Patent Status: Pending
   Inventors: KOZAK; Robert; (London, CA) ; BRIDLE; Byram; (Guelph, CA) ; NAGY; Eva; (Puslinch, CA) ; THOMPSON; Bradley; (Calgary, CA)
   The present disclosure relates to one or more modified avian-virus based agents, therapies, treatments, and methods of use of the modified avian-virus based agents and/or therapies and/or treatments for cancer. The disclosure also provides for methods of generating modified avian-virus based agents. One of the five claims is particularly notable: "The oncolytic agent of claim 1, where the modified avian virus is one of an avian pox virus, an avian reovirus, a Newcastle's disease virus, a duck hepatitis virus, an infectious bursal disease virus, a chicken parvovirus and a combination thereof."

3. A METHOD OF VACCINATION COMPRISING A HISTONE DEACETYLASE INHIBITOR. Canada. International Application No.: PCT/CA2012/000212. 2012/09/03.
Patent Status: Pending
A vaccination method is provided. The method comprises administering to a mammal a histone deacytelase inhibitor in conjunction with a vaccine that expresses an antigen to which the mammal has a pre-existing immunity.

   Funding Sources: Canadian Institutes of Health Research (CIHR) - MOP-67066

4. VACCINATION METHODS. Canada. PCT/CA2010/000379. 2011/09/16.
Patent Status: Pending
In one aspect, a method of treating cancer in a mammal is provided. The method comprises administering to the mammal an oncolytic vector that expresses a tumour antigen to which the mammal has a pre-existing immunity. In another aspect, a method of boosting immune response in a mammal having a pre-existing immunity to an antigen is provided comprising intra-venous administration to the mammal of a B-cell infecting vector that expresses the antigen.

   Funding Sources: Canadian Institutes of Health Research (CIHR) - MOP-67066

Disclosures

1. Heat-Adapted Maraba Virus for Treating Cancers
Disclosed
Filing Date: 2019/08/09
An application was submitted to patent a novel oncolytic virus. There is one other co-inventor (my PhD student Jacob van Vloten).

2. Quantifying Antigen-Specific T-Cell Responses When Using Antigen-Agnostic Immunotherapies
Disclosed
Filing Date: 2019/07/05
A report of invention for a novel method to quantify T cell responses was submitted to the intellectual property office at the University of Guelph. There is one other co-inventor (my PhD student Jacob van Vloten).

3. Quantifying Antibody Responses Induced by Antigen-Agnostic Immunotherapies
Disclosed
Filing Date: 2019/07/05
A report of invention for a novel method to quantify antibody responses was submitted to the intellectual property office at the University of Guelph. There is one other co-inventor (my PhD student Jacob van Vloten).

4. Avian Orthoreovirus Strain PB1: A Novel Oncolytic Virus
Disclosed
Filing Date: 2019/02/05
An application was submitted to patent a novel oncolytic virus. There are two other co-inventors (research collaborators).

5. Combining Epigenetic Modifiers with Oncolytic Viruses for the Treatment of Leukemias
Disclosed
Filing Date: 2018/03/21
A report of invention was submitted to the University of Guelph's intellectual property office. There are four other co-inventors (all former students of mine; Megan Strachan-Whaley, Christian Ternamian, Jason Morgenstern and Evan Lusty).

6. Avian orthoreovirus (ARV) strain PB1: a potential oncolytic, vaccine and adjuvant
Disclosed
Filing Date: 2014/01/31

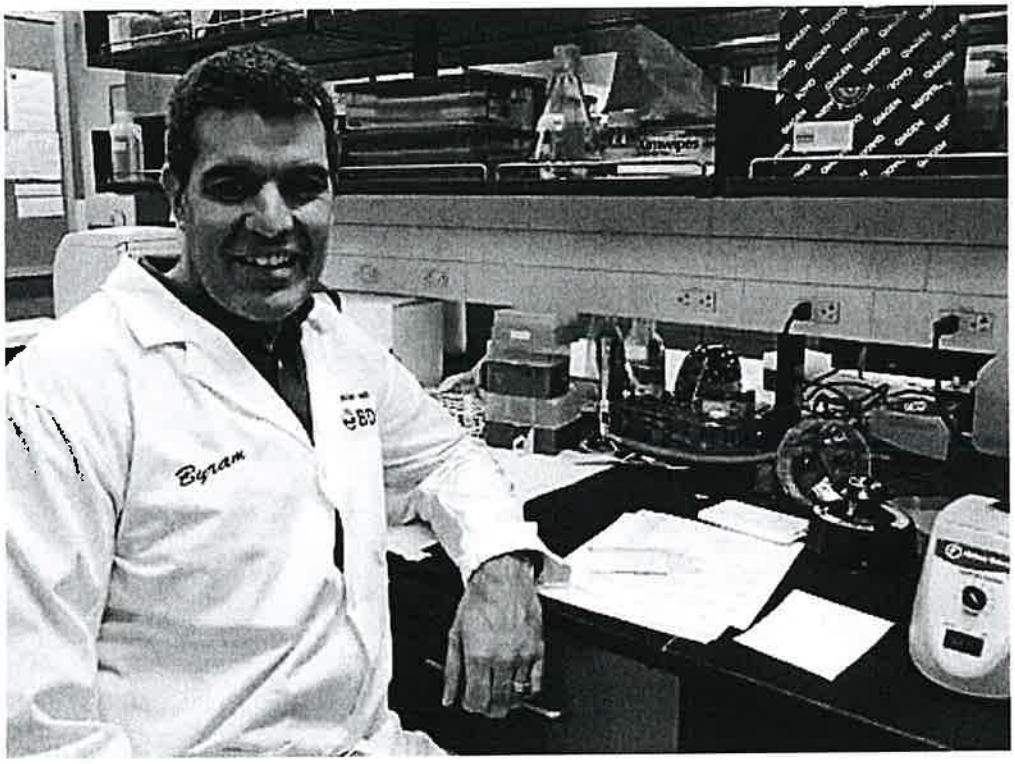
This is Exhibit " B " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

U of G COVID-19 Vaccine Research Awarded Provincial Funding

University of Guelph researchers have received $230,000 to develop potential COVID-19 vaccines under the province's Ontario Together investment to advance research to combat the pandemic.



Prof. Byram Bridle

Pathobiology professor Byram Bridle said he believes the team's vaccine platform – adapted from U of G research into vaccines as cancer therapies — will be a leading candidate

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among the roughly 120 Canadian projects currently racing to develop an effective vaccine against the pandemic virus.

This project is one of 15 included in today's provincial funding announcement and is the only one aimed at developing a vaccine.

"We have been focused on cancer for years, but this collaboration shows the flexibility of the technology we have at Guelph," he said. "We can rapidly apply cancer technology and move it over to infectious disease."

The team received a one-year, $230,000 grant this week in COVID-19 rapid research funding from the Ontario government to test four vaccines already developed in University labs. Nearly a dozen researchers are involved, including Bridle and co-principal investigators Sarah Wootton and Leo Susta, also faculty members in the Department of Pathobiology.

All three researchers' labs have been approved for critical research status, allowing them to conduct studies while observing pandemic safety protocols.

Following immunological and safety testing at U of G, the researchers expect to share their top two vaccine candidates in about eight months with collaborators led by Darwyn Kobasa, head of respiratory virus pathogenesis and therapeutics at the National Microbiology Laboratory (NML) in Winnipeg, for efficacy testing.

Bridle said he hopes to see a viable vaccine based on the technology ready for Health Canada approval in 2021.

Their vaccines target a protein found on the surface of the coronavirus. After ferrying the protein into mice using a common adenovirus and an avian virus that normally infects chickens, they will measure immune responses in two ways.

They plan to look for levels of specific antibodies that recognize the protein and prevent the virus from entering lung cells. For any virus that does get past the body's defences, they will also monitor production of T cells that normally fight off infection.

Out of four potential vaccines, they plan to send the top two candidates to the NML for further testing. The team will work with Health Canada to ensure "fast tracking" for any potential vaccine to be released to the public.

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Prof. Sarah Wootton

Bridle said Canadian researchers are working on an estimated 120 vaccines for the coronavirus. He said he's confident the U of G approach will be among the top candidates.

The technology uses a proven testing platform of viruses already used to develop cancer vaccines. By using live vectors to deliver the vaccine directly into cells, he said, the approach ensures an appropriate immune response. Other approaches using a killed virus may be developed more quickly, he said, but many of those vaccines will fail to trigger the body's proper immune response.

Bridle, Wootton and Susta have collaborated on using viruses in cancer therapy, including one of the viruses that they are now testing for a possible coronavirus vaccine.

He said that unlike other "one-off" approaches to developing a COVID-19 vaccine, the team's platforms can be adapted to develop vaccines for future versions of a coronavirus. That means future vaccines might be made more quickly and cheaply, giving Canada a foundation for subsequent vaccine development.

"With these vaccine vectors, we designed them to be 'plug and play.' You can put any gene into the vectors within two weeks. It could be a target protein in a cancer cell, but it could just as easily be a protein on a virus."

"I would like to congratulate Byram Bridle and the whole team at the University of Guelph on receiving this project approval through the COVID-19 Rapid Research Fund," said

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Kitchener-Conestoga MPP Mike Harris. "The Ontario government is committed to supporting our world-class researchers and institutions in their fight against the current global pandemic."

Malcolm Campbell, vice-president (research), said, "This very foresighted, incredibly smart support from our provincial government is outstanding."

By combining three U of G research teams, he said, the project "will in turn power discoveries and fuel innovations aimed at creating a vaccine against SARS-CoV-2, the virus underpinning the COVID-19 pandemic. In doing so, our government's intelligent investment will ensure that this University of Guelph research will address the challenges of this pandemic, as well as any coronavirus diseases that may emerge in the future."

Prof. Leo Susta

Overall, the province has committed $20 million through its COVID-19 Rapid Research Fund – part of the Ontario Together fund — for research to help combat the pandemic.

The team has also received support from the Department of Pathobiology, the Ontario Veterinary College and the University's COVID-19 Research Development and Catalyst Fund.

Noting that the team brings together experts in viral immunology, virology and pathology, Bridle said the group responded rapidly to the provincial government's call for research proposals. "We have a strong history of working on developing cancer vaccines. As soon

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as the call came out for COVID-19 vaccines, we realized we have potential vaccination strategies."

Contact:

Prof. Byram Bridle
bbridle@uoguelph.ca

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5 Factors That Could Dictate the Success or Failure of the COVID-19 Vaccine Rollout

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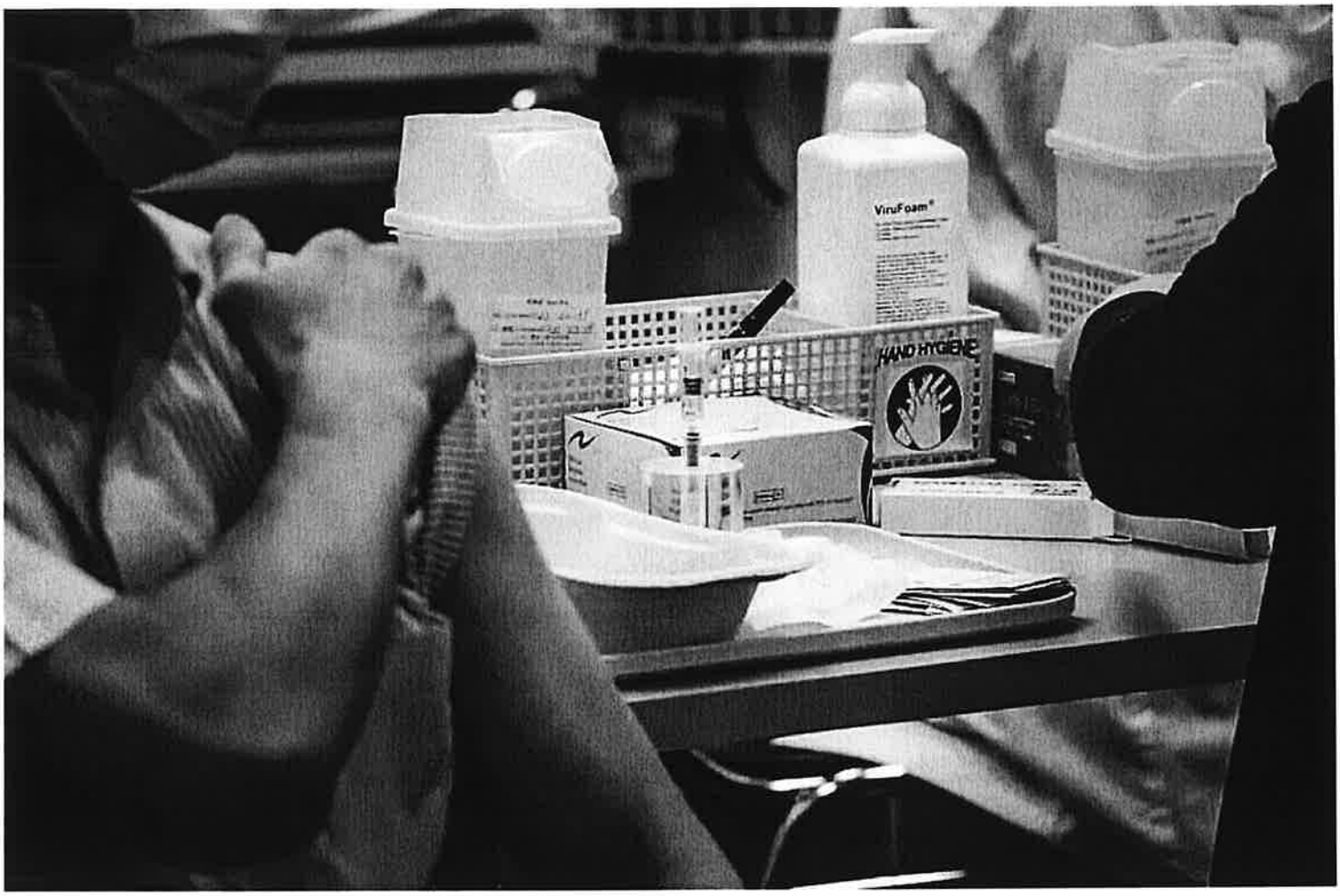

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As a viral immunologist who develops immunization strategies to prevent infectious diseases and treat cancers, I would like to highlight outstanding questions about the emergency use of vaccines against SARS-CoV-2, the coronavirus that causes COVID-19.

These vaccines have raised hopes that the pandemic is nearing an end. Hopefully this is true, but here are some potential sticking points.

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Dr. Byram Bridle

1. Long-term safety profile of COVID-19 vaccines

Because COVID-19 vaccines have received regulatory approval in record-shattering time, these vaccines are being distributed with uniquely short safety profiles: only months' worth of data are available.

Short-term safety of approved COVID-19 vaccines looks good. However, induction of anaphylactic reactions in some vaccine recipients hasn't helped the optics for those with vaccine hesitancy. But these cases are rare and usually associated with pre-existing severe allergies.

Twenty-three frail elderly individuals in Norway died shortly after receiving the Pfizer vaccine. It is difficult to ascertain the reason for these deaths and they may have had nothing to do with the vaccine. It has put pressure on physicians in that country to try to determine which members of this demographic at high risk for COVID-19 mortality should and should not be vaccinated.

If too many unpredicted severe long-term side-effects were to accrue over time, this could be cause for withdrawal of approval for a vaccine.

2. Duration of immunity of COVID-19 vaccines

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Duration of immunity refers to how long a person is protected after being vaccinated. For previous vaccines, we could have reasonable confidence that immunity would last at least a few years prior to public rollouts. COVID-19 vaccines only have a few months' worth of data on duration of immunity.

If immunity declines before "herd immunity" is achieved, previously vaccinated individuals will become susceptible to infection again and the rollout could fail.

3. Effectiveness of COVID-19 vaccines

There were public declarations of greater than 90 per cent effectiveness for the Moderna and Pfizer vaccines. Unfortunately, Pfizer did not publicly disclose the fact that there were large numbers of suspected, but unconfirmed cases of COVID-19 that were excluded from their calculation of efficacy. This was revealed in a summary report issued by the United States Food and Drug Administration (FDA).

Re-analysis of the data with this new information accounted for was performed by the associate editor of the *British Medical Journal*, who reported his non-peer-reviewed findings in the journal's opinion column. His estimate suggests the true effectiveness of the vaccine might be as low as 19 to 29 per cent. This can't be confirmed or refuted until raw data not included in the FDA report are released.

The effectiveness reported for Sinovac Biotech's currently unapproved vaccine dropped from 78 per cent early in a clinical trial being run in Brazil to 50.38 per cent in the late stages of the trial. The cut-off for approval of COVID-19 vaccines has been set at 50 per cent effectiveness. If efficacy during public rollouts ends up being less than "advertised," COVID-19 vaccines will under-perform relative to expectations.

4. Risk of variants that can evade vaccine-induced immunity

Several novel variants of SARS-CoV-2 have been identified recently. Coronaviruses copy their genetic material in a way that inherently induces random mutations. If these mutations promote survival of the virus in vaccinated people, it could spell disaster for the current immunization strategy.

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Although the risk of mutations that can evade vaccine-induced immunity cannot be accurately quantified, the way COVID-19 vaccines are being rolled out will likely increase the potential for this to occur for at least two reasons. First, the current vaccines confer narrowly focused immunity that targets a single viral spike protein. That means SARS-CoV-2 only needs to mutate one protein to evade vaccine-induced immunity. In contrast, it would be more difficult for the virus if it had to mutate several proteins to become immune-evasive.

Secondly, the vaccination program is being rolled out in piece-meal fashion. This slow expansion of narrowly focused immunity among people who are surrounded by others who are not immune provides the time and contact with a "reservoir population" that a virus would need to generate random variants that can probe their potential to infect vaccinated people.

If a variant emerges that has altered its spike protein enough to bypass vaccine-induced immunity, the vaccine rollout could fail. If this happens, vaccines may need to be re-engineered to express a novel version of the spike protein, preferably with other proteins added to broaden immunity.

Importantly, acquisition of natural immunity, which targets multiple components of the virus, may reduce the risk of re-infection with variants that can bypass spike protein-specific immunity.

5. Untested COVID-19 vaccine regimens

Due to logistical challenges of rolling out two-shot vaccines and with the goal of maximizing how many and how quickly people can be vaccinated, single-dose regimens, combining vaccines from different manufacturers, and regimens that alter the intervals between doses are all being considered.

Note that the efficacy of Pfizer's and Moderna's vaccines only holds true beginning one to two weeks after the second shot, and using the recommended interval and dose. The performance of vaccines cannot be guaranteed if administered differently than the way in which they obtained regulatory approval. Indeed, results of a single-dose regimen with the Pfizer vaccine in Israel were reported as disappointing, although this is being debated.

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The overall magnitude and/or quality of immune responses could be compromised by lengthening the interval between the two doses. Deviations in protocols should not be tolerated unless backed up by clinical trial data.

Herd immunity without rollout success?

Can herd immunity still be achieved if COVID-19 vaccines underperform? Probably. Mounting evidence suggests most people that have been infected with SARS-CoV-2 have naturally acquired immunity that can protect them from re-infection. In fact, we have much longer duration data for naturally acquired immunity than for vaccine-induced immunity against SARS-CoV-2.

There is even evidence that pre-existing immunity against other coronaviruses, including those that merely cause colds, can cross-protect some people against SARS-CoV-2. This is not surprising because this is what our immune system is designed to do. All these people will contribute to the acquisition of herd immunity.

At the beginning of the pandemic most governments decided against using naturally acquired immunity as a primary way to achieve herd immunity to allow hospitals time to deal with severe illnesses. However, one year into the pandemic a huge unanswered question is: how close/far are we from natural herd immunity?

In Canada, we have done a poor job of tracking this. A starting point would be extensive antibody testing. If someone has antibodies in their blood against SARS-CoV-2, then they were infected at some point. If this had been combined with the direct detection of SARS-CoV-2 being done at testing centres, we could have had a massive data set in-hand.

Natural immunity acquired by an ever-growing number of people means fewer people require vaccination to reach herd immunity. As a bonus, natural immunity also equates to broader immunity; these people should be less susceptible to re-infection if an immuno-evasive SARS-CoV-2 variant emerges.

Statistics Canada is initiating a large-scale study to conduct antibody testing on randomly selected Canadians. A smaller study by a researcher at the University of Toronto was started in June 2020. Data from these studies could be used to estimate how much natural immunity exists in the general population. However, looking only for

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circulating antibodies against SARS-CoV-2 will likely underestimate immunity. These will often disappear, but the memory B cells that produce them are usually long-lasting and can confer protection.

By Dr. Byram W. Bridle, associate professor of viral immunology, Department of Pathobiology

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The Guardian Consults Virologist on Children's Immunity Concerns

Dr. Byram Bridle

Dr. Byram Bridle, a professor of immunology with the Department of Pathobiology at U of G's Ontario Veterinary College, spoke to *The Guardian* newspaper in the U.K. about whether extended quarantines might be harmful to children's immune systems.

Bridle said he's concerned that limiting children's exposure to the natural world, as has been done often in the last year, could lead to a rise in immunological disorders in children. He noted that the immune systems of young children go through an important period of immune system development before they reach the age of six.

Bridle studies oncolytic viruses and has received provincial research funding to adapt technology to develop a vaccine against SARS-CoV-2, the coronavirus that causes COVID-19.

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How will isolation affect long-term immunity?

Healthy immune systems work best when exposed to microbes. So what will lockdown have done to our resistance to germs?

Playing dirty: as humans evolved, our immune systems learned to cope with the microbes around us in the natural world. Illustration: Lehel Kovács/The Observer

Amelia Tait

Sun 16 May 2021 10.00 BST

Every time you kiss another human being intimately for 10 seconds, more than 80m bacteria are transferred from mouth to mouth. If you're at a party and double dip your tortilla chip into the salsa three times, around 10,000 bacteria will be transferred from your lips to the dip. Say "hi" to your co-workers as you sit down at your office desk and you'll also be greeted by over 10m bacteria on its surface.

Disturbing as these figures may seem, many scientists believe that exposure to these microbes helps fine-tune our immune systems – the network of cells and molecules that protect us from diseases. In 1989, epidemiologist David Strachan first proposed the "hygiene hypothesis" – the idea that being too clean causes defects in the immune system, leading to a rise in inflammatory diseases, such as asthma and allergies. While Strachan's theory is debated and hygiene saves countless lives, decades of data support the idea that exposure to microbes helps the immune system develop.

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kissing strangers, double dipping at parties or sitting down to work in a crowded office. Instead we've been locked up at home by ourselves, sanitising our hands every time we go to the shop and holding on to distant memories of restaurants and gyms. So what's happened to our immune systems in lockdown? What's going to happen now that the country is opening back up?

Graham Rook, a microbiologist at University College London, proposed an alternative to the hygiene hypothesis in 2003. Rook's "old friends hypothesis" posits that as humans evolved, our immune systems learned to cope with the microbes around us in the natural world. Rook argues that we need to be exposed to these "old friend" microbes in order for our immune systems to develop properly. (Strachan's hygiene hypothesis focused on infections, while Rook's focuses on more harmless micro-organisms.)

"Our immune system is a learning system, just like the brain," Rook says, explaining that the system has two branches. We are born with an "innate" immune system encoded in our genes, but this is "tuned" by our "adaptive" immune system, which collects data from the microbes around us to determine which are safe and which are dangerous. Without the right data, the immune system starts attacking things it shouldn't, causing allergies, asthma and autoimmune diseases (when the immune system targets your body's own tissues).

So first, the good news. By the time you're an adult, you've already encountered a whole host of microbes. Your microbiota – the trillions of microbes living on and in you – is "fairly stable and established," says Rook. A year of isolation, then, is unlikely to severely damage your immune system's regulatory mechanisms. But when it comes to children, Rook and other scientists have concerns about the effects of lockdown measures. "A child on the 24th floor of a tower block is simply not meeting the appropriate microbiota," Rook says, explaining that staying indoors away from the natural world and other people limits the microbes encountered, as does having an unvaried diet (which he fears may be a problem for children going without school meals). "It is worrying."

Pet protection: children who grow up with dogs have a lower risk of developing autoimmune diseases. Illustration: Lehel Kovács/The Observer

Byram W Bridle is an immunologist at the University of Guelph in Canada. Early on during global lockdowns, Bridle wasn't too concerned for children's immune development because, after all, kids often get stuck at home for a

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chunk of development of the immune system. So it's hard to imagine that this cannot have a negative impact on our children."

Like Rook, Bridle worries about a rise in immunological disorders caused by lockdown limiting children's exposure to the natural world - even before the pandemic, scientists documented that "those who grow up in large urban centres tend to have a much higher incidence of allergies, asthma and autoimmune diseases". Bridle explains that while the immune system doesn't fully mature until adolescence, birth to age six is the critical period for its development.

Various studies have posited that problems can arise when infants have limited microbial exposure. It has been shown that children born by caesarean section are exposed to less of their mother's microbiota than others - they are also statistically more likely to suffer from allergies and inflammatory diseases. One 2014 study from the University of Pennsylvania and Bloomberg School of Public Health found that children who are given repeated courses of antibiotics early in life face a greater risk of obesity (the researchers theorised that the medicine killed off the good bacteria in the children's guts). Rook says as well as allergies and autoimmune diseases, poor immunoregulation can cause chronic inflammation which can lead to diabetes, obesity, and cardiovascular diseases. "It's a pretty impressive list."

Let's take a moment to press the big "don't panic" button in our brains. While children's microbial exposure may have been limited by lockdown, it remains to be seen just how much.

As we have been in and out of lockdown in the UK, many of us haven't actually been isolated for an entire year. Many children may also have been outside more than usual - one global analysis in the *Journal of Forestry Research* found that lockdown restrictions correlated with more visits to parks. There has also been a boom in puppy purchases over the past year: studies have shown that children who grow up with dogs have a lower risk of developing autoimmune diseases. Then there's the fact that microbial exposure isn't everything: our immune response is also determined by our genes.

Sheena Cruickshank, an immunology professor at the University of Manchester, is more optimistic than Rook and Bridle. "With the best will in the world, how super-duper clean are kids?" she says. Cruickshank notes that research about our immune systems is continually ongoing: "Both of them could be partially right, both of them could be partially wrong," she says of the hygiene hypothesis and the old friends hypothesis. "It's something that we're very much investigating."

Bridle stresses that while his concerns are based on "sound scientific principles" they do, of course, remain speculation: "We won't know for sure until we actually see how all this plays out." It may yet be a few years before we know whether the children of lockdown have higher rates of immunological disorders. "It takes about five years for asthma to really kick in," says Brett Finlay, co-author of *Let Them Eat Dirt: How Microbes Can Make Your Child Healthier*. "The data is not there yet, it's too early, but we're imploring people to look," he says. "We've really changed the world we live in, and every time we change the world, we change the microbes."

Immunological disorders are one thing, but what about viral infections? Many of us - adults and children - haven't so much as sniffled for an entire year: does this mean our immune systems will be ill-equipped to deal with viruses as the world opens up? When it comes to the common cold, Cruickshank says we don't have too much to worry about. "We don't really build up a long-term resistance," she explains - and, "we've got an advantage coming out of lockdown now, because we're going into the warmer seasons

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> ***Every time we change our world, we also change our microbes***

Between October and November 2020 in Hong Kong, schools reopened after a three-month closure and a large number of common cold outbreaks were reported. Ron Eccles, founder of the Common Cold Centre at Cardiff University, says such outbreaks are to be expected when children crowd together after being apart. Thankfully, however, he says, "There's very little to indicate that just because you've not had a cold for a while the next one you get is going to be more severe." Yet when it comes to the flu, Bridle has concerns. In January 2021, data from the Royal College of General Practitioners revealed that flu rates had plummeted to a 130-year low – researchers argued that travel bans, social distancing and hand-washing helped stop the spread. While this might sound like good news, Bridle says it puts us on the back foot when it comes to our next flu season.

"We deal with the flu virus on an annual basis because it mutates rapidly," he explains. "From year to year, we're actually dealing with fundamentally different variants." This means flu vaccinations are also constantly changing – every year, scientists base the vaccine on the predominance of variants spreading the year before. "We will potentially be dealing with vaccines that are based on variants that were circulating two years ago instead of one." Bridle says our immune responses will also be a year out of date.

"Our immune systems and the vaccines that we're using are going to be targeting a virus that has now been able to accumulate two times the mutations than what we would normally be facing." Although there is a counter-argument that, with so little flu virus in circulation, it will have had less chance to mutate and therefore using last year's formulations is an acceptable strategy.

Nevertheless, Bridle says this is most concerning for "the two ends of the spectrum" – the elderly and the very young. Rook also has concerns that limited microbial exposure could affect the elderly. Although there is little evidence that having a less-diverse microbiota means you're more susceptible to viruses, the kind of isolation induced by lockdown that affects microbial exposure could have knock-on effects in terms of bacterial infections that might otherwise have been less of a problem. One 2012 article in *Nature* found that the gut microbiota of people in long-term care was less diverse than those out in the community and, in turn, "loss of community-associated microbiota correlated with increased frailty".

Younger and middle-aged adults aren't totally off the hook – while they are not at the highest risk for flu complications, there is evidence that both loneliness and stress can weaken the immune system.

So, what on earth should we do? Rook says children should continue to be exposed to the natural environment and "run around in the park as often as possible". Finlay advises to "think from a microbial exposure point of view" – go outside, hug a dog, and also eat fruit, nuts, legumes, "all the stuff your mum tells you to eat" as nutrition is crucial for a healthy immune system. Cruickshank says the immune system can also be mobilised by moderate exercise. Crucially, don't be misled into throwing away your disinfectant – lack of hygiene does not lead to better immunological development and it's important to continue to keep clean in order to ward off harmful pathogens.

Finally, Rook also stresses that it's imperative to keep up to date with your child's vaccination schedule. "Not only do vaccines stop you from getting the infection that they are targeting, they also help with the training of the immune system in a nonspecific way," he says.

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The question is, will they develop appropriately?" Bridle says. Personally, he is concerned. "In some of our children as a result of this excessive isolation, we are likely causing irreparable harm. It's frustrating as a scientist when you consider this in the context of children being at an extremely low risk from the Sars-CoV-2."

The data isn't here yet - it's too early to see the lasting effects of lockdown. Finlay hopes that scientists will use this opportunity to learn more about microbial exposure. "Here's, I think, one of the biggest experiments we've ever been able to do with humanity - we've got the whole globe involved," he says. "Let's make use of this opportunity and characterise the microbes over time and follow these things. Let's see what happens to us because it's really an experiment that's happening right now."

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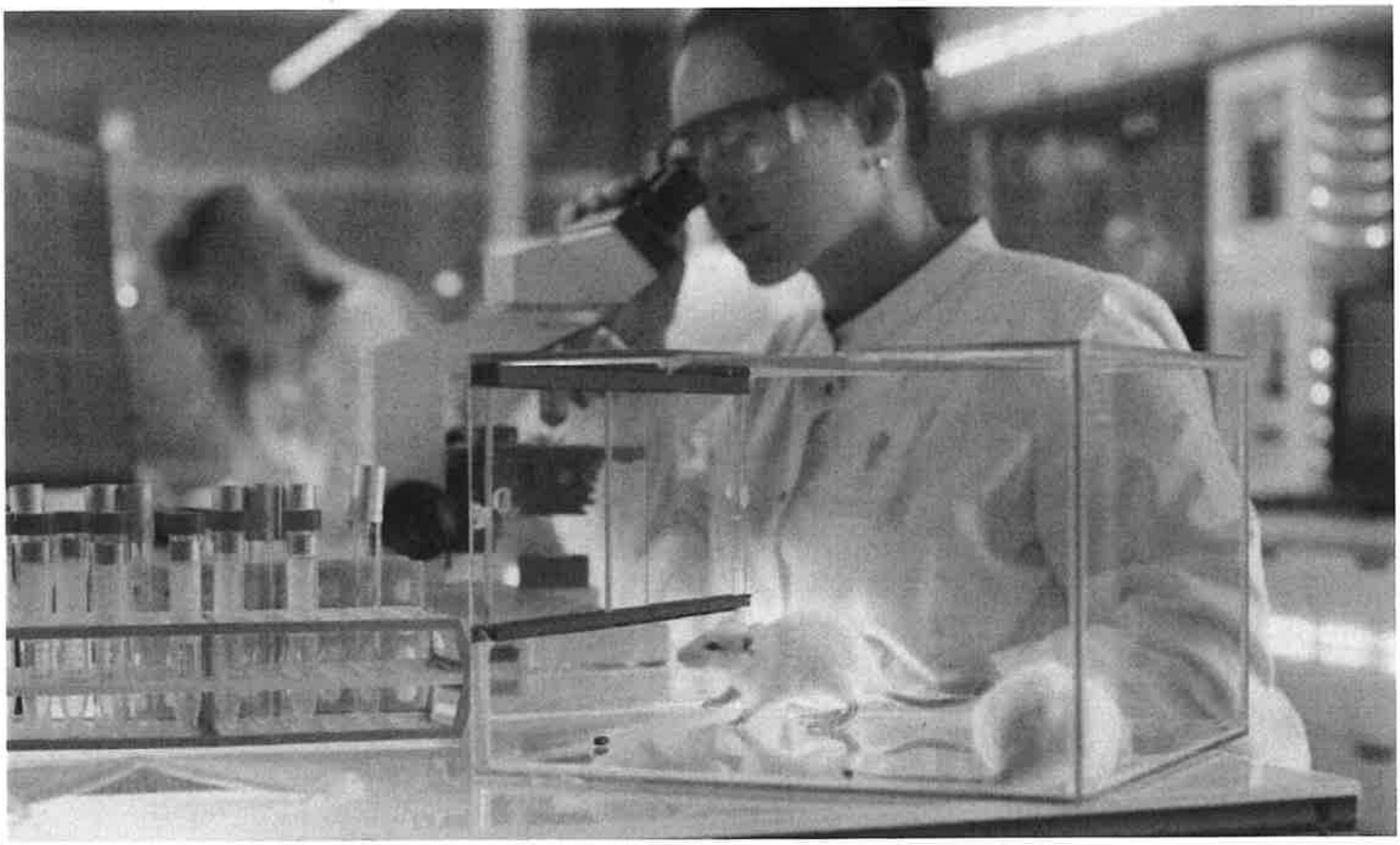
Why Vaccines Are Less Effective in Older People, What It Means for COVID-19

Vaccine developers use processes that bias vaccines toward young people with healthy immune systems

HEALTH

Byram W. Bridle
Shayan Sharif
Jul 30 2020



Vaccinologists have largely failed to focus on tailoring vaccines for those most as risk—older people with weaker immune systems.(Gorodenkoff/Shutterstock)

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cause of COVID-19–continues, we learn more about the effects of this new virus.

For many respiratory pathogens, including influenza viruses and respiratory syncytial viruses, older adults experience the most severe forms of disease and the highest death rates. For example, for every 10,000 Americans between 18 and 49 years old, only 0.4 people die from the annual flu. That number increases to 5.9 people per 10,000 for those aged 65–74 years, and 47.5 people per 10,000 for those over 74 years old.

However, most of these diseases can also have a predilection for causing severe disease in those who are very young.

In this respect, COVID-19 is very different. Data from relatively early in the COVID-19 pandemic showed a dramatic difference in the rates of age-associated deaths, with a case fatality rate of 4.5 percent for patients ages 60 and up, versus only 1.4 percent for those under 60 years old, with those under 30 years ranging from zero to 0.19 percent.

Immunosenescence

We are immunologists with research programs devoted to developing vaccines. With COVID-19 placing a spotlight on the elderly as the age demographic most in need of a vaccine, we have felt compelled to evaluate how well scientists are doing at tailoring immunization strategies for this population.

Our conclusion is that vaccinologists have largely failed to focus on tailoring vaccines for those most as risk–older people with weaker immune systems.

This is also associated with an increase in the incidence of inflammatory diseases, because an elderly body tends to be in a state of chronic low-grade inflammation.

This "inflamm-aging" is one reason why older people have tendencies to develop more severe forms of respiratory diseases.

The key problem with SARS-CoV-2 infection is inflammation in the respiratory tract, which can be exacerbated in individuals predisposed toward potent inflammatory responses.

Immunosenescence also results in diminished responses to vaccination. Indeed, annual flu vaccines are notoriously less effective in the elderly. This phenomenon is very important in the context of the massive efforts and funds being invested worldwide into the ultra-rapid development of vaccines for COVID-19.

most discussions of COVID-19 vaccines, despite this being the group in greatest need. Most of the scientific community's experience with vaccine development for any disease has been focused on vaccinating the relatively young.

Young Mice and Older Humans

Here is an interesting exercise for people reading this article: Find as many original research articles as you can on the topic of vaccine development that have used animal models (it could be for any disease). Then look in the subsection of the "materials and methods" section and check the age of the animals. We were shocked by what we found.

Mice are the most common animals used in preclinical vaccine research and the overwhelming majority of these are 12 weeks old or younger. This is equivalent to people 20 years old and younger. It's comparatively much rarer for studies to use immunosenescent mice that are at least 18 months old and equivalent to an older human.

Translational studies that take promising preclinical discoveries and move them toward clinical trials often use non-human primates such as Rhesus macaques. In the majority of cases, these are around 3 to 6 years old, which is equivalent to an adolescent or young-adult human. The same trend applies to all other animals used in vaccine research.

Early-phase clinical trials focus on safety, not efficacy of vaccines. Therefore, far too many vaccines never get tested in the context of aged immune systems until Phase 2 and 3 clinical trials. The time to find out that a vaccine doesn't work well in the context of immunosenescence isn't at this extremely late stage, when it is too late to fix the problem. This testing should begin in the preclinical phase where an iterative process can be followed to tailor a vaccine for a senescent immune system.

Interestingly, many commercial suppliers of animals that are purpose-bred for research don't have adequate inventories of old animals. Of concern, most old mice that are readily available are of the C57BL/6 strain. This is the most common strain used in research, and is known to have an immune system with a strong bias toward effective responses against viruses.

Intriguingly, aged mice experience a more severe form of SARS after infection, akin to senior humans. The excessive use of young mice with immune systems that are optimal for antiviral responses, and that experience less severe disease, could bias results in a way that overestimates the potential of vaccines to perform well in the elderly.

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People age 65 and over suffer the most severe cases of COVID-19 and have the highest associated mortality rate. If the goal is to have COVID-19 vaccines ready for public use by early 2021, the only ones that have a chance are those that are currently in clinical trials. It is likely that most of these did not undergo preclinical optimization for an elderly population, meaning these first-generation COVID-19 vaccines may perform poorly in the people that need them most.

For the COVID-19 pandemic, it's too late to go back and build these considerations into preclinical testing. However, it's imperative that researchers still in the preclinical phase incorporate head-to-head testing of their vaccine candidates in young versus aged animals and develop strategies to optimize them in the latter. This will help the world prepare for the next outbreak of a dangerous coronavirus.

For that matter, a focus on older adults should be incorporated into other vaccine development programs, including those to treat cancers, which have the highest incidence in senior citizens.

There are viable strategies to improve the effectiveness of vaccines in older people, including changes in formulations, doses, and routes of administration. However, it takes substantial time and appropriate animal models to conduct this research. It is possible that the elderly may need fundamentally different vaccination regimens than younger people.

Although a few researchers do conduct vaccine studies in old animals, considerations for the elderly need to be adopted by far more vaccinologists. This is of growing importance for countries with aging populations. This will mean changing the current philosophy of the field of vaccine development and incorporating age as a critical variable.

Byram W. Bridle is an associate professor of viral immunology in the department of pathobiology at the University of Guelph in Canada, and Shayan Sharif is a professor of immunology and the associate dean or research and graduate studies at the University of Guelph. This article was first published on The Conversation.

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A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

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June 18, 2020: CFRA 580 News Talk Radio (Ottawa, Ontario, Canada); Byram was interviewed live on-air by host Kristy Cameron.

June 19, 2020: Byram was interviewed by Roxanne Khamsi, Science journalist, for an on-line story to be published by National Geographic.

June 19, 2020: Byram was interviewed by Mercedes Stephenson, who is the host of The West Block (a national news show). It is scheduled to air on Sunday June 21, 2020 at 11:00 A.M. ET on Global Television.

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This is Exhibit " D " to the Affidavit of
Byram Bridle, sworn before me on
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March 3, 2021

Dear Professor Charlotte Yates, President and Vice-Chancellor, and **Professor Gwen Chapman**, Interim Provost and Vice-President (Academic):

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought (*i.e.* acquisition of immunity). In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have been commissioned by the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area. Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses. Among the many reasons for this is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to allow SARS-CoV-2 to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada. It has become clear that we can't continue to rely on continual lockdowns. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. **It is from this perspective that we would like to recommend the following core strategies to support re-opening the University of Guelph campus to in-person learning in the Fall 2021 semester:**

1. **Offer comprehensive and sensitive testing for evidence of seroconversion (antibodies) against SARS-CoV-2.** Ever-accumulating data demonstrate that both naturally acquired, and vaccine-induced immunity can provide at least some level of protection from reinfection from the parental and current variant forms of SARS-CoV-2. Evidence of protective immunity either prior to and/or after vaccination would provide valuable information to guide decisions. This testing should be offered to members of the university that are both on- and off-campus. Several options for antibody testing are currently available in Canada. For example, LifeLabs currently has a test available. Even better, we have a colleague at the University of British Columbia who has developed the most comprehensive and sensitive test for seroconversion that we are currently aware of. Through collaboration with this colleague, we would be happy to assist with getting a local lab (possibly our own Animal Health Laboratory, which has an excellent quality control program and experience getting novel tests up and running) set-up to run this cutting-edge test.
2. **Offer strategically prioritized vaccinations.** Vaccination against SARS-CoV-2 should be offered to individuals wanting to return to campus. Prioritization should be based on risk of an infection progressing to disease (*i.e.* COVID-19). If doses are limited, vaccines would best be used in individuals with no evidence of immunity (based on testing in highlighted in point #1). Importantly,

vaccines should be administered precisely according the protocol that was used to have them approved for emergency use until further data is available on alternative protocols. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented evidence of it being relatively ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf). Vaccinations should be offered to university community members that are both on- and off-campus.

3. **Offer rapid antigen screening tests to detect the presence of SARS-CoV-2.** This is currently being tested on campus, and if successful, it would be logical to implement this approach more widely. It is very convenient for the workplace and should be offered to university community members that are both on- and off-campus.
4. **Offer off-campus learning/working accommodations for high-risk individuals.**
5. **Consider implementing supplemental testing.** Additional tests could help manage COVID-19 on-campus. For example, testing wastewater from buildings on campus, with an emphasis on residences could help identify 'hot spots'.
6. **Consider incorporating comprehensive data collection in consultation with our Research Ethics Board.** A lack of concerted efforts to collect comprehensive data sets has slowed the progress of research in many jurisdictions in Canada. The University of Guelph could provide a detailed analysis to support a return to campus at other institutions. Our Department of Population Medicine would be well-equipped to oversee this type of data collection. However, the rollout of vaccines and tests should not be delayed for establishing such a data collection infrastructure; rather, the infrastructure for research-quality data collection could interface with the rollout when it is ready.

Note: Implementation of suggestions 1-5 could have an impact on public health directives. Specifically, it would facilitate discussions around reduced physical distancing. Reducing physical distancing from two meters to one meter in classrooms could have a major positive impact on returning to in-person learning.

We would be happy to offer advice as our campus community moves forward. Specifically, Dr. Bridle is willing to serve on any relevant advisory committees and/or he can be a point of contact for our group, with whom he consults regularly. We also have many colleagues in the fields of virology, immunology, and public health at a variety of institutions that we consult with. We look forward to hearing your thoughts about the University of Guelph showing leadership among the academic community in getting students back to in-class learning.

Sincerely,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

March 5, 2021

Dear Dr. Nicola Mercer, Medical Officer of Health and CEO of Wellington-Dufferin-Guelph Public Health:

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought (*i.e.* acquisition of immunity). In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have been commissioned by the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive and in-depth expertise in this area. Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses. Among the many reasons for this is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to allow SARS-CoV-2 to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada. It has become clear that we can't continue to rely on continual lockdowns. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. **It is from this perspective that we would like to recommend the following core strategies to support re-opening the City of Guelph and the surrounding regions by this Fall:**

1. **Offer comprehensive and sensitive testing for evidence of seroconversion (antibodies) against SARS-CoV-2.** Ever-accumulating data demonstrate that both naturally acquired, and vaccine-induced immunity can provide at least some level of protection from reinfection from the parental and current variant forms of SARS-CoV-2. Evidence of protective immunity either prior to and/or after vaccination would provide valuable information to guide decisions. Several options for antibody testing are currently available in Canada. For example, LifeLabs currently has a test available. Even better, we have a colleague at the University of British Columbia who has developed the most comprehensive and sensitive test for seroconversion that we are currently aware of. Through collaboration with this colleague, we would be happy to assist with getting a local lab (possibly our own Animal Health Laboratory, which has an excellent quality control program and experience getting novel tests up and running) set-up to run this cutting-edge test.
2. **Offer strategically prioritized vaccinations.** Prioritization should be based on risk of an infection progressing to disease (*i.e.* COVID-19). If doses are limited, vaccines would best be used in individuals with no evidence of immunity (based on testing highlighted in point #1). Importantly, vaccines should be administered precisely according to the protocol that was used to have them approved for emergency use until further data is available on alternative protocols. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented

evidence of it being relatively ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf).

3. **Offer rapid antigen screening tests to detect the presence of SARS-CoV-2.** This is currently being tested on the University of Guelph campus, and if successful, it would be logical to implement this approach more widely. It is very convenient for the workplace.
4. **Offer accommodations for remote working/learning for high-risk individuals.**
5. **Consider implementing supplemental testing.** Additional tests could help manage COVID-19. For example, testing wastewater from buildings, with an emphasis on high-density housing and workplaces could help identify 'hot spots'.
6. **Consider incorporating comprehensive data collection in consultation.** A lack of concerted efforts to collect comprehensive data sets has slowed the progress of research in many jurisdictions in Canada. The Wellington-Dufferin-Guelph Public Health in conjunction with the University of Guelph could provide a detailed analysis to support return-to-work and return-to-school policies at other institutions. Our Department of Population Medicine would be well-equipped to oversee this type of data collection. However, the rollout of vaccines and tests should not be delayed for establishing such a data collection infrastructure; rather, the infrastructure for research-quality data collection could interface with the rollout when it is ready.

Note: Implementation of suggestions 1-5 could have an impact on public health directives. Specifically, it would facilitate discussions around reduced physical distancing. Reducing physical distancing from two meters to one meter in workplaces and classrooms could have a major positive impact on returning to in-person work and learning.

We would be happy to offer advice as our regional community moves forward. Specifically, Dr. Bridle is willing to serve on any relevant advisory committees and/or he can be a point of contact for our group, with whom he consults regularly. We also have many colleagues in the fields of virology, immunology, and public health at a variety of institutions that we consult with. We look forward to hearing your thoughts about the Wellington-Dufferin-Guelph Public Health Unite showing leadership within Canada in getting local citizens back to in-person work and in-class learning.

Sincerely,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

March 16, 2021

Dear Fellow Canadians:

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought, which is acquisition of immunity against the virus SARS-CoV-2. In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have received funding from the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area.

Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses.

Among the many reasons for this virus becoming endemic is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to potentiate SARS-CoV-2 being able to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada.

It has become clear that we can't continue to rely on continual lockdowns due to the impact on mental health, delays to other medical treatments, a sinking economy, and so on. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. It is also important to remember that the majority of cases of COVID-19 in Canada are mild-to-moderate, and the death rate has been quite low (22,514 deaths out of 914,697 cases or 592/million as of March 16 2021 - Coronavirus Dashboard [ncov2019.live]). Sadly, at least 70% of those deaths have been in people over 80 years of age, in long-term care (Dr. R. Bibby, Sociologist, University of Lethbridge; http://www.reginaldbibby.com/specialcovid19analyses.html). On the upside, there is now also good evidence that the majority of those recovered from COVID-19 have protective immunity (reviewed by Sette and Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell (2021), DOI: https://doi.org/10.1016/j.cell.2021.01.007).

It is from this perspective that we have been advocating for several core strategies to support re-opening our country to in-person work and learning. An important aspect of this is offering strategically prioritized vaccinations. Specifically, we have been advocating for the administration of safe and effective COVID-19 vaccines according the protocol that was used to have them approved for emergency use, until further data is available and reviewed and approved by Health Canada to support alternative protocols. In support of this goal, we have two recommendations:

1. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented evidence of it being ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. Specifically, it was shown to be only 10% effective against the South African variant, with the cut-off for approval being 50%. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf). Additionally, its use has been suspended in at least ten European countries until undesirable potential side-effects can be further investigated. For Ontarians, the Chief Medical Officer definitively stated in a letter to pubic health units in the province that individuals may opt out of receiving the AstraZeneca vaccine on the basis that it is admittedly of lower efficacy than the others (see the highlighted text on page 2 of the attached letter).

2. The intervals for the two-dose COVID-19 vaccines should adhere to what was officially approved by Health Canada and the manufacturers, which is 21- and 28-days for the Pfizer and Moderna vaccines, respectively. The rationale for this is presented below...

The history of Canada's move to extend COVID-19 intervals to an unprecedented four months.

Last week, the CBC launched a story to highlight the path that has led many jurisdictions in Canada to begin implementing an interval of up to four months for both the Pfizer and Moderna COVID-19 vaccines (https://www.cbc.ca/news/health/canada-covid-19-vaccine-delay-risk-1.5939134). It apparently began with a letter from an epidemiologist at the British Columbian Centre for Disease Control to the editor of *The New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMc2036242). In this letter it was claimed that Pfizer failed to realize the efficacy of its own vaccine and that its effectiveness as a single-dose regimen is actually a remarkable 92%. It is important to note that this is based on an extrapolation of a statistically underpowered, biased, limited data set from a trial that was never designed to test single-dose efficacy. Further, the extrapolation required several assumptions to be made that may or may not be true; there simply is no empirical data to know either way.

What many do not realize is that the researchers for Pfizer published a rebuttal to this letter in which they stated: "**In response to Skowronski and De Serres: we would like to emphasize that alternative dosing regimens of BNT162b2 have not been evaluated.**" Pfizer's own data has suggested that single-dose effectiveness might be just over 50%, with their admission of the caveat that their study was never designed to test this properly. Nonetheless, the idea that extended intervals will work well is being propagated, despite a lack of empirical evidence. Indeed, Dr. Bridle has confirmed via interviews with people coming out of local vaccine clinics that some of them are being told that a single dose has been shown to be 92% effective based on 'published data'. This is simply untrue and not the way science is supposed to work. The validity of alternative protocols is up for debate in the scientific community.

Any intervals that deviate from what Health Canada and the vaccine manufacturers have agreed to, represents experimentation, especially in the absence of any new validated data from a phase 3 clinical trial. However, in Ontario and many other jurisdictions in Canada, the change in the vaccine interval has been proposed. See the attached letter from Ontario's Chief Medical Officer as an example of this. In short, the intervals have been lengthened without sufficient empirical data to justify it. In contrast, the intervals provided by Health Canada are based on empirical data. The effectiveness of the two-dose regimens with 3- or 4-week intervals is known. The effectiveness of the two-dose regimens with any other interval is a 'best guess'. This background leads into a potentially more serious issue regarding informed consent...

Is informed consent being practiced properly in COVID-19 vaccine clinics?

In Ontario, the attached consent form should be hard-signed by everybody prior to receiving one of the experimental vaccines. Please note that this form requires a person to have read or to have read to them the vaccine information sheet (see the highlighted text on page 3 of the consent form). Please note the highlighted text on pages 4 and 6 of the vaccine information sheet that is appended to this letter. Consent is being given to receiving the dose at Health Canada's recommended interval of 3- (Pfizer) or 4-weeks (Moderna). No alternative intervals are described. Remarkably, however, many (if not most) attendees at the COVID-19 vaccine clinics are being told after receiving their first dose (*i.e.* once they are committed to the treatment) that they will likely have to wait up to four months to receive the second dose. **People are consenting to the 3-4-week interval** (3 weeks for Pfizer's vaccine; four weeks for the Moderna vaccine) **but are then being told that they cannot receive the second dose for another four months.** For those who would like to insist on receiving their vaccine as per Health Canada's recommended interval, we suggest you take a hard-copy of the vaccine information sheet to the clinic and have

them confirm that they will adhere to the protocol you are consenting to prior to letting them administer the first dose.

Why might the interval for two-dose vaccines matter?

Some proponents of lengthening the interval argue there can be no harm. However, there is some scientific basis for suggesting that lengthening intervals could cause harm: 1. The companies themselves suggest a single dose is significantly less efficacious than two doses. This could put individuals at prolonged risk of getting infected while waiting for the second dose. This could be a particular problem for those who are at high risk. 2. It is unknown if the duration of immunity (i.e. how long a person is protected) conferred by a single dose extends to four months; it is possible that there may be no protection at this point. 3. It is unknown if immunological memory conferred by the first vaccine will last long enough for a second dose, given four months later, to serve as a proper 'booster vaccine'. If a proper boost is not conferred, the two-dose effectiveness could be reduced below the 95% effectiveness shown with the approved interval. 4. Induction of long-term, relatively weak immunity could potentially promote the emergence of immune-evasive mutants. This would be similar to what has been observed over and over again with the emergence of dangerous antibiotic-resistant bacteria; it is potentiated by the misuse of the therapeutic agents designed to effectively treat the pathogens. Promotion of immune-evasive SARS-CoV-2 would put everyone at greater risk. Although these are cautionary possibilities, **they are no less valid than the speculations that led to adopting untested long intervals**. Given these are novel nucleic acid vaccine platforms, approved for emergency use only, it might be wise to err on the side of caution. The take-home message is: Longer intervals might be OK, but they also might create problems. We simply don't know yet. On this basis, **those who want to receive the vaccines according to how they were approved for emergency use should be entitled to this.** However, **public health officials seem to be over-riding this right, even though it contradicts their own informed consent procedure, Health Canada, and the vaccine manufacturers.**

With sincere concern for our fellow Canadians,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

This is Exhibit " E " to the Affidavit of

Byram Bridle, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

March 23, 2021

Dear Fellow Canadians:

Scientists Express Urgent Concerns Over Current COVID-19 Vaccine Policies

University Of Guelph Faculty Speak Up:

The following urgent concerns are being expressed by the following faculty members at the University of Guelph:

- Dr. Byram Bridle is a viral immunologist
- Dr. Bonnie Mallard is an immunologist
- Dr. Neil Karrow is an immunologist

Generally, policies for COVID-19 have been generated with relatively little consultation with immunologists, including viral immunologists. However, at its core, COVID-19 is a problem at the interface of immunology and virology.

This interface is both in terms of its pathogenesis and the primary solution being sought, which is acquisition of immunity against the virus SARS-CoV-2. In addition to our group having in-depth knowledge of these fields, Dr. Bridle received funding from the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area. Please note that information about COVID-19 vaccines is rapidly changing. The information presented below is accurate as of March 23, 2021.

Has The Goal To Flatten The Curve Been Forgotten?

Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks. The purpose was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed.

Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses.

Will SARS-CoV-2 Become Endemic?

Among the many reasons for this virus becoming endemic is the propensity of SARS-CoV-2 to mutate over time. This will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly focused immunity that targets a single protein known as the spike.

These two major issues will combine to potentiate SARS-CoV-2 being able to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada.

How Can We Live With This Virus While Still Maximizing Health And Safety?

It has become clear that we can't continue to rely on continual lockdowns due to impact on mental health, delays to other medical treatments, a sinking economy and so on. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities.

It is also important to remember that the majority of cases of COVID-19 in Canada are mild-moderate, and the death rate has been quite low (22,676 deaths out of 933,798 cases or 596/million people as of March 22, 2021 - Coronavirus Dashboard (ncov2019.live).

Sadly, at least 70% of those deaths have been in people over 80 years of age, in long-term care (Dr. R. Bibby, Sociologist, at the University of Lethbridge – Research of Reginald W. Bibby (reginaldbibby.com)).

On the upside, there is now also good evidence that the majority of those recovered from COVID-19 have protective immunity (reviewed by Sette and Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell (2021), https://doi.org/10.1016/ j.cell.2021.01.007).

Therefore, we need to identify those with immunity from natural exposure using available antibody testing, and strategically prioritize those at highest risk, who need and want to be vaccinated, according to the manufacturers currently approved vaccination protocols.

How Can Vaccines Be Prioritized According To Manufacturers Approved Protocols?

It is from this perspective that we have been advocating for several core strategies to support re-opening our country to in-person work and learning. An important aspect of this is offering strategically prioritized vaccinations.

Specifically, we have been advocating for the administration of safe and effective COVID-19 vaccines according the protocol that was used to have them approved for emergency use, until further data is available and reviewed and approved by Health Canada to support alternative protocols.

In support of this goal, we have two recommendations:

1. Consideration should be given to avoiding the AstraZeneca vaccine, for which there is documented evidence of it being ineffective against the South African variant of SARS-CoV-2, which is now in Canada. It was only 10% effective against the South African variant, with the cut-off for approval being 50% (https://www.nejm.org/doi/full/10.1056/NEJMoa2102214?query=featured_home).

2. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf).

   For Ontarians, the Chief Medical Officer definitively stated in a letter to pubic health units in the province that individuals may opt out of receiving the AstraZeneca vaccine on the basis that it is admittedly of lower efficacy than the others (see the highlighted text on page 2 of the attached letter).

3. The intervals for the two-dose COVID-19 mRNA vaccines should adhere to what was officially approved by Health Canada and the manufacturers, which is 21- and 28-days for the Pfizer and Moderna vaccines, respectively. The rationale for this is presented below...

Why The Concern Over Changing The Manufacturers Approved Protocols?

The history of Canada's move to extend COVID-19 intervals to four months is unprecedented. Recently, the CBC launched a story to highlight the path that has led many jurisdictions in Canada to begin implementing an interval of up to four months for both the Pfizer and Moderna COVID-19 vaccines (https://www.cbc.ca/news/health/canada-covid-19-vaccine-delay-risk-1.5939134).

It apparently began with a letter from an epidemiologist at the British Columbian Centre for Disease Control to the editor of *The New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMc2036242).

In this letter it was claimed that Pfizer failed to realize the efficacy of its own vaccine and that its effectiveness as a single-dose regimen is a remarkable 92%. It is important to note that this is based on an extrapolation of a statistically underpowered, biased, limited data set from a trial that was never designed to test single-dose efficacy. Further, the extrapolation required several assumptions to be made that may or may not be true; there simply is no empirical data to know either way.

What many do not realize is that the researchers for Pfizer published a rebuttal to this letter in which they stated: "In response to Skowronski and De Serres: **we would like to emphasize that alternative dosing regimens of BNT162b2 have not been evaluated**." Pfizer's own data has suggested that single-dose effectiveness might be just over 50%, with their admission of the caveat that their study was never designed to test this properly.

Nonetheless, the idea that extended intervals will work well is being propagated, despite a lack of empirical evidence. Indeed, Dr. Bridle has confirmed via interviews with people coming out of local vaccine clinics that some of them are being told that a single dose has been shown to be 92% effective based on 'published data'. This is simply untrue and not the way science is supposed to work. The validity of alternative protocols is up for debate in the scientific community.

Notably, on March 22nd, Canada's chief science adviser, Dr. Mona Nemer, spoke out against lengthening dosing intervals for Canadian seniors, citing not only a lack of scientific evidence to support it, but even emerging evidence to contraindicate it (https://www.ctvnews.ca/health/coronavirus/research-doesn-t-back-vaccine-dose-delay-for-seniors-canada-s-chief-science-adviser-says-1.5358075).

Any intervals that deviate from what Health Canada and the vaccine manufacturers have agreed to, represents experimentation, especially in the absence of any new validated data from a phase 3 clinical trial. However, in Ontario and many other jurisdictions in Canada, the change in the vaccine interval has been implemented.

See the attached letter from Ontario's Chief Medical Officer as an example of this. In short, the intervals have been lengthened without sufficient empirical data to justify it. In contrast, the intervals provided by Health Canada are based on empirical data. The effectiveness of the two-dose regimens with three-

or four-week intervals is known. The effectiveness of the two-dose regimens with any other interval is a 'best guess'. This background leads into another potentially serious issue regarding informed consent...

Is Informed Consent Being Practiced Properly In Canadian COVID-19 Clinics?

According to Ontario's Ministry of Health website, the attached consent form should be hand-signed by everybody prior to receiving one of the experimental vaccines. Please note that this form requires a person to have read or to have read to them the vaccine information sheet (see the highlighted text on page 3 of the consent form). Please note the highlighted text on pages 4 and 6 of the vaccine information sheet that is appended to this letter.

The Ontario Ministry of Health website appears to be requiring consent to be given to receiving the second dose of the mRNA vaccines at Health Canada's recommended interval of three- (Pfizer) or four-weeks (Moderna). No alternative intervals are described. Remarkably, however, most attendees at the COVID-19 vaccination clinics are being told that they cannot receive the second dose for another four months.

For those who would like to insist on receiving their vaccine as per Health Canada's recommended interval, we suggest you take a hard-copy of the vaccine information sheet to the clinic and have them confirm that they will adhere to the protocol you are consenting to prior to letting them administer the first dose.

WHY MIGHT THE INTERVAL FOR TWO-DOSE VACCINES MATTER?

Some proponents of lengthening the interval argue there can be no harm. However, there is some scientific basis for suggesting that lengthening intervals could cause harm:

1. The companies themselves suggest a single dose is significantly less efficacious than two doses. This could put individuals at prolonged risk of getting infected while waiting for the second dose. This could be a particular problem for those who are at high risk.

2. It is unknown if the duration of immunity (*i.e.* how long a person is protected) conferred by a single dose extends to four months; it is possible that there may be no protection at, or even before this point.

3. It is unknown if immunological memory conferred by the first vaccine will last long enough for a second dose, given four months later, to serve as a proper 'booster vaccine'. If a proper boost is not conferred, the two-dose effectiveness could be reduced below the 95% effectiveness shown with the approved interval.

4. Induction of long-term, relatively weak immunity could potentially promote the emergence of immune-evasive mutants. This would be similar to what has been observed over and over again with the emergence of dangerous antibiotic-resistant bacteria; it is potentiated by the misuse of the therapeutic agents designed to effectively treat the pathogens.

Promotion of immune-evasive SARS-CoV-2 would put everyone at greater risk. Although these are cautionary possibilities, they are no less valid than the speculations that led to adopting untested long

intervals. Given these are novel nucleic acid vaccine platforms, approved for emergency use only, it might be wise to err on the side of caution.

5. A pre-print of a relevant scientific article was posted on-line (https://www.medrxiv.org/content/10.1101/2021.03.03.21251066v1). It has not yet undergone peer review. However, we routinely review these kinds of articles and have concluded that the core data set appears to be valid. This article describes results of a study with the Pfizer vaccine. Importantly, the authors have concluded "since the majority of vaccinees did not obtain neutralizing antibody titers after the first vaccination, we suggest that **postponing a second vaccination with this vaccine is neither advisable for younger nor elderly populations**." In short, a single dose of Pfizer's vaccine would be expected to leave most people unprotected against SARS-CoV-2. Therefore, extending the interval to four months would not meet the goal of getting twice as many people partially protected, as our public health officials are claiming. Instead, it could cause large numbers of people to be left unprotected for a prolonged period.

What's the Take-Home Message?

A longer interval might be okay for the Moderna vaccine, but it also might create problems. We simply don't know yet. Cutting-edge data from a properly conducted scientific study suggested that a prolonged interval for the Pfizer vaccine is dangerous. On this basis, those who want to receive the vaccines according to how they were approved for emergency use should be entitled to this.

However, public health officials seem to be over-riding this right, even though it appears to contradict Health Canada, the vaccine manufacturers, Canada's chief science advisor, and the informed consent procedure posted on the Ontario Ministry of Health website.

With sincere concern for our fellow Canadians,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

This is Exhibit " F " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

Yeah, I'd love to hear her talk about it. It would be interesting and she would presumably not pull any punches.

Scott

J. Scott Weese DVM DVSc DACVIM FCAHS
Professor, Ontario Veterinary College
Director, Centre for Public Health and Zoonoses
University of Guelph
http://www.wormsandgermsblog.com
Twitter: @Weese_scott

From: Glen Pyle <gpyle@uoguelph.ca>
Date: Wednesday, June 2, 2021 at 12:09 PM
To: J. Scott Weese <jsweese@uoguelph.ca>
Subject: Re: University Response to Bridle Enquiries

Thanks Scott. I declined to comment, but offered to reach out to others. I may have suggested your name :) Angie Rasmussen has said she can try to provide comment, but she just moved to Saskatchewan and is a bit busy at the moment. Not sure if you know her, but she knows her science and she takes no shit from anyone. She's gone head-to-head with Alex Berenson and that was a treat to watch.

Glen.

W. Glen Pyle, PhD
Senior Career Investigator
Improving the Heart & Brain Health for Women in Canada, Heart & Stroke Foundation
Distinguished Professor, Innovation in Teaching
Co-Lead, COVID-19 Resources Canada Science Explained
Professor & Assistant Chair, Department of Biomedical Sciences
Ontario Veterinary College, University of Guelph
Associate Member, IMPART, Dalhousie University
LinkedIn: https://www.linkedin.com/in/glenpyle
Twitter: @glenpyle
"By a divine paradox, wherever there is one slave there are two. So in the wonderful reciprocities of being, we can never reach the higher levels until all our fellows ascend with us."
-- Edwin Markham

From: J. Scott Weese <jsweese@uoguelph.ca>
Sent: 02 June 2021 11:45 AM
To: Glen Pyle <gpyle@uoguelph.ca>
Subject: Re: University Response to Bridle Enquiries

Nice letter. Agree 100%. I've been waiting for a lawsuit threat from him and have been careful with my wording. The good thing is I can amplify lots of other great takedowns of the work without having to add my own commentary. The Mercury probably contacted you about him, since I assume they emailed a couple of the more visible critical people at Guelph. It will be interesting to see if they go anywhere with it. I ended up providing an email comment...tried not to get too far into it but said it was dangerous misinformation so if they end up using that, I'm sure it will evoke a response. It's sad that his bullying behaviour is winning out so far.

Scott

J. Scott Weese DVM DVSc DACVIM FCAHS
Professor, Ontario Veterinary College
Director, Centre for Public Health and Zoonoses
University of Guelph
http://www.wormsandgermsblog.com
Twitter: @Weese_scott

From: Glen Pyle <gpyle@uoguelph.ca>
Date: Wednesday, June 2, 2021 at 11:31 AM
To: Jeffrey Wichtel <jwichtel@uoguelph.ca>
Subject: RE: University Response to Bridle Enquiries

Thanks Jeff.

I appreciate the difficulty in responding to this situation. To be clear, while I do take issue with the scientific accuracy of the claims, I have never called for curtailung Byram's freedom to make those claims.

My specific concerns are that he is criticizing a group of products, but holds a grant to develop a competing product, and he does not disclose the conflict of interest. This is a fundamental error in research. Furthermore, he has on at least one occasion distributed a document with the header from an outside organization, using his University of Guelph email and the University logo attached (to the email, not the document). This implies an endorsement. As academics we might understand the nature of the university and the difficulty in policing such issues, but the general public does not. They see this as a stamp of approval from the university.

Finally, I will end by pointing out that while the university is standing squarely behind Byram and his right to freedom of expression, his threat of a lawsuit has silenced my ability to speak out. He has, without any evidence, suggested I am behind the website that was created to counter his claims. To be clear: I had nothing to do with the website, I have not endorsed it, nor have I promoted it in any way. At no time did anyone from the university speak out on this issue, and that threat remains. I have declined multiple requests to comment on the science because of this, and in each case explained my reasoning. The double standard here is astounding, disappointing, and comes with real consequences.

I am an alumni of the University of Guelph and specifically chose to come back and work here. I enjoy the environment, my colleagues, and most of all, the students. But I now find myself embarrassed by the University and the lack of moral leadership. This has created an indelible stain on the reputation of the institution and all of us who are associated with it.

Again, I appreciate the update, but wish not to be part of this discussion any further. I think we will have to agree to disagree and simply move on.

Glen.

W. Glen Pyle, PhD
Senior Career Investigator
Improving the Heart & Brain Health for Women in Canada, Heart & Stroke Foundation
Distinguished Professor, Innovation in Teaching
Co-Lead, COVID-19 Resources Canada Science Explained
Professor & Assistant Chair, Department of Biomedical Sciences
Ontario Veterinary College, University of Guelph
Associate Member, IMPART, Dalhousie University
LinkedIn: www.linkedin.com/in/glenpyle
Twitter: @glenpyle
"By a divine paradox, wherever there is one slave there are two. So in the wonderful reciprocities of being, we can never reach the higher levels until all our fellows ascend with us."
-- Edwin Markham

-------- Original message --------
From: Jeffrey Wichtel <jwichtel@uoguelph.ca>
Date: 2021-06-02 10:51 AM (GMT-05:00)
To: Glen Pyle <gpyle@uoguelph.ca>
Subject: FW: University Response to Bridle Enquiries

Glen, this has just been sent to OVC leadership. I will be letting Byram know this has been circulated.

Jeff

From: JJW <jwichtel@uoguelph.ca>
Date: Wednesday, June 2, 2021 at 10:44 AM
To: Todd Duffield <tduffiel@uoguelph.ca>, Brandon Lillie <blillie@uoguelph.ca>, Carolyn Kerr <ckerr@ovc.uoguelph.ca>, Tarek Saleh <tsaleh@uoguelph.ca>, Carol Ann Higgins <chiggins@uoguelph.ca>, Ilya Bogorad <ibogorad@uoguelph.ca>, Joanne Hewson <jhewson@uoguelph.ca>, Shayan Sharif <shayan@uoguelph.ca>, Stephanie Nykamp <snykamp@uoguelph.ca>, Kim Robinson <krobin01@uoguelph.ca>, Julie Byczynski <jbyczyns@uoguelph.ca>, Katherine Galley <kgalley@uoguelph.ca>

Cc: Jane Dawkins <jdawkins@uoguelph.ca>, Karen Mantel <kmantel@uoguelph.ca>, Lori Bona Hunt <l.hunt@exec.uoguelph.ca>
Subject: University Response to Bridle Enquiries

To OVC leadership team:

We have experienced a great deal of activity and concern associated with Dr. Bridle's recent media engagements. The university and college communications teams have been working hard to come up with a strategy to respond to concerns while honouring our institutional commitment to freedom of expression. I thank them for the excellent advice they have provided to OVC and UofG leadership.

The attached statement (or appropriate excerpts) is university approved, and is made available to you to be use as needed to respond to concerns that are being directed to you or your team. You may refer to Dr. Bridle in email communications if appropriate to the enquiry.

The university will not be posting anything to do with Dr. Bridle on its home pages at this time, nor posting anything to social unless in the context of a specific enquiry directed to us, in which case the attached text can be used.

There will be further updates on this topic, including how we manage internal communications at OVC.

Thanks,

Jeff

Response to emails or social media posts re: Byram Bridle.

Note that the first paragraph should only be used when responding to emails. Delete the first paragraph when using this response on social media, etc.

Thank you for sharing your concerns about research/media reports regarding Dr. Byram Bridle.

The University of Guelph's core values include the advancement of learning and dissemination of knowledge to serve society and improve life. To embody these values, the University has clearly established policies and procedures that govern research, academic freedom and freedom of expression.

As stated in our Policy Statement on Freedom of Expression, "To achieve its purpose and fulfill its mission, the University is committed to the principle of freedom of expression, which includes freedom of speech and means the ability to examine, question, critique, investigate, enquire, speculate and communicate on issues without deference to prescribed doctrine."

This overarching commitment and mission aligns with the right of individual faculty to express their own opinions or to pursue curiosity-driven research, even when it may be perceived or believed to be controversial and at odds with the common understanding.

Specifically, opinions expressed by U of G faculty or researchers are their own; they do not reflect the opinions of the University.

The University of Guelph has stated publicly that vaccinations are an important step in bringing us safely out of the COVID-19 pandemic. The University is strongly encouraging everyone who is eligible for vaccination to get vaccinated.

No community of scholars holds a unanimous opinion on this topic or any issue. Indeed, faculty members publish research or make statements that are at times controversial or that provoke discussion and debate.

It is through exposure to alternative and controversial perspectives and academic debate, among other things, that students are enabled to achieve the University's learning outcomes, especially those of critical and creative thinking.

Universities must continue to be places that value differing viewpoints, champion free speech, and promote inquiry and academic freedom. We do expect that all researchers adhere to the highest levels of scholastic integrity and comply with applicable laws and regulations.

Details regarding research integrity and freedom of expression policies are available publicly.

Hi Karen and Jane,

If it helps, I do not want to be part of the story. I know that I am to be censored and crushed right now. However, I would like my trainees to feel supported by their institution. And the story would help promote the excellent relationship that our college has with the Cancer Research Society. I have received four consecutive grants from them, spanning 4+ years and now extending to at least 6.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
ogy/peop

From: Karen Mantel <kmantel@uoguelph.ca>
Sent: Wednesday, September 1, 2021 5:20 PM
To: Byram Bridle <bbridle@uoguelph.ca>; Jane Dawkins <jdawkins@uoguelph.ca>; Deirdre Healey <healeyd@uoguelph.ca>
Cc: Irina Navarrete <inavarrete@src-crs.ca>; Jason Knapp <jknapp03@uoguelph.ca>; Julia Kakish <jkakish@uoguelph.ca>; Van Vloten, Jacob P. <vanVloten.Jacob@mayo.edu>; Arthane Kodeeswaran

<akodeesw@uoguelph.ca>
Subject: RE: CRS funding for research

Hi Byram,

Thank you for your note and congratulations on this funding success.
We appreciate the update and your suggestion related to a trainee focus but unfortunately don't have capacity at this time to put together a story on this. We will add this research news to our list to explore later this fall.
Thank you again and hope you are having a good week.

Best regards
Karen

From: Byram Bridle <bbridle@uoguelph.ca>
Sent: Friday, August 27, 2021 5:17 PM
To: Jane Dawkins <jdawkins@uoguelph.ca>; Karen Mantel <kmantel@uoguelph.ca>; Deirdre Healey <healeyd@uoguelph.ca>
Cc: Irina Navarrete <inavarrete@src-crs.ca>; Jason Knapp <jknapp03@uoguelph.ca>; Julia Kakish <jkakish@uoguelph.ca>; Van Vloten, Jacob P. <vanVloten.Jacob@mayo.edu>; Arthane Kodeeswaran <akodeesw@uoguelph.ca>
Subject: CRS funding for research

Hi Jane, Karen, and Deirdre,

I am pleased to let you know that my research team has received two years of funding worth $120,000 from the Cancer Research Society for a project entitled "Heat- and Cold-Adaptation of Oncolytic Rhabdoviruses to Improve Their Clinical Utility". I have attached a copy of the research proposal. I have also copied several of the trainees involved in this research (Arthane started this work as a high school student through the Sanofi Biogenius Canada program and is now an undergraduate student at U of G; Dr. van Vloten is now a postdoctoral fellow at the Mayo Clinic in Rochester, Minnesota, USA, who worked extensively on this; Jason and Julia are current team members who will be advancing the research funded by the current grant). With morale so low among trainees on most academic campuses, I thought it might be a good idea to interview these four great young scientists about their involvement with the research, where they see it going, and why we are so proud to partner with the Cancer Research Society to advance this research. I have also copied Ms. Irina Navarrete from the Cancer Research Society, so that any story is coordinated with them to avoid pre-empting their public release of this news.

Please note that I am leaving for a remote vacation (no phone/computer), but will be back to work on Sept. 7th.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
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Lab Room #3808
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Department of Pathobiology
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E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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This is Exhibit " G " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

_____

Dr. Byram Bridle's transcript of the interview with Alex Pierson:

As per the link provided in Dr. David Fisman's motion (*i.e.*, https://podcasts.apple.com/ca/podcast/new-peer-reviewed-study-on-covid-19-vaccines-suggests/id1318830191?i=1000523346577)

Starts at 0:30 (an advertisement runs prior to this)…

Alex Pierson (0:30-1:44): We're talking about a lot of science these days. It's coming at us fast and furious. And a lot of people asking, well, good questions. You know, the vaccines, are they safe for kids? Um, certainly there's a big push to get kids as young as twelve the shot as soon as possible. But, um, not everyone's confident about, about it. Even if you're not an anti-vaxxer. There are lot of parents who are kind of nervous about putting something into their kids. Um, and then I read that there have been several dozen cases of heart problems in teens and young adults, which Israel is now looking into. Um, and what they're looking into, which they released the results of, are why mostly males, not all, but around twenty-two years of age and younger are getting heart inflammation. So, one to four days after getting the shot, um, they get like a shortness of breath, a fatigue, and some very specific chest pain. It's mild, so no one's gotten really sick or died. But you want to know what you don't know if you are going to put something into your kids. Let us bring in Dr. Byram Bridle. He's an associate professor of viral immunology at the University of Guelph. Doctor, you've been very, um, you know, ah, very open, um, on this whole issue and, and you know, you aren't an anti-vaxxer by any stretch. But what do you think about this inflammation in the heart and, and if, is it an actual threat?

Byram Bridle (1:45-3:11): Yeah, thanks for having me on, Alex. Ah, yeah, as you said, I, I am very much pro-vaccine, but, ah, always making sure that the science is done properly and that we follow the science carefully before going into, ah, you know, public rollout of vaccines. Um, I, I hope you, that you will let me run with this a little bit Alex. I'll provide, I, I, I can provide, I, I, I, I'll forewarn you and, and your listeners that, um, the story I am about to tell is, is a bit of a scary one. Um, this is cutting-edge science. Ah, there's a couple of key, um, pieces of scientific information that I have become privy to just within the past few days that has, ah, made the final link, ah, to, so we understand now, myself and some key coll… international collaborators, we understand exactly why these problems are happening, and many others associated with these vaccines. And the story is a bit of a scary one, so just to brace you for this. But I am going to walk you through this. The, the science that, that I am going to be talking about, um, I don't have the time here to describe exactly the scientific data but let me assure you that everything I am stating here, that I am going to state right now, is completely backed up by peer-reviewed scientific publications in, uh, well-known and, ah, well-respected scientific journals. I have all of this information, ah, in-hand. I am in the process of madly trying to put it all into a, a, a, a document that I, I can hopefully circulate widely. So, your listeners are going to be the first to hear the public release of this conclusion and I'll, I can…

Alex Pierson (3:12-3:13): That was very ominous.

Byram Bridle (3:12-3:14): …back this up with science.

Alex (3:13-3:14): [chuckles]

Byram Bridle (3:14-6:52): So, this is what it is. The SARS-coronavirus-2 has a spike protein on its surface. That spike protein is what it, allows it to infect our bodies. That is why we have been using the spike protein in our vaccines. The vaccines we're using get our cells in our body to manufacture that protein. If we can mount an immune response against that protein, in theory, we, we can prevent this virus from infecting the body. That's the theory behind the vaccine. However, when studying the disease, severe COVID-19, everything that you just described, heart problems, lots of problems with the cardiovascular system, bleeding, and clotting is all associated with severe COVID-19. And looking, and, and doing that research, what has been discovered by the scientific community is the spike protein on its own is almost entirely responsible for the damage to the cardiovascular system, if it gets into circulation. Indeed, if you inject the, the purified spike protein into the blood of research animals they get all kinds of damage to the cardiovascular system, and it can cross the blood-brain barrier and cause damage to the brain. Now, at first glance, that doesn't seem too concerning because we're injecting these vaccines into the shoulder muscle. The assumption all up until now has been that these vaccines behave like all of our traditional vaccines, that they don't go anywhere other than the injection site. So, they stay in our shoulder, some of the protein will go to the draining lymph node in order to activate the immune system. However, this, this is where the cutting-edge science is come in, and, and this is where it gets scary. Ahm, through a request for, ah, information from the Japanese regulatory agency, myself and several international collaborators have been able to get access to what's called a biodistribution study. It's the first time ever that, ah, scientists have been privy to seeing where these mRNA vaccines go after vaccination. In other words, is it a safe assumption that it stays in the shoulder muscle? The short answer is absolutely not. It's, ah, very disconcerting. The spike protein gets into the blood, circulates through the blood in individuals, ah, over several days post-vaccination. It accumulates, once it gets into blood, it accumulates in a number of tissues such as the spleen, the bone marrow, ah, the liver, the adrenal glands. Ah, one that is of particular concern for me is, ah, it accumulates at quite high concentrations in the ovaries. And, um, and then also a publication that was just accepted for, ah, ah, ah, a scientific paper just accepted for publication, ah, that, that backs this up looked at thirteen, ah, young health care workers that had received the Moderna vaccine, right, which is the other messenger RNA-based vaccine we have in Canada. And they, they confirmed this. They found the spike protein in circulation, so in the blood of eleven of those thirteen health care workers that had received the vaccine. Ah, what this means is, so we have known for a long time that the spike protein is a pathogenic protein. It is a toxin. It can cause damage in our body if it gets into circulation. Now, we have clear-cut evidence that the vaccines that make our bodies, or, or the muscles, or the cells in our, in our deltoid muscles, right, manufacture this protein. Not... The vaccine itself, plus the protein gets into blood circulation. When in circulation the spike protein can bind to the receptors that are on our platelets and the cells that line our blood vessels. When that happens, it can do one of two things. It can either cause platelets to clump and that can lead to clotting. That's exactly why we've been seeing clotting disorders associated with these vaccines. It can also lead to bleeding. And, of course, the heart's involved. It's part, it's actually part of the…

Alex Pierson (6:52-6:53): Hmm.

Byram Bridle (6:53-7:51): …cardiovascular system. That's why we are seeing heart problems. The protein can also cross the blood-brain barrier and cause neurological damage. That's why also in the fatal cases of blood clots, many times it's seen in the brain. And, ah, also of concern is, um, there's also evidence of a, of a study, this has not yet been accepted for publication yet. This one, they were trying to show that the antibodies from the vaccine get transferred through breast milk. And the idea was this may be a good thing because it prefer… it would confer some passive protection to babies. However, what they found inadvertently was that the, the, ah, vaccines, the messenger RNA vaccines actually get transferred through the br-breast milk. So, delivering the vaccine vector itself, ah, into infants that are breastfeeding. Also, what this, we now know the spike protein gets into circulation. Any proteins in the blood will get concentrated in breast milk. Looking into the adverse event data base in the United States, we have found evidence of suckling infants experiencing bleeding disorders in the gastrointestinal tract. So,…

Alex Pierson (7:51-7:57): Okay. Let me pause you there because I've only got about forty-five seconds left. I mean, the bottom line is this is scaring a lot of people. This will freak a lot of people out. Yeah.

Byram Bridle (7:52-8:57): …what this means. Sure. Sure. I, I, I'll wrap it up. This is very important this, this message. Yes. So, so, this has implications for blood donation, right? Now Canadian Blood Services, Canadian Blood Services is saying people that, who have been vaccinated can donate. We don't want transfer of these, ah, pathogenic spike proteins to fragile patients who are being trans…, transfused with that blood. This has implications for, ah, infants that are suckling. And this, this has serious implications for people for whom SARS-coronavirus-2 is not a high-risk pathogen, and that includes all of our children. In short, the conclusion is, we made a big mistake. We didn't realize it until now. We thought the spike protein was a great target antigen. We never knew the spike protein itself was a toxin and was a pathogenic protein. So, by vaccinating people, we are inadvertently inoculating them with a toxin and in some people, this gets into circulation and when that happens in some people it can cause damage, especially in the cardiovascular system. And I have many other, I don't have time, but many other legitimate questions about the long-term safety, therefore, of this vaccine.

Alex Pierson (8:57): Right.

Byram Bridle (8:58-9:06): For example, with it accumulating in the ovaries, one of my questions is 'will we be rendering young people infertile, some of them infertile'? So, I'll stop there.

Alex Pierson (9:06): Okay.

Byram Bridle (9:06): I know it is heavy-hitting, but…

Alex Pierson (9:07-9:24): I, well I am up against the clock. I need an hour when I talk to you because you, you have so much information and of course you're, your're one opinion of many. But you, you know it, it's interesting because you have a different look at it and certainly, ah,

time will tell on this. But we'll have to have you on again, um, because I always get an interesting and different perspective from you. Doctor, thank you.

Byram Bridle (9:24-9:26): Ah, it was my pleasure, take care.

Alex Pierson (9:26-9:42): That is, ah, Dr. Bridle who a lot of you like and like to hear. And, again, ah, that's wh… his findings. Again, we get lots of different medical opinions. Um, that'll scare a lot of people, but there are already a lot of people who don't trust, ah, the vaccines given the speed at which they've come out.

(An advertisement runs after this.)

This is Exhibit " H " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

UNIVERSITY of GUELPH

From: Byram Bridle
Sent: Sunday, May 30, 2021 2:07 AM
To: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>
Cc: Karen Mantel <kmantel@uoguelph.ca>; Jane Dawkins <jdawkins@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>
Subject: smear campaign

Dear Jeff and Shayan,

It has been brought to my attention that a smear campaign has been launched against me because I answered a question about COVID-19 vaccines that was posed to me by a radio show host. Everything I said is backed up by peer-reviewed scientific articles. Of course, however, I had no way to show these references in the context of a radio interview. FYI, this libelous website was set-up...

http://byrambridle.com/

Because of this I have found myself the victim of vicious attacks. This has forced me to cancel my commitment to a grant review panel for CIHR (reviews were due tomorrow [Mon.], the panel was to meet the week after). I have had to leave them and applicants short of eight reviews. This is a very embarrassing thing to do and reflects very poorly on me as a professional. I have also had to contact two editors to plead for extensions to submission deadlines for two manuscripts from my group that were due tomorrow (Monday). This is taking a toll on my mental and physical health. I should not have to be up at 2 in the morning on a Sunday having to deal with this. Thankfully, I have had numerous colleagues, both locally and from around the world jump to my defence. I have already been in contact with a legal team that has offered to investigate should I wish to follow through. There is a second lawyer who may be willing to help. Of incredible concern was this tweet that was forwarded to me....

https://twitter.com/glenpyle/status/1398810510234206210

Glen Pyle | #GetVaccinated on Twitter

"@maggieoutabout @DFisman @UofGuelphOAC It's not a

From:	Byram Bridle
To:	Glen Pyle
Cc:	Jeffrey Wichtel; Shayan Sharif; Brandon Lillie; Karen Mantel; Jane Dawkins; Charlotte Yates; Gwen Chapman; Cate Dewey
Subject:	Re: smear campaign
Date:	Sunday, May 30, 2021 12:06:22 PM
Attachments:	Outlook-zmx0zh0s.png Outlook-5224tkqb.png Outlook-klbt4d1x.png
Importance:	High

Hi Glen,

You failed to answer the most important question: **Who is the scientist that made the website?** They need to take it down immediately. You know who this person is. If you do not facilitate taking it down, then you are complicit in the harm it is causing me.

My comment Re: your article was supposed to be interpreted as "The website slammed me using an article that Glen wrote". Please excuse my weak use of grammar under great duress in the wee hours of the morning.

Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
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https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

Date: 2021-05-30 4:11 AM (GMT-05:00)
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Subject: Re: smear campaign

Glen,

Can you please explain your role in the smear campaign against me? Who is the scientist that made the website to slander me? I need this information now! ...or are you going to continue to revel in the harm being caused to a colleague that you are embarrassed about? If I do not receive a reply from you by noon on Monday, I will contact the police to see if they can get the information from you.

Byram

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From: Byram Bridle <bbridle@uoguelph.ca>

I

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

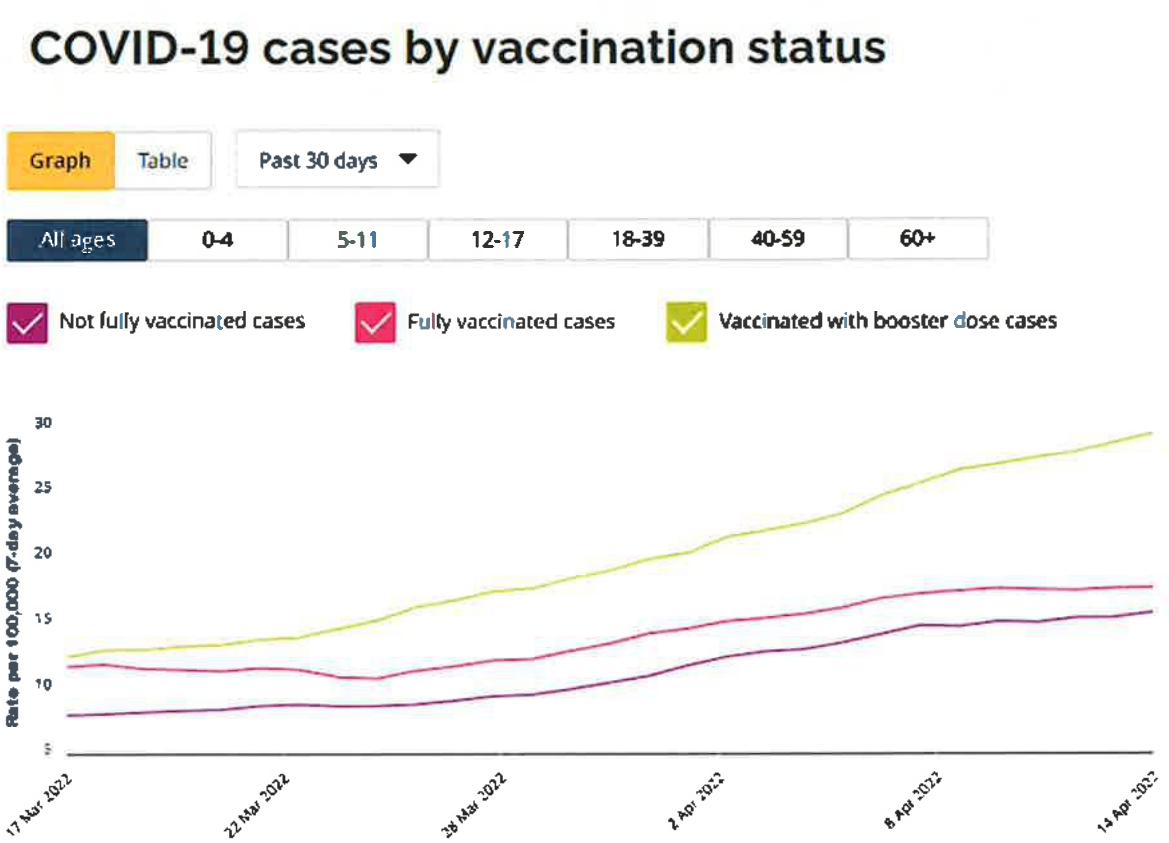
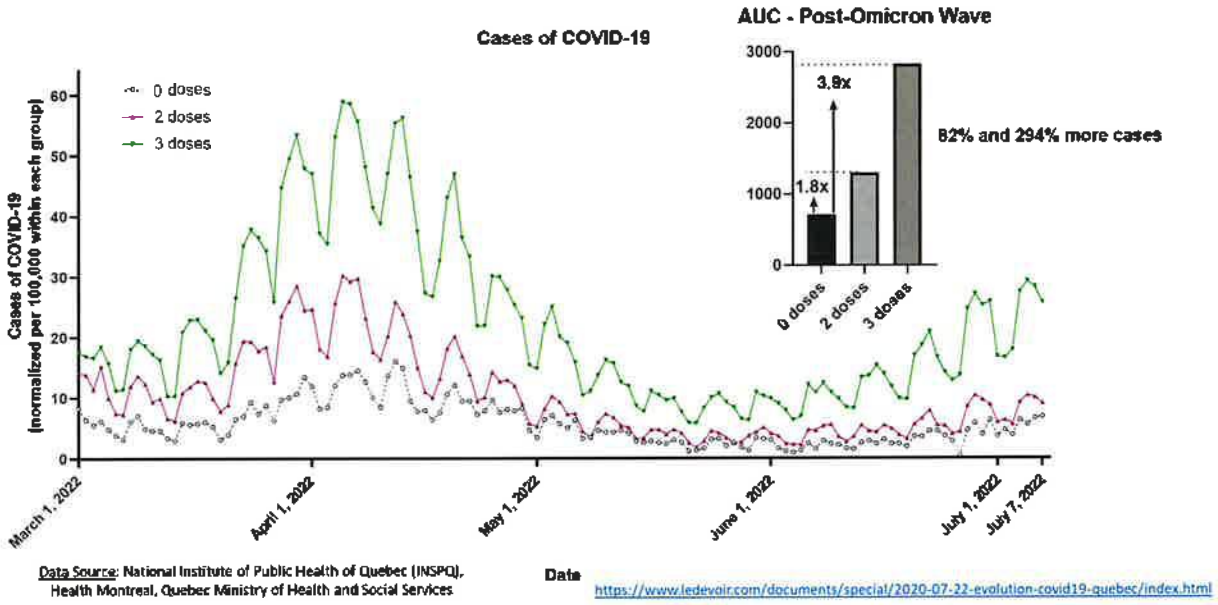
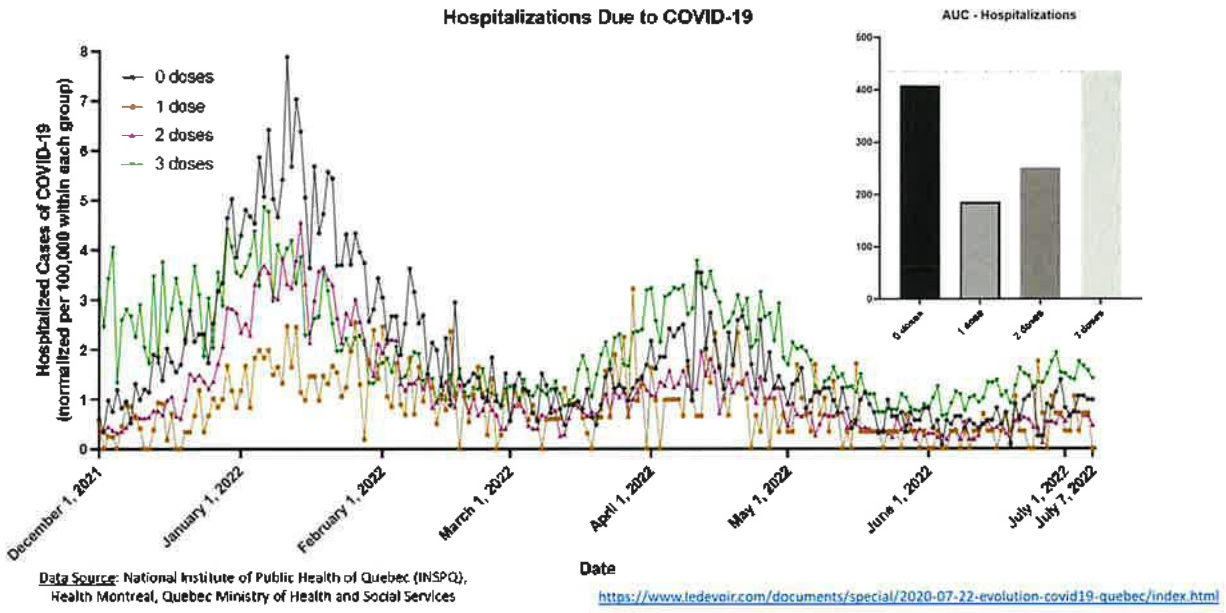


Figure 7: Proportional daily cases of COVID-19 occurring among Ontarians who were 'not fully vaccinated' (*i.e.*, unvaccinated or a single dose; purple line), 'fully vaccinated' (*i.e.*, two doses; pink line), or 'vaccinated with booster dose' (*i.e.*, three or more doses; green line). This graph was copied from the Public Health Ontario website on April 14, 2022 (https://covid-19.ontario.ca/data). No data for this graph are available prior to March 17, 2022. Cases of COVID-19 have been occurring disproportionately among the fully vaccinated, and even more among those who have been boosted. This suggests that the best way to reduce the risk of acquiring COVID-19 is to remain within the 'not fully vaccinated' group. At present, requiring a person to become 'fully vaccinated', and especially giving them a booster dose, would increase their risk of getting COVID-19.



Data Source: National Institute of Public Health of Quebec (INSPQ), Health Montreal, Quebec Ministry of Health and Social Services

Data https://www.ledevoir.com/documents/special/2020-07-22-evolution-covid19-quebec/index.html



Data Source: National Institute of Public Health of Quebec (INSPQ), Health Montreal, Quebec Ministry of Health and Social Services

https://www.ledevoir.com/documents/special/2020-07-22-evolution-covid19-quebec/index.html

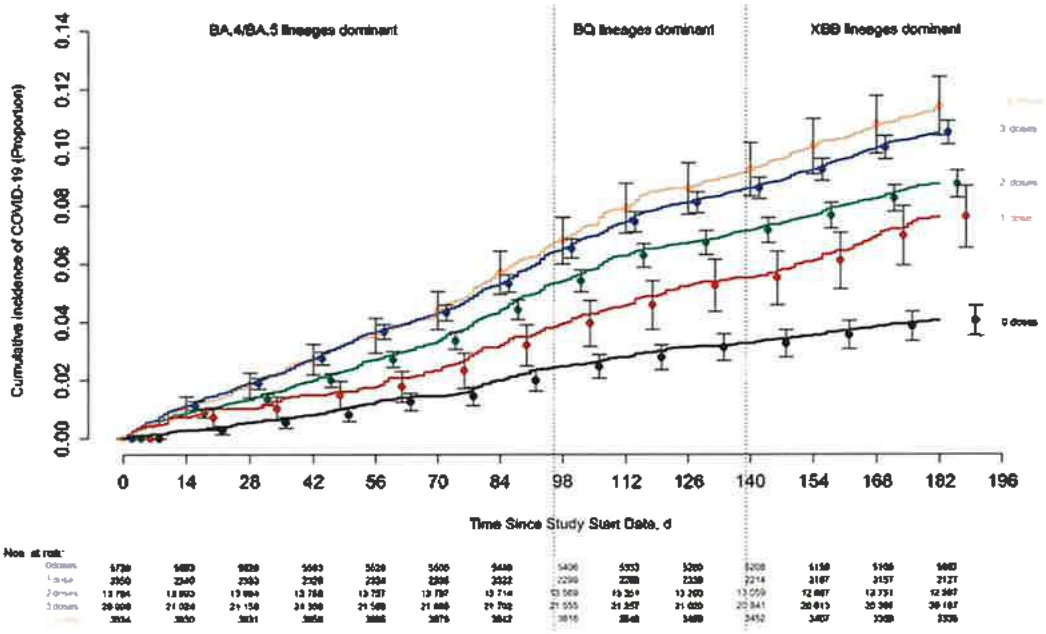


Figure 2. Cumulative incidence of coronavirus disease 2019 (COVID-19) for study participants stratified by the number of COVID-19 vaccine doses previously received. Day 0 was 12 September 2022, the date the bivalent vaccine was first offered to employees. Point estimates and 95% confidence intervals are jittered along the x-axis to improve visibility.

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Detection of Messenger RNA COVID-19 Vaccines in Human Breast Milk

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Correction: This article was corrected on September 30, 2022, to fix the year of the study period and other minor typographical errors in the eMethods in the Supplement.

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Author Contributions: Dr Hanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Hanna, Heffes-Doon, Lin, Nayak.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Hanna, Lin.

Obtained funding: Hanna.

Supervision: Hanna.

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Role of the Funder/Sponsor: The supporting organization had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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This cohort study investigates the presence of COVID-19 vaccine mRNA in the expressed breast milk of lactating individuals who received the vaccination within 6 months after delivery.

Vaccination is a cornerstone in fighting the COVID-19 pandemic. However, the initial messenger RNA (mRNA) vaccine clinical trials excluded several vulnerable groups, including young children and lactating individuals.[1] The US Food and Drug Administration deferred the decision to authorize COVID-19 mRNA vaccines for infants younger than 6 months until more data are available because of the potential priming of the children's immune responses that may alter their immunity.[2] The Centers for Disease Control and Prevention recommends offering the COVID-19 mRNA vaccines to breastfeeding individuals,[3] although the possible passage of vaccine mRNAs in breast milk resulting in infants' exposure at younger than 6 months was not investigated. This study investigated whether the COVID-19 vaccine mRNA can be detected in the expressed breast milk (EBM) of lactating individuals receiving the vaccination within 6 months after delivery.

This cohort study included 11 healthy lactating individuals who received either the Moderna mRNA-1273 vaccine (n = 5) or the Pfizer BNT162b2 vaccine (n = 6) within 6 months after delivery (Table 1). Participants were asked to collect and immediately freeze EBM samples at home until transported to the laboratory. Samples of EBM were collected before vaccination (control) and for 5 days postvaccination. A total of 131 EBM samples were collected 1 hour to 5 days after vaccine administration. Extracellular vesicles (EVs) were isolated in EBM using sequential centrifugation, and the EV concentrations were determined by ZetaView (Analytik) (eMethods in the Supplement). The presence of COVID-19 vaccine mRNA in different milk fractions (whole EBM, fat, cells, and supernatant EVs) was assayed using 2-step quantitative reverse transcriptase–polymerase chain reaction. The vaccine detection limit was 1 pg/mL of EBM (eMethods in the Supplement).

Results

Of 11 lactating individuals enrolled, trace amounts of BNT162b2 and mRNA-1273 COVID-19 mRNA vaccines were detected in 7 samples from 5 different participants at various times up to 45 hours postvaccination (Table 2). The mean (SD) yield of EVs isolated from EBM was 9.1^{10} (5.0^{10}) particles/mL, and the mean (SD) particle size was 110.0 (3.0) nm. The vaccine mRNA appears in higher concentrations in the EVs than in whole milk (Table 2). No vaccine mRNA was detected in prevaccination or postvaccination EBM samples beyond 48 hours of collection. Also, no COVID-19 vaccine mRNA was detected in the EBM fat fraction or the EBM cell pellets.

Discussion

The sporadic presence and trace quantities of COVID-19 vaccine mRNA detected in EBM suggest that breastfeeding after COVID-19 mRNA vaccination is safe, particularly beyond 48 hours after vaccination. These data demonstrate for the first time to our knowledge the biodistribution of COVID-19 vaccine mRNA to mammary cells and the potential ability of tissue EVs to package the vaccine mRNA that can be transported to distant cells. Little has been reported on lipid nanoparticle biodistribution and localization in human tissues after COVID-19 mRNA vaccination. In rats, up to 3 days following intramuscular administration, low vaccine mRNA levels were detected in the heart, lung, testis, and brain tissues, indicating tissue biodistribution.[4] We speculate that, following the vaccine administration, lipid nanoparticles containing the vaccine mRNA are carried to mammary glands via hematogenous and/or lymphatic routes.[5,6] Furthermore, we speculate that vaccine mRNA released into mammary cell cytosol can be recruited into developing EVs that are later secreted in EBM.

The limitations of this study include the relatively small sample size and the lack of functional studies demonstrating whether detected vaccine mRNA is translationally active. Also, we did not test the possible cumulative vaccine mRNA exposure after frequent breastfeeding in infants. We believe it is safe to breastfeed after maternal COVID-19 vaccination. However, caution is warranted about breastfeeding children younger than 6 months in the first 48 hours after maternal vaccina-

vaccine mRNA with the immune response to multiple routine vaccines given to infants during the first 6 months of age needs to be considered. It is critical that lactating individuals be included in future vaccination trials to better evaluate the effect of mRNA vaccines on lactation outcomes.

Notes

Supplement

eMethods

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Figures and Tables

Table 1.

Demographic and Clinical Information About Breast Milk Samples Collected From 11 Lactating Individuals After Receiving an mRNA COVID-19 Vaccine

Participant No.	Maternal age, y	Race and ethnicity	Mode of delivery	Gestational age at birth, wk	Vaccine timing after delivery, wk	Vaccine type[a]
1	33	White	Vaginal	26	10	mRNA-1273
2	33	White	Vaginal	39	25	BNT162b2
3	35	White	Vaginal	37	9	BNT162b2
4[b]	34	Asian	Cesarean	39	18	BNT162b2
5	37	White	Cesarean	39	7	mRNA-1273
6[b]	37	White	Vaginal	32	6	mRNA-1273
7[b]	22	White	Vaginal	38	24	BNT162b2
8[b]	35	White	Cesarean	39	4	BNT162b2
9	38	Black	Vaginal	39	20	BNT162b2
10[b]	34	White	Cesarean	39	7	mRNA-1273
11	35	White	Cesarean	26	5	mRNA-1273

Abbreviation: mRNA, messenger RNA.

[a] mRNA-1273 was manufactured by Moderna and BNT162b2 by Pfizer-BioNTech.

[b] Participants who had detectable vaccine mRNA in their breast milk.

Detection of Vaccine RNA in Whole Expressed Breast Milk and Extracellular Vesicles in 5 Patients at Various Time Points Postvaccination

Participant No.	Vaccine type	Time points of vaccine mRNA detection in EBM	Concentration of vaccine mRNA detected in whole milk[a]	Concentration of vaccine mRNA detected in EBM EVs[a]
4	BNT162b2	27-h[b] Sample	Not detected	14.01 pg/mL
6	mRNA-1273	27-h and 42-h[b] Samples	11.7 pg/mL	16.78 pg/mL
7	BNT162b2	37-h[b] Sample	Not detected	4.69 pg/mL
8	BNT162b2	1-h and 3-h[b] Samples	1.3 pg/mL	6.77 pg/mL
10	mRNA-1273	45-h[b] Sample	2.5 pg/mL	2.13 pg/mL

Abbreviation: EBM, expressed breast milk; EVs, extracellular vesicles; mRNA, messenger RNA.

[a] Units for concentration are picogram of mRNA per milliliter of whole milk equivalent.

[b] Sample used for vaccine mRNA concentration detection.

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Biodistribution of mRNA COVID-19 vaccines in human breast milk

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Summary

Background COVID-19 mRNA vaccines play a vital role in the fight against SARS-CoV-2 infection. However, lactating women have been largely excluded from most vaccine clinical trials. As a result, limited research has been conducted on the systemic distribution of vaccine mRNA during lactation and whether it is excreted in human breast milk (BM). Here, we evaluated if COVID-19 vaccine mRNA is detectable in BM after maternal vaccination and determined its potential translational activity.

Methods We collected BM samples from 13 lactating, healthy, post-partum women before and after COVID-19 mRNA vaccination. Vaccine mRNA in whole BM and BM extracellular vesicles (EVs) was assayed using quantitative Droplet Digital PCR, and its integrity and translational activity were evaluated.

Findings Of 13 lactating women receiving the vaccine (20 exposures), trace mRNA amounts were detected in 10 exposures up to 45 h post-vaccination. The mRNA was concentrated in the BM EVs; however, these EVs neither expressed SARS-COV-2 spike protein nor induced its expression in the HT-29 cell line. Linkage analysis suggests vaccine mRNA integrity was reduced to 12–25% in BM.

Interpretation Our findings demonstrate that the COVID-19 vaccine mRNA is not confined to the injection site but spreads systemically and is packaged into BM EVs. However, as only trace quantities are present and a clear translational activity is absent, we believe breastfeeding post-vaccination is safe, especially 48 h after vaccination. Nevertheless, since the minimum mRNA vaccine dose to elicit an immune reaction in infants <6 months is unknown, a dialogue between a breastfeeding mother and her healthcare provider should address the benefit/risk considerations of breastfeeding in the first two days after maternal vaccination.

Funding This study was supported by the Department of Pediatrics, NYU-Grossman Long Island School of Medicine.

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Keywords: COVID-19; Vaccine mRNA; Biodistribution; Breast milk; Lipid nanoparticles; Extracellular vesicles

Introduction

The SARS-CoV-2 spike (S) protein was identified as the primary vaccine target for COVID-19 disease, as it contains the receptor-binding domain that allows for viral host cell entry.[1] This effort has led to the development of two effective nucleoside-modified mRNA vaccines encoding the SARS-CoV-2 spike (S) protein—BNT162b2 manufactured by Pfizer-BioNTech and mRNA-1273 manufactured by Moderna. Clinical trials for the COVID-19 vaccines were established in what seemed like record time; however, hundreds of scientists had worked on mRNA vaccines for decades before developing these life-saving vaccines.[2,3] However, several vulnerable groups, such as pregnant and lactating women, have been excluded from the initial vaccine clinical trials.[4,5] Nevertheless, based on favorable

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Research in context

Evidence before this study

COVID-19 mRNA vaccines are crucial in combating SARS-CoV-2 infection; however, most clinical trials have excluded lactating women. The previous assumption that the mRNA vaccine is rapidly broken down at its intramuscular administration site with no biodistribution to other organs in human subjects has been challenged. In murine models, the biodistribution of the mRNA-loaded lipid nanoparticles after intramuscular administration demonstrated transportation and active translation of the vaccine mRNA in several organs. Few human studies have evaluated the vaccine mRNA biodistribution during lactation, whether it reaches the human breast milk, and if it is intact and biologically active.

Added value of this study

Our findings suggest that the COVID-19 vaccine mRNA administered to lactating mothers can spread systemically to breast milk in the first two days after maternal vaccination. However, the mRNA was only occasionally detected in breast milk, in trace amounts, and mainly concentrated in the breast milk extracellular vesicles. Our proposed model suggests that after intramuscular administration, the vaccine mRNA enclosed in lipid nanoparticles is transported to the mammary glands through either hematogenous or lymphatic pathways. Within the mammary cells' cytosol, a portion of the released vaccine mRNA is recruited and packaged into the developing extracellular vesicles, which are then released into the breast milk. Furthermore, our analysis demonstrated that the vaccine mRNA detected in breast milk extracellular vesicles was largely fragmented, retaining only 12–25% of its original integrity. Although the vaccine mRNA appears to be translationally inactive, further investigation is required to determine the minimum amount of mRNA needed to elicit an immune response in newborns.

Implications of all the available evidence

This research would prompt a discussion among the experts responsible for formulating policies related to breastfeeding after mRNA vaccination. Although we believe breastfeeding after mRNA vaccination is safe, a dialogue between a breastfeeding mother and her healthcare provider should address the benefit/risk considerations of breastfeeding in the first two days after maternal mRNA vaccination. The significance of this research extends beyond the scope of COVID-19 mRNA vaccines. The findings provide valuable insights into the transport and presence of vaccine mRNA in breast milk, which can be relevant for assessing the safety and efficacy of future mRNA-based therapies administered to lactating women.

safety profiles and its high efficacy in non-lactating adults, the COVID mRNA vaccine was recommended for breastfeeding mothers.[3–4] However, the possible passage of the vaccine mRNA to breast milk (BM), resulting in neonatal exposure, was not investigated. Notably, the Centers for Disease Control and Prevention (CDC) does not recommend COVID-19 vaccination in infants <6 months of age because of the lack of safety studies and the possible interaction with other routine vaccinations in this age group.[5] The mRNA COVID-19 vaccines comprise lipid nanoparticles (LNPs) that contain mRNA coding the SARS-CoV-2 S protein as the active component.[1] At present, relatively little has been reported on the tissue localization of the LNPs after intramuscular administration of the vaccine.[11] The assumption that the mRNA vaccine is rapidly broken down at its intramuscular administration site with no biodistribution to other organs may not be accurate.[12,13] Following intramuscular administration, the vaccine LNPs were rapidly disseminated to several organs in the murine model.[13,14] Few studies have explored the biodistribution of mRNA vaccines in humans[15–17] and examined the impact of the protein corona on the modification of nanoparticles, which can potentially affect their biodistribution and mRNA release.[18–20] Our recently published research letter[21] demonstrated the presence of COVID vaccine mRNA in the BM extracellular vesicles (EVs); however, the exact mRNA quantification, its integrity (either intact or fragmented), and its potential translational activity were not evaluated. The primary objective of this study was to investigate, using a highly sensitive methodology, whether COVID-19 vaccine mRNA could be detected in the BM of lactating women and, if so, to evaluate their integrity and translational activity.

Methods

This cohort study included 13 post-partum mothers with no significant past medical history or comorbidities who received either the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) COVID-19 vaccine during lactation from February to October 2021. Mothers were asked to collect and immediately freeze expressed BM samples at home until samples were transported to the laboratory. BM samples were collected before vaccination (used as negative control samples) and daily (at least twice/day if possible) for at least 5 days post-vaccination or longer when possible. Seven mothers provided BM samples after both the first and second vaccine doses (Table 1). For this study, we considered each vaccine dose as a separate exposure (13 mothers with 20 exposures). Mothers were instructed to write the "hour of collection post-vaccination" on each container and store the expressed BM in the freezer immediately after collection. The research team transported the samples to the

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Participant No.	Exposure	Maternal Age (years)	Ethnicity	Mode of Delivery	Gestational age at birth, wk	Vaccine adminstration after delivery (wk)	Vaccine type	Vaccine dose
P1	E1	33	White	Vaginal	39.3	22.4	BNT162b2	1
	E2	33	White	Vaginal	39.3	25.4	BNT162b2	2
P2	E3	36	White	Vaginal	37.4	5.3	BNT162b2	1
	E4	36	White	Vaginal	37.4	5.3	BNT162b2	2
P3	E5	34	Asian	Cesarean	39.6	15	BNT162b2	1
	E6	34	Asian	Cesarean	39.6	18.2	BNT162b2	2
P4	E7	32	White	Vaginal	38.1	27.1	BNT162b2	1
P5	E8	36	White	Cesarean	39.2	1.4	BNT162b2	1
	E9	36	White	Cesarean	39.2	4.6	BNT162b2	2
P6	E10	29	White	Vaginal	38.6	26.3	BNT162b2	2
P7	E11	38	Black	Vaginal	39.5	23	BNT162b2	1
P8	E12	33	White	Vaginal	26.6	10.1	mRNA-1273	2
P9	E13	37	Asian	Cesarean	39	50.1	mRNA-1273	2
P10	E14	37	White	Cesarean	39.5	2.2	mRNA-1273	1
	E15	37	White	Cesarean	39.5	7.1	mRNA-1273	2
P11	E16	37	White	Vaginal	32.1	1.4	mRNA-1273	1
	E17	37	White	Vaginal	32.1	6.4	mRNA-1273	2
P12	E18	34	White	Cesarean	39.4	3	mRNA-1273	1
P13	E19	36	White	Cesarean	26.2	1.1	mRNA-1273	1
	E20	36	White	Cesarean	26.2	5.1	mRNA-1273	2

Shaded rows indicate subjects that had detectable vaccine mRNA. mRNA-1273 manufactured by Moderna and BNT162b2 manufactured by Pfizer-BioNTech. For the week value, the digit after the decimal point represents the additional days beyond the whole number of weeks. For example, a gestational age of 39.3 represents 39 weeks and 3 days gestation.

Table 1: **Breast milk (BM) samples collected from 13 lactating mothers after receiving COVID-19 mRNA vaccine.**

laboratory on ice for analysis. Before BM collection, all participants tested negative for COVID-19 using a SARS-CoV-2 nasal swab test. No participant reported any unusual vaccine side effects or allergic reactions other than the usual mild discomfort in the arm. Also, no mothers reported COVID-19 disease within a week before the vaccination or during the samples' collection. Despite the instructions given to the mothers to provide a minimum of 5 mL of BM for each sample, the actual amounts collected were often below this threshold. Our primary focus was on detecting vaccine mRNA using droplet digital PCR (ddPCR), which was performed for all samples. Following this step, we prioritized the isolation and characterization of BM EVs for further experimentation, as detailed below. However, in several cases, the inadequate volume of BM collected hindered the completion of all intended experiments, as specified below.

Isolation of extracellular vesicles from breastmilk

As described previously,[22] BM EVs were isolated by sequential centrifugation (Supplemental Methods). The EVs number and characterization were determined by ZetaView (Particle Metrix, Ammersee, Germany), and the EVs recovery rate after the isolation procedure was calculated. Expression of exosome markers CD63 and CD9 was confirmed by anti-CD63 antibody (cat# ab134045, RRID: AB-2800495, Abcam, Waltham, MA)[23] and anti-CD9 antibody (cat# 13403, RRID: AB-2732848, Cell Signaling Technology, Danvers, MA)[24] detection using automated capillary western blot system.

Detection of COVID-19 vaccine mRNA

The level of COVID-19 vaccine mRNA was assayed by ddPCR, which provides higher precision, ultrasensitive mRNA detection, and absolute quantification by providing the absolute count of target mRNA copies per input sample and is superior to RT-qPCR in detection and quantifying low-level mRNA.[25,26] Total RNA was isolated from 0.6 mL of the whole BM. Whenever enough BM samples were available, EVs were isolated (requiring 2.3 mL of whole BM) by miRNeasy mini kit (cat# 217004, Qiagen, Germantown, MD) according to manufacturer instructions. One-third of the eluted RNA was used for reverse transcription reaction (cat# 4368814, ThermoFisher, Waltham, MA) with random primers. Based on the putative sequences of vaccines BNT162b2 (Pfizer) and mRNA1273 (Moderna)[22] two sets of vaccine mRNA detection assays were designed to target two different regions of each vaccine mRNA (Supplemental Table S1), the primers and probes were synthesized by Integrated DNA Technologies (Coralville, IA). These primer sets are specific to the respective codon-modified vaccine mRNA sequences and do not amplify wild-type S-gene (Supplemental Table S2). ddPCR was performed with the QX200 Droplet Digital PCR system (Bio-Rad, Hercules, California, USA) using

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2X Supermix for Probes (Bio-Rad, USA, cat# 1863024) following the manufacturer's instruction. RNA from BM spiked with vaccine solution was used as a positive control and for setting the positive droplet threshold. Samples with 3 or more positive droplets were considered vaccine mRNA positive. The copy number of the vaccine mRNA template in the PCR reaction was used to derive the copy number per mL of whole milk, or in the case of EVs, the whole milk equivalent corresponding to the whole milk volume used for EVs isolation.

Detection of S protein in skimmed milk, BM cells, and BM EVs

BM cell pellets were collected by centrifugation at 2000×g for 10 min at 4 °C and were lysed in RIPA buffer with proteinase inhibitor cocktail (cat# 32955, Thermo Scientific, Rockford, IL, USA). The resulting supernatant was transferred into new tubes and centrifuged again at 17,000g for 60 min at 4 °C to obtain the skimmed acellular sample. The cell pellets and BM EVs were lysed in RIPA buffer with proteinase inhibitor cocktail (cat# 32955, Thermo Scientific, Rockford, IL, USA). The S protein expression was assayed by anti-S antibody (cat# 99423, Cell Signaling Technology, Danvers, MA, USA)[27] detection using an automated capillary western blot system. The presence of the SARS-CoV-2 Spike protein in the skimmed milk was determined using the COVID-19 S-Protein (S1RBD) ELISA Kit (Cat # ab284402, Abcam). The sensitivity of the kit is 4.5 pg/mL. In addition to the Spike protein standard included in the kit, vaccine mRNA translated Spike protein in the cell lysate of BNT162b2 and mRNA1273 treated HT-29 cells were used to validate further the specificity of the ELISA kit.

Expression of S protein in HT-29 cells treated with BM EVs

HT-29 cells, a human colorectal adenocarcinoma cell line with epithelial morphology (ATCC HTB-38 RRID: CVCL-0320), were seeded in a 48-well plate, and after attachment for 24 h, cells were treated with a suspension of BM EVs (2×10^{10} particles/well) and incubated for 24 h. Thereafter, the cells were lysed in RIPA buffer, and the expression of S protein was assayed as described above. As a positive control, HT-29 cells were treated with mRNA-1273 at various dilutions ($1{:}10^4$, $1{:}10^6$, and $1{:}10^7$). The concentration of the vaccine mRNA at the dilution of $1{:}10^7$ is similar to the average concentration detected in BM EVs. Cells were lysed, and the expression of spike protein was assayed using automated capillary western blotting.

Linkage duplex assays

The above-mentioned PCR-based assays detect the presence of very short mRNA sequences but do not distinguish whether these sequences are derived from the full-length vaccine mRNA present in the sample or a fragmented mRNA segment. Linkage studies can provide information on the quality of the vaccine mRNA in a sample and allow the determination of how degraded or fragmented the mRNA is. The ddPCR duplex assay[28,29] uses two probes targeting the flanks of the intact vaccine mRNA. By quantifying the proportion of droplets in which both assays yield amplification, samples containing intact vaccine mRNA (positive linkage) can be distinguished from samples containing only fragmented mRNA.[30]

To investigate the integrity of vaccine mRNA in our samples, linkage ddPCR was performed using a ONE Step RT ddPCR advanced Kit for Probes (cat# 1664021, BioRad, Hercules, CA) following the manufacturer's instructions. Two 20X assays (mRNA-1273-FAM and mRNA1273-2-HEX) spanning 1598nt of the vaccine mRNA (nt876–nt2474) were combined with Supermix, reverse transcriptase, DTT, and RNA to a 20 µL reaction. RT-PCR amplification was carried out on a T100 Touch thermal cycler (Bio-Rad, USA) using a thermal profile beginning with reverse transcription at 46 °C for 60 min, followed by Taq polymerase activation at 95 °C for 10 min; amplification for 40 cycles of 95 °C for 30 s and 59 °C for 60 s; and concluding with 98 °C for 10 min. After PCR, the plate was analyzed on a droplet reader (Bio-Rad, Hercules, California, USA). Values for the copies/µL of linked molecules were derived using a method described previously.[28,29] The percent linkage of each sample was expressed as the percentage of linked molecules in relation to the total molecules detected, normalized to the original vaccine stock solution. The concentration of the target molecule sequence was determined by using the ratio of negative partitions to the total number of partitions and applying the Poisson distribution accomplished by the QX Manager Software.[31] Linkage was calculated by QX Manager Software, which determined the excess of double-positive droplets over the expected due to random colocalization of unlinked targets. Percent linkage of each sample was expressed as the percentage of linked molecules in relation to the total molecules detected, normalized to the original vaccine stock solution. QX Manager Software makes two assumptions to fit the Poisson distribution: a) all the partitions are of equal volume, and b) target molecules are randomly distributed across partitions.[32] Software algorithm by QX Manager Software developed by BioRad was used to ensure the validity of the Poisson distribution assumption.

Cytokines secretion in vaccine-stimulated cord blood mononuclear cells and HT-29 cells

Cord blood mononuclear cells (CBMCs) were isolated from umbilical cord blood collected from pregnant women with no COVID-19 disease or COVID-19 vaccination history. CBMCs were isolated using Lymphoprep™ Tube (cat# 1019818, Alere Technologies AS, Oslo, Norway) following the manufacturer's instructions. Isolated CBMCs were aliquoted and stored in

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the gas phase above the liquid nitrogen until use. One day before vaccine stimulation, aliquots of CBMCs were thawed and recovered in RPMI-1640 supplemented with 10% human serum from AB Plasma (H3367, Sigma) and penicillin-streptomycin. On the day of vaccine treatment, CBMCs and HT-29 cells were seeded at a density of 1×10^6/well in 24-well plates. BNT162b2 and mRNA-1273 at $1{:}10^3$ and $1{:}10^6$ dilution; LPS (3 EU/mL, *E. coli* 026; B6 cat# L8274, Sigma Aldrich, St. Louis, MO), Poly (I:C) (10 μg/mL, catalog code tlrl-pic, Invivogen, San Diego, CA), R848 (2 μg/mL catalog code tlrl-r848, Invivogen, San Diego, CA) were added as a positive control for TLR4, TLR3, and TLR7/8 agonists, respectively. After 24 h treatment, condition media were collected and centrifugated at 12,000g, 10 min at 4 °C. Cytokines in the supernatant was assayed by commercial ELISA kits: TNFa, Invitrogen™ TNF alpha Human Uncoated ELISA Kit (cat# 88-7346, ThermoFisher); IL6, Invitrogen™ IL-6 Human Uncoated ELISA Kit (cat# 88-7066, ThermoFisher); IFNr, Human IFN-gamma DuoSet ELISA (cat# DY285B, RnDSystems); IFNa, ProQuantum Human IFNa immunoassay Kit (cat# A42897, ThermoFisher). In addition, as a positive control to confirm the functional activity of the vaccine used, we incubated CBMCs with the mRNA vaccine at $1{:}10^3$ and $1{:}10^6$ dilution for 24 h. Thereafter, the cells were lysed in RIPA buffer, and the expression of S protein was assayed using automated capillary western blotting. The $1{:}10^6$ mRNA vaccine dilution is similar to the maximum levels detected in the BM EVs, and the $1{:}10^3$ dilution (100 ng/mL) represents the maximum possible level detected in the serum of vaccinated women.[11] Yeo et al.[11] have detected the presence of COVID-19 vaccine mRNA in 20 serum samples collected from lactating mothers who received the vaccine, with maximum levels reaching approximately 70 ng/mL.

Automated capillary western blot (WES)

Proteins in cell lysate and EV were analyzed with a WES system (ProteinSimple) according to the manufacturer's instructions, using a 12–230 kDa Separation Module (ProteinSimple SM-W002). The proteins of interest were assayed with rabbit monoclonal antibody detection as described above, and the signal was detected using the Anti-Rabbit Detection Module (ProteinSimple DM-001). Data were analyzed using Compass™ software (V.2.6.5, Protein Simple).

Ethics committee approval

New York University institutional review board approval (approval number: s18-01725) was obtained before initiating the study. Written informed consent was obtained from all volunteers before enrollment in the study.

Statistical analysis

Statistical analysis was performed by using GraphPad Prism v9.00. The data's normality was tested by the Shapiro–Wilk test and visual assessment of Q–Q plot. If the samples followed a normal distribution, we chose the appropriate parametric test; otherwise, the non-parametric counterpart was chosen. For multiple groups comparison, repeated-measures one-way analysis of variance (ANOVA) with posttest Holm-Šídák's multiple comparisons test or Friedman with posttest Dunn's multiple comparisons were used as indicated. Sphericity was assessed by Mauchly's test using Mauchly package in Stata version 18.0. When the significance level of the Mauchly's test is >0.05, sphericity is assumed, if $p \leq 0.05$, Geisser-Greenhouse correction will be implemented in repeated-measures one-way ANOVA. The choice of each test was dependent on the underlying distribution and is indicated in the legend of the figures.

Role of funding source

All financial and material support for this work was supported by the Department of Pediatrics, NYU Langone Hospital-Long Island, New York University Grossman Long Island School of Medicine. This support includes the design and conduct of the study, collection, management, analysis, interpretation of the data, preparation, review, and approval of the manuscript, as well as the decision to submit the manuscript for publication.

Results

A total of 13 subjects (representing 20 exposures) were enrolled, with 11 exposures to the BNT162b2 vaccine and 9 exposures to the mRNA-1273 vaccine, as detailed in Table 1. Daily collection of BM samples (2–5 samples/day) for the first 5 days post-vaccine exposure was achieved for 11 of the 20 exposures. Daily sample collections were not feasible for the other exposures because of the scant BM produced by the lactating mothers. A total of 154 samples were collected from the 20 vaccine exposures.

Detection of COVID-19 vaccine mRNA in whole BM and BM EVs using quantitative ddPCR

All pre-vaccination BM samples were negative for COVID-19 vaccine mRNA. Small amounts of vaccine mRNA were detected in the whole BM in 15 samples from 10 exposures at 3–45 h post-vaccination (Fig. 1). No vaccine mRNA was detected in any collected whole BM samples beyond the 48-h post-vaccination time point. Also, no vaccine mRNA was detected in the BM fat fraction or the BM cell pellets (data not shown). We also investigated if the vaccine mRNA could be packaged and detected in EVs secreted in BM. Isolated BM EVs were analyzed using Particle Metrix ZetaView Nanoparticle Tracking Analysis (NTA) (Supplemental Figure S1). The yield of EVs from BM was a median of 8.08×10^9 (IQR 2.66×10^9–3.02×10^{10}) particles/mL, and the mean (SD) particle size was 110.0 (3.0) nm. No

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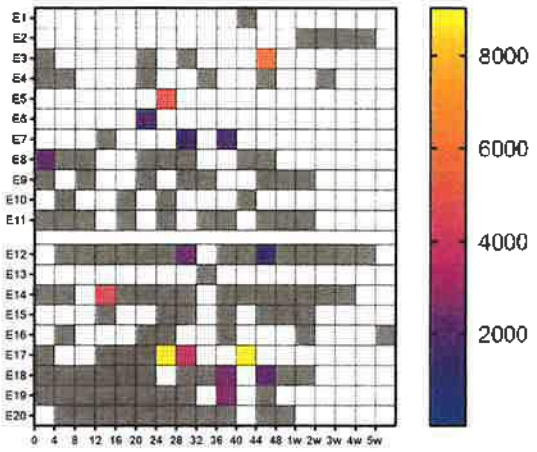

Fig. 1: **COVID Vaccine mRNA detected in breast milk (BM) measured by ddPCR.** The heat map represents the vaccine mRNA concentrations in the BM. The X-axis represents the time points between vaccination and sample collection (hours/weeks). The Y axis represents different individual exposures (as detailed in Table 1) to BNT162b2 (upper panel) and mRNA1273 (lower panel). White cells indicate there were no samples collected in that time interval. Gray cells indicate vaccine mRNA was not detected. The amount of mRNA (copies/mL BM) in the sample is indicated by the color gradient.

vaccine mRNA was detected in the pre-vaccinated BM EV samples. Whenever sufficient BM samples were available, EVs were isolated from BM samples that tested positive for the vaccine mRNA. Owing to the scant amount of BM supplied by some mothers in the first week of life, only a few samples contained sufficient BM to isolate EVs. Approximately 90% of the EVs from BM were recovered with our method. The vaccine mRNA was consistently detected in EVs whenever their corresponding whole BM samples were positive. The vaccine mRNA copy numbers in whole BM samples and their corresponding EV fractions, normalized to the starting BM volume (mL), are presented in Table 2. As shown in Table 2, vaccine mRNA in the BM was concentrated in the EVs, with approximately 12–90% of vaccine mRNA found in the EV fraction, even though the EVs only account for a very small fraction of the whole BM volume. The effect of the milk type (colostrum vs. transitional vs. mature milk) on EV count and mRNA content could not be evaluated since the mRNA-positive samples included only one colostrum and three transitional milk samples. Although the number of EVs was similar in the transitional samples compared to mature milk samples, the small sample size hindered a meaningful comparison.

S protein was not detected in skimmed BM, cell pellets, or EV samples positive for vaccine mRNA

Using the automated capillary western blotting, the S protein was not detected in EV samples derived from pre-vaccination BM samples nor in the post-vaccination BM EV samples that tested positive for vaccine mRNA. Furthermore, all skimmed and cell pellets of the BM samples tested were negative for S protein expression (data not shown).

Vaccine mRNA-positive EVs did not induce S protein expression in HT-29 cells

Isolated EVs from BM samples that tested negative for vaccine mRNA (pre-vaccination BM samples) and EVs from BM samples that tested positive for vaccine mRNA were incubated with HT-29 cells for 24 h (samples E5, E7, and E17). As shown in Fig. 2, no S protein was detected in any of the samples tested. However, positive control samples used in concentrations similar to those of BM EVs also failed to induce S protein expression.

Vaccine mRNA in the EVs is partially intact

Vaccine mRNA integrity was assayed in a duplex ddPCR using two probes targeting the flanks of the intact mRNA vaccine. Positive linkage indicates vaccine mRNA integrity, and negative linkage indicates fragmented vaccine mRNA.[28,29,34] Due to limited availability, only five samples were assayed (Fig. 3). Percent linkage of each sample was expressed as the percentage of linked molecules in relation to the total molecules detected, normalized to the original vaccine stock solution.[33,37,38] As demonstrated in Fig. 3c, the vaccine

Sample ID	Vaccine type	Time of sample collection (h)	Vaccine RNA (copies/mL)		% of mRNA in EVs (%)
			Whole BM	EV fraction	
E5	BNT-162b2	27	5035	595	12
E7	BNT-162b2	37	1544	340	22
E12	mRNA-1273	44	1247	1120	90
E17	mRNA-1273	42	7604	1953	26

EVs of breast milk (BM) from 4 positive samples were isolated by differential centrifugation method. Vaccine mRNA copy numbers in whole milk and EV fraction were normalized to the starting BM volume (mL). All positive samples were detected within the first 48 h after vaccination. Vaccine mRNA in the BM was concentrated in the EVs, with approximately 12–90% of total vaccine mRNA found in the EV fractions even though the EVs only account for a very small fraction of the whole milk volume.

Table 2: **Distribution of vaccine mRNA in whole milk and extracellular vesicles (EVs) from vaccinated women.**

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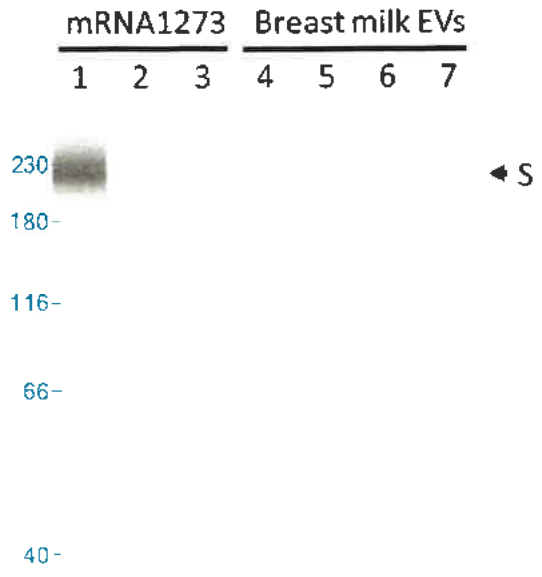

Fig. 2: **Vaccine mRNA-positive BM EVS did not induce spike protein expression when incubated with intestinal HT-29 cells for 24 h.** HT-29 cells treated with vaccine mRNA1273 at different dilutions were used as positive controls (1:10^4, 1:10^6, and 1:10^7, lanes 1-3, respectively). Lane 4 represents EVs from pre-vaccination BM. Lanes 5–7 represent EVs positive for the vaccine mRNA (lane 5, E5; lane 6, E7; lane 7, E17, respectively). Cells were lysed, and the expression of spike protein was assayed by automated capillary western blot (WES). S: Full-length spike protein. No S protein was detected in any of the BM EV samples tested. However, positive control samples in concentrations similar to those of BM EVs (lane 3) also failed to induce S protein expression. The only positive control sample that induced spike protein was the HT-29 cells treated with a higher concentration of stock mRNA vaccine (1:10^4, lane 1).

mRNA in BM samples retained only 12–25% of its original mRNA vaccine integrity.

Vaccine mRNA did not induce significant cytokines secretion in CBMCs or HT-29 cells

As shown in Fig. 4a, ssRNA-sensing toll-like receptor TLR7/8 (ssRNA) agonists R848 induced the secretion of TNFa, IL-6, and IFNa in CBMCs. Double-stranded RNA-sensing TLR3 agonist Poly (I:C) induced TNFa secretion in HT-29 cells. However, cells treated with 1:10^3 and 1:10^6 vaccine mRNA dilution did not induce cytokines secretion. However, only 1:10^3 and not 1:10^6 vaccine mRNA dilution induced S protein expression in CBMCs (Fig. 4b).

Discussion

Our findings suggest that the COVID-19 vaccine mRNA administered to lactating mothers can spread systemically to the BM in the first two days after maternal vaccination. However, the mRNA was only occasionally detected in BM, in trace amounts, and mainly concentrated in BM EVs. The linkage analysis showed that the vaccine mRNA detected in BM was largely fragmented and retained only 12–25% of the original vaccine mRNA integrity. While the vaccine mRNA seems to be translationally inactive, further investigation is required to determine the minimum amount of mRNA needed to elicit an immune response in newborns.

Initially, it was thought that the vaccine mRNA encapsulated in LNPs would remain localized at the injection site and quickly degrade. However, several reports suggest that the LNPs/mRNA can enter the bloodstream and accumulate in distant tissues.[14,15] The Pfizer and Moderna Assessment Reports provided to the European Medicines Agency[16,17] concluded that a small fraction of the administered mRNA dose was distributed to distant tissues, mainly the liver, adrenal glands, spleen, and ovaries. Additionally, mRNA constructs persisted for 1–3 days in tissues other than the injection site. For lactating mothers receiving the vaccine, our results suggest that the vaccine LNPs will reach the breast tissue. However, since the intact blood-milk barrier prevents an uncontrolled exchange of soluble and cellular components between blood and milk in the mammary gland[16] it is unlikely that intact LNPs will pass the blood-milk barrier to the BM. Using the fraction of RNA we detected in breast milk/mL, we calculated that the expected level of lipids in the same volume of milk was below the level of detection using the currently available analytical methodology. Our model (Fig. 5) proposes that following intramuscular administration, the LNPs containing the vaccine mRNA are likely carried to mammary glands via hematogenous or lymphatic transport.[13,14] The LNPs will release their mRNA content into the cytosol of the mammary gland cells, and a portion of this mRNA will be recruited, packaged, and released in the BM EVs (exosomes or microvesicles). This can be significant as the BM EVs act as natural LNPs, protecting the mRNA from degradation. Milk-derived EVs are resistant to proteolysis by gastric and pancreatic secretions and can be readily absorbed by intestinal epithelial cells.[17] Because of their ability to transfer and protect the mRNA, milk EVs have been tested as a vehicle for COVID mRNA oral vaccine.[18] Since the cells likely to encounter BM EVs-loaded mRNA are intestinal epithelial cells, our study used intestinal epithelial HT-29 cells, a human colorectal adenocarcinoma cell line with epithelial morphology. Due to their similarities with enterocytes of the small intestine, it has been used as an in-vitro model to study absorption, transport, and secretion by intestinal cells and has been used to study intestinal cell response to human milk factors and human milk oligosaccharides.[19,20]

Notably, the detected mRNA in whole BM samples includes both mRNA in the EVs and the mRNA outside the EVs. These results indicated that the vaccine mRNA was concentrated mainly in the BM EVs.

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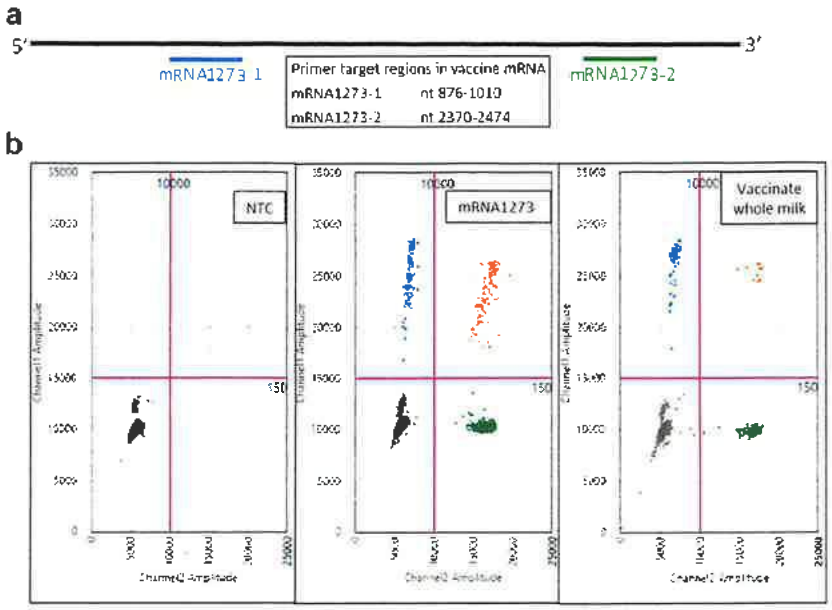

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Sample ID	Sample type	Time of sample collection	% linkage
E17	Whole milk	27 hrs	25.7
E17	Whole milk	42 hrs	19.5
E17	EVs	42 hrs	19.6
E18	Whole milk	45 hrs	12.1
E18	EVs	45hrs	23.3

Fig. 3: **Integrity of vaccine mRNA in breast milk from vaccinated women.** (a) Vaccine mRNA integrity was assayed in a duplex ddPCR assay using a two-primer set targeting 1602 nt of the mRNA1273 sequence. (b) Representative dot plot profiles of FAM-labeled mRNA1273-1 primer and probe (channel 1, amplitude) and HEX-labeled mRNA1273-2 primer and probe (channel 2, amplitude). Droplets emitting 2D signals were separated into four groups (Gray, double negative for mRNA1273-1 and mRNA1273-2; Blue, positive for mRNA1273-1, negative for mRNA1273-2; Green, positive for mRNA1273-2, negative for mRNA1273-1; Orange, double positive for both mRNA1273-1 and mRNA1273-2). Left panel, No template control; middle panel, RNA isolated from vaccine mRNA1273 stock (positive control); right panel, a representative BM sample from a vaccinated woman. (c) The number of droplets in each single or double positive group was derived by QX Manager Software. Percent linkage of each sample was expressed as the percentage of linked molecules in relation to the total molecules detected, normalized to the original vaccine stock solution.

These results confirm our previous findings.[22] Furthermore, our results demonstrated that the vaccine mRNA-positive EVs did not induce S protein expression in HT-29 cells. However, positive control samples used in concentrations similar to those of BM EVs also failed to induce S protein expression. Although this may indicate that the vaccine mRNA in the EVs is not translationally active, it may also indicate that the methodology used is not sensitive enough to detect S protein expression. Thus, confirming the lack of translational activity needs further investigation. Our finding that the COVID-19 mRNA vaccines do not induce cytokine secretion in cord blood immune cells is in agreement with previous reports demonstrating that mRNA vaccine does not induce various cytokine secretion in adults.[16,17,31]

Other studies have also detected the COVID-19 vaccine mRNA in BM.[22,31,32] Low et al.[22] detected the vaccine mRNA in BM samples at a maximum concentration of 2 ng/mL, which is much higher than the concentrations we observed. Yeo et al.[31] detected vaccine mRNA in BM and serum samples in comparable concentrations. One published study[33] did not detect the COVID-19 vaccine mRNA in BM in a limited number of samples (15 BM samples, compared to 154 samples in our study). Similar to our study, self-collected post-vaccination BM

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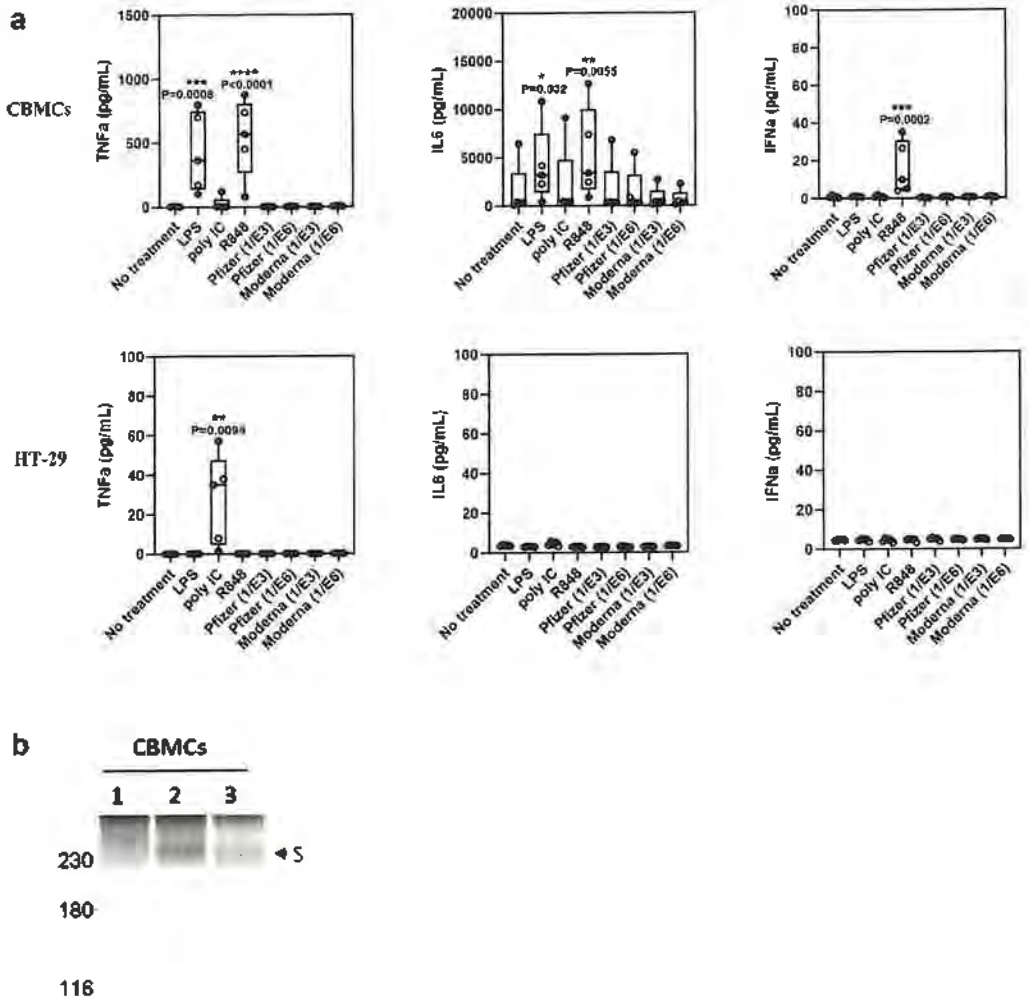

Fig. 4: **Cytokine levels in COVID-19 mRNA vaccines stimulated CBMCs and HT-29 cells** (a) Following 24 h stimulation with $1\text{-}10^3$ and $1\text{-}10^6$ diluted reconstituted vaccine product, cytokine concentrations in supernatant from CBMC (5 biological replicates) and HT-29 cells (n = 5) were measured by ELISA as described in Material and Methods. TLR agonists LPS, Poly IC, and R848 were used as positive control. Cytokine concentrations of CBMC (Upper panel) and HT-29 cells (Lower panel) are presented as box-and-whisker plot showing the median and IQR with minimum and maximum whiskers. p values were computed using repeated measure one-way ANOVA with posttest Holm-Šídák's multiple comparisons test (CBMC: TNFa, IFNa and HT-29: IL6, IFNa) or Friedman with posttest Dunn's multiple comparisons (CBMC: IL6 and HT-29: TNFa). $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, and $^{****}p < 0.0001$. (b) Representative sample of S protein expression in vaccine BNT162b2 treated CBMCs. 1) CBMCs received no treatment; 2) CBMCs treated with $1{:}10^3$ diluted BNT162b2, and 3) treated with $1{:}10^6$ diluted BNT162b2. S: full-length spike protein

samples were frozen at home until transported to the laboratory. However, the study did not evaluate vaccine mRNA in BM EVs and used a single primer set, which covers only 131 bases of the 5′ end of the vaccine mRNA sequence. This primer carries a one-base mismatch for mRNA-1273, which might have reduced RT-qPCR sensitivity. In our study, considering the differences in nucleotide sequence between BNT162b2 and mRNA1273, two distinct sets of primers were designed, each specifically targeting the respective vaccines' mRNA. Also, each pair of primers covers approximately 1.5 kb of the full-length vaccine mRNA, increasing assay specificity and sensitivity. In addition, using quantitative ddPCR significantly improves the sensitivity of the detection.

Based on the sporadic detection of trace amounts of the vaccine mRNA in BM, the likelihood that the vaccine might be biologically inactive, the excellent safety profile of the COVID-19 mRNA vaccines thus far, and their efficacy in protecting lactating women, the

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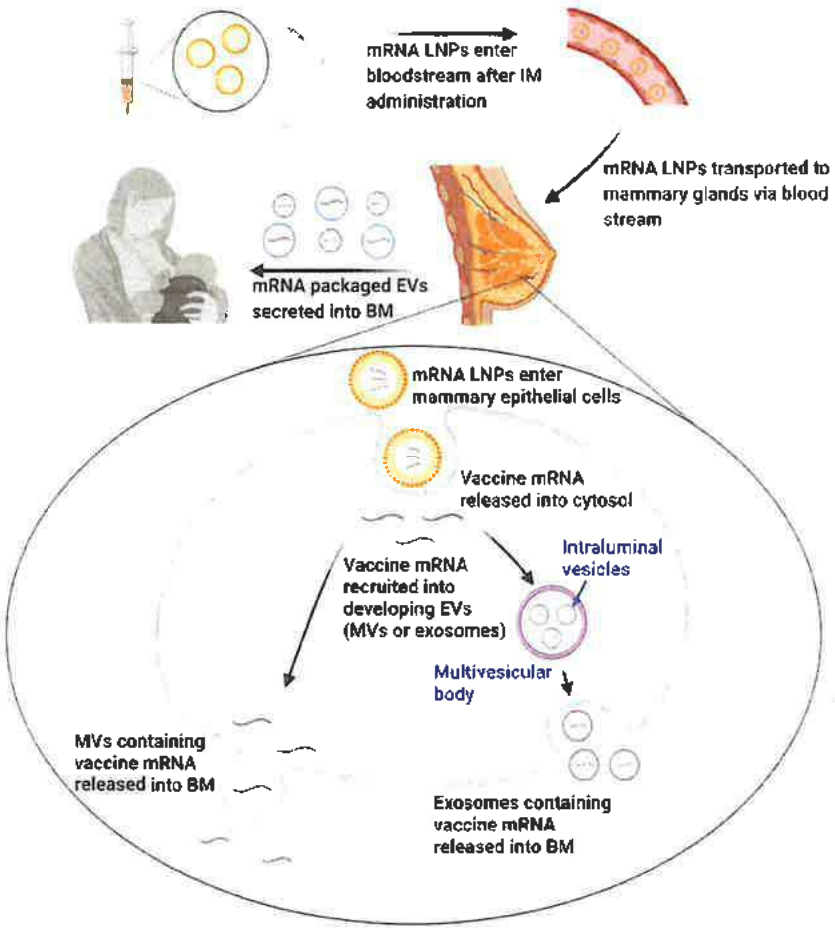

Fig. 5: Proposed model of biodistribution of vaccine mRNA to breast milk (BM). Following intramuscular administration, the vaccine mRNA enclosed in lipid nanoparticles (LNPs) is transported to the mammary glands through either hematogenous or lymphatic pathways. Within the mammary cell cytosol, a portion of the released vaccine mRNA is recruited and packaged into developing extracellular vesicles (EVs). The vaccine mRNA can be packaged into multivesicular bodies as intraluminal vesicles that will fuse with the mammary cell's plasma membrane, resulting in the release of mRNA-containing exosomes/EVs into breast milk. Some vaccine mRNA can also be packaged into microvesicles (MVs) formed by the outward budding of the mammary cell's plasma membrane and released into BM. This illustration was created with BioRender.com

benefits of these vaccines in protecting lactating women appear to outweigh the potential risks, especially after 48 h post-vaccination. However, for the first 48 h, when mRNA can be detected in the BM, a risk/benefit assessment is warranted. The potential bioactivity of the mRNA vaccine in BM will depend on several factors, including the concentration of biologically active mRNA and the specific cell type responding to the mRNA vaccine. The COVID mRNA serum levels required for vaccine efficacy after intramuscular vaccination are not defined. A recent report[3] suggested that the dose of COVID-19 vaccine detected in BM is of no concern because it is 0.002% of the intramuscular vaccine dose. However, this assumption may not be accurate. After vaccine mRNA biodistribution, the effective serum concentration is expected to be a very small fraction of the intramuscular dose. For example, the peak ampicillin serum level after intramuscular administration of 1000 mg is approximately 10 mcg/mL after 1 h[14]; this is 0.001% of the dose. Another study demonstrated that a lactating mother's vaccine mRNA serum concentration was comparable to that in her BM.[11] This can be of concern in breastfed infants, considering the minimum mRNA dose needed to elicit an immune reaction in infants <6 months of age is unknown. A recent report demonstrated an inflammatory response to COVID mRNA vaccines 48 h following the second vaccine dose.[15] As the risk/benefit balance of the COVID-19 vaccine can change over time, information transparency is imperative. A discussion between a breastfeeding mother and her healthcare provider will address the benefit/risk considerations of

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continuing breastfeeding or withholding it temporarily (but continuing feeding her infant pre-vaccination collected BM) for 48 h after vaccination. This is consistent with the CDC's position not recommending COVID-19 vaccine exposure in infants <6 months of age because of the lack of safety studies. Concerns regarding vaccine exposure in BM are not unprecedented. The Yellow Fever live-attenuated vaccine was detected in BM; hence, the CDC recommends against breastfeeding in women until the vaccine exposure risks are evaluated.[46] It was suggested to temporarily withhold breastfeeding in the 10 days following the Yellow Fever vaccination, during which time the vaccine content is detectable in BM.[47] Notably, passive antibody transfer via BM does occur after maternal COVID-19 vaccination on the order of days to weeks post-vaccination and minimally in the first 48 h.[43]

Our study has some limitations, including the small sample size. Given the novelty of the vaccine, the narrow focus of our cohort, and the rarity of women receiving the vaccine during lactation, there were inherent limitations to achieving a larger sample size. Other limitations include the potential underestimation of the mRNA concentrations due to differences in the mothers' collection techniques and storage conditions following self-collection, which may contribute to mRNA degradation. Another limitation includes the limited volume of BM provided by mothers, which limited the feasibility of further experiments. Also, we did not test the possible cumulative vaccine mRNA exposure following frequent breastfeeding in infants, which can add up to 150–200 mL/kg/day of BM.

Conclusion

Our findings suggest that vaccine mRNA is not localized to the injection site but spreads systemically and can be packaged into BM EVs. While the mRNA vaccine seems to be translationally inactive, further investigation is required to determine the minimum amount of mRNA needed to elicit an immune response in newborns. This research would prompt a discussion among the experts responsible for formulating policies related to breastfeeding after mRNA vaccination. Although we believe breastfeeding after mRNA vaccination is safe, a dialogue between a breastfeeding mother and her healthcare provider should address the benefit/risk considerations of breastfeeding in the first two days after maternal mRNA vaccination. This is particularly important given the currently limited data on the effectiveness of booster mRNA vaccines, the varied health statuses of lactating women, and the diverse risk perceptions within our society. Furthermore, the significance of this research extends beyond the scope of COVID-19 mRNA vaccines. The findings provide valuable insights into the transport and presence of vaccine mRNA in BM, which can be relevant for assessing the safety and efficacy of future mRNA-based treatments administered to lactating women. Although there is a theoretical risk for the biodistribution of the mRNA vaccine in the BM, it also may provide a vaccination-protection benefit to the infant. Enhancing our understanding of the distribution patterns, factors that alter the LNPs, such as the corona protein, and the cellular responses to mRNA vaccines can potentially enhance the development of LNP designs and the duration of action of these therapies in lactating and pregnant women. Ultimately, this will contribute to the creation of safer and more effective mRNA therapies for lactating and pregnant women. Regulatory agents should establish comprehensive regulations and allocate necessary resources to facilitate the inclusion of lactating and pregnant women in clinical research, ensuring equal opportunities to benefit from advancements in new therapies and medical science.

Contributors

Dr. Hanna had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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All authors read and approved the final version of the manuscript.

Data sharing statement

The data or materials for the experiments reported here can be available at reasonable request and within relevant legal constraints.

Declaration of interests

The authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2023.104800.

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Trends in Molecular Medicine

Opinion

Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis

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Vaccination is a major tool for mitigating the coronavirus disease 2019 (COVID-19) pandemic, and mRNA vaccines are central to the ongoing vaccination campaign that is undoubtedly saving thousands of lives. However, adverse effects (AEs) following vaccination have been noted which may relate to a proinflammatory action of the lipid nanoparticles used or the delivered mRNA (i.e., the vaccine formulation), as well as to the unique nature, expression pattern, binding profile, and proinflammatory effects of the produced antigens – spike (S) protein and/or its subunits/peptide fragments – in human tissues or organs. Current knowledge on this topic originates mostly from cell-based assays or from model organisms; further research on the cellular/molecular basis of the mRNA vaccine-induced AEs will therefore promise safety, maintain trust, and direct health policies.

Highlights

Coronavirus disease 2019 (COVID-19) mRNA vaccines induce robust immune responses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), yet their cellular/molecular mode of action and the etiology of the induced adverse events (AEs) remain elusive.

Lipid nanoparticles (LNPs) probably have a broad distribution in human tissues/organs; they may also (along with the packaged mRNA) exert a proinflammatory action.

COVID-19 mRNA vaccines encode a transmembrane SARS-CoV-2 spike (S) protein; however, shedding of the antigen and/or related peptide fragments into the circulation may occur.

Binding of circulating S protein to angiotensin-converting enzyme 2 (ACE2) (that is critical for the renin–angiotensin system balance) or to other targets, along with the possibility of molecular mimicry with human proteins, may contribute to the vaccination-related AEs.

The benefit–risk profile remains in favor of COVID-19 vaccination, yet prospective pharmacovigilance and long-term monitoring of vaccinated recipients should be a public health priority.

Fighting the COVID-19 pandemic with SARS-CoV-2 S protein-encoding mRNA vaccines

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ( ) and has resulted in millions of deaths worldwide. Nevertheless, for the majority of SARS-CoV-2-infected individuals, COVID-19 will remain asymptomatic or only mildly symptomatic [,2]. Although SARS-CoV-2 may also circulate in the gastrointestinal tract [3], being a respiratory virus, the virus itself or its related antigens will not, in most cases, impact tissues and organs other than the respiratory system (RS) ( ) [6]. In patients with severe disease, infection of airway and lung tissues may cause pneumonia and excessive inflammation which can lead to **acute respiratory distress syndrome (ARDS)** (see ( ) [0]. ARDS may then lead to organ damage beyond the RS because of micro-/macro-thromboembolism, hyperinflammation, aberrant complement activation, or extended **viremia** [3]. This may be due to the broad expression of its receptor **angiotensin-converting enzyme 2 (ACE2)** in several cell types and tissues [6] which results in an expanding tropism of SARS-CoV-2 for various critical organs (heart, pancreas, kidneys, etc.). If systemic collapse and death are avoided, the postulated direct virus 'attack' – or indirect effects due to **cytokine storm** [, 3] or imbalance of the **renin–angiotensin system (RAS)** [3] – causing multiorgan damage, possibly foster systemic defects which cause a chronic condition (referred to as **long COVID-19**) which is independently associated with the severity of the initial illness [7].

Following an unprecedented effort of biomedical research and mobilization of resources, two mRNA vaccines – namely BNT162b2 (Comirnaty™) from Pfizer-BioNTech and the mRNA-1273 of Moderna (encoded antigen: SARS-CoV-2 S protein of the Wuhan-Hu-1 strain) [18–20] – were the first to receive FDA emergency use authorization. In mRNA vaccines, which are characterized by relatively rapid prototyping and manufacturing on a large scale, the S protein-encoding mRNA is delivered via lipid nanoparticles (LNPs) to human cells that produce the mature viral protein or related antigens (Figure 1, Key figure), which can exhibit a rather wide tissue/organ distribution

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Box 1. SARS-CoV-2 infection of human cells

SARS-CoV-2 infection of human cells proceeds via its binding to the cell surface protein ACE2 through the RBD of its protruding S glycoprotein [127] which remains in a metastable prefusion state through the association of subunits 1 (S1) and 2 (S2) via noncovalent interactions [18,19]; the infection process is also facilitated by host proteases [127,128]. In most of SARS-CoV-2-infected carriers the virus is contained in the upper RS, resulting in either no symptoms or mild symptoms [1,2]. A minority will require hospitalization; this is due to severe symptoms which develop due to extensive inflammation, a process often referred to as a 'cytokine storm', causing ARDS which may be accompanied by viremia and can lead to systemic multiorgan collapse [7–10]. The risk for severe COVID-19 increases significantly with age or pre-existing comorbidities [1,2,129], and younger individuals have a substantially lower risk – even compared to influenza infection [129] – for developing severe COVID-19 [130,131]. It has been postulated that higher pediatric innate interferon responses restrict viral replication and disease progression [132]. In a recent trial, in which young people were intentionally exposed to a low dose of SARS-CoV-2, nearly half of the participants did not become infected, some were asymptomatic, and those who developed COVID-19 reported mild to moderate symptoms, including sore throats, runny noses, sneezing, and loss of sense of smell and taste; fever was less common, and no one developed a persistent cough [133].

SARS-CoV-2 infection in healthy individuals triggers innate as well as adaptive immune system responses, that is, $CD4^+$ and $CD8^+$ T cells and antibodies, including neutralizing antibodies (NAbs) produced by terminally differentiated B cells, which altogether suppress the extent of infection [132,134,135]. As SARS-CoV-2 initially infects the upper RS, defensive immune responses start to develop at respiratory mucosal surfaces, and this is followed by systemic immunity [136,137]. These immune responses are age- and gender-dependent and may either mount poorly in a background of genetic causes and pre-existing morbidities, or become very intense and essentially uncontrolled in severe disease leading to ARDS and systemic failure [11–13].

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(discussed later) [20–22]. In addition to the plausible proinflammatory role of LNPs (evidenced also from reported immediate allergic reactions) [23,24] and of packaged mRNA – which has nonetheless been engineered by a replacement of uridine with pseudouridine [20,25,26] so as not to trigger innate immunity through pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) receptors – we surmise that vaccination-mediated **adverse effects (AEs)** can be attributed to the unique characteristics of the S protein itself (antigen) either due to **molecular mimicry** with human proteins or as an ACE2 ligand.

As delivered mRNAs can theoretically trigger the production of distinct antigens that can distribute systemically [20], they are radically different from conventional platforms (i.e., inactivated whole-virus vaccines or even protein-subunit nanoparticle vaccines) (Box 2) where the produced antigen and its distribution are more predictable. As all COVID-19 vaccines rely on the S protein of the original Wuhan-Hu-1 strain [19,20], the differences across different vaccination platforms thus far reported (Box 2) may relate to the various vectors and formulations and/or the S protein constructs employed.

Anti-SARS-CoV-2 mRNA vaccines and their reported adverse effects

Both the BNT162b2 and mRNA-1273 vaccines are administered intramuscularly and mobilize robust and likely durable innate, humoral, and cellular adaptive immune responses [27–30]. Existing data on the available mRNA vaccines are mostly limited to **serological analyses**. Nonetheless, beyond the assessment of immune responses, the understanding of the safety profile of these vaccines is critical to ensure safety, maintain trust, and inform policy. Reportedly, mRNA vaccines are in general well tolerated, with very low frequencies of associated severe postimmunization AEs. Although rare, AEs include serious clinical manifestations such as acute myocardial infarction, **Bell's palsy**, **cerebral venous sinus thrombosis**, **Guillain–Barré syndrome**, myocarditis/pericarditis (mostly in younger ages), pulmonary embolism, stroke, thrombosis with thrombocytopenia syndrome, lymphadenopathy, appendicitis, herpes zoster reactivation, neurological complications, and autoimmunity (e.g., autoimmune hepatitis and autoimmune peripheral neuropathies [31–34]) (see Clinician's corner). Apart from AEs documented in clinical trials, most of the syndromes or isolated manifestations have been reported in multicenter or even nationwide retrospective observational studies and case series. Although correlation does not necessarily mean

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causation, active monitoring and awareness regarding reported postvaccination AEs are essential. Importantly, these associated AEs are significantly less frequent than analogous or additional serious AEs induced after severe COVID-19 [31,32,34]. Some vaccine-induced AEs (e.g., myocardial infarction, Guillain–Barré syndrome) were found to increase with age, while others (e.g., myocarditis, anaphylaxis, appendicitis) were more common in younger people [35,36]. Although myocarditis cases are rather rare, in a study of US military personnel the number was higher than expected among males after a second vaccine dose [37]; similarly, the rate of postvaccination cardiac AEs was higher in young boys following the second dose [38,39]. Finally, a recent study showed an increased risk of neurological complications in COVID-19 vaccine recipients (which was nevertheless lower than the risk in COVID-19 patients) [34]. The molecular basis of these AEs remains largely unknown. We postulate that, since most (if not all) of them are also apparent in severe COVID-19 [31], they may be related to acute inflammation caused by both the virus and the vaccine, as well as in the common denominator between the virus and the vaccine, namely, the SARS-CoV-2 S protein (Box 1). The vaccine-encoded antigen (S protein) is stabilized in its prefusion form in the BNT162b2 and mRNA-1273 vaccines [19,20]; it is therefore plausible that, if entering the circulation and distributing systemically throughout the human body (Figure 2), it can contribute to these AEs in susceptible individuals.

There is also evidence that ionizable lipids within LNPs can trigger proinflammatory responses by activating Toll-like receptors (TLRs) [40]. A recent report showed that LNPs used in preclinical nucleoside-modified mRNA vaccine studies are (independently of the delivery route) highly inflammatory in mice, as evidenced by excessive neutrophil infiltration, activation of diverse inflammatory pathways, and production of various inflammatory cytokines and chemokines [41]. This finding could explain the LNPs' potent adjuvant activity, supporting the induction of robust adaptive immune responses [24]. Interestingly, inflammatory responses can be exacerbated on a background of pre-existing inflammatory conditions, as was recently shown in a mouse model after administration of mRNA–LNPs [42]; this effect was proven to be specific to the LNP, acting independently of the mRNA cargo.

Although chemical modifications in the RNA molecules used in vaccines (detailed earlier) are intended to decrease TLR sensing of external single-stranded RNAs (and thus proinflammatory signals), there is some evidence that modified uracil residues do not completely abrogate TLR detection of the mRNA; also, while efforts are made to reduce double-stranded (ds) RNA production, there may be small amounts of dsRNA that can occasionally get packaged within mRNA vaccines [26].

In this context, frequent booster immunizations may increase the frequency and/or the severity of the reported AEs.

Vaccine-encoded antigen distribution in the human body and possible interactions with human proteins

Following vaccination, a cell may present the produced S protein (or its subunits/peptide fragments) to mobilize immune responses or be abolished by the immune system (e.g., cytotoxic T cells) [25]. Consequently, the debris produced, or even the direct secretion (including shedding) of the antigen by the transfected cells, may release large amounts of the S protein or its subunits/peptide fragments to the circulation (Figure 1) [19,20]. The anti-SARS-CoV-2 vaccine mRNA-containing LNPs are injected into the deltoid muscle and exert an effect in the muscle tissue itself, the lymphatic system, and the spleen, but can also localize in the liver and other tissues [21,22,43,44] from where the S protein or its subunits/peptide fragments may enter the circulation and distribute throughout the body. It is worth mentioning that liver localization of LNPs is not a

Glossary

Acute respiratory distress syndrome (ARDS): a life-threatening condition in which fluid builds up in the lungs, interfering with the gas exchange function and preventing oxygenation of the blood and organs.
Adverse effect (AE): an undesired effect of a medication or clinical intervention with potentially harmful consequences.
Angiotensin-converting enzyme 2 (ACE2): an enzyme involved in the homeostatic regulation of circulating angiotensin I and angiotensin II levels by converting them to angiotensin (1–9) and angiotensin (1–7) peptides respectively.
Bell's palsy: an idiopathic episode of facial muscle weakness or paralysis on one side of the face. This condition results from dysfunction of the seventh cranial nerve (the facial nerve).
Cerebral venous sinus thrombosis: a rare blood-clotting event that occurs in the venous sinuses of the brain and prevents blood from draining out of the brain. As a result, pressure builds up and can lead to swelling and hemorrhage.
Cytokine storm: a characteristic of COVID-19 (or other disease) where abnormally high levels of circulating cytokines are produced and contribute to disease severity.
Guillain–Barré syndrome: a rare, autoimmune neurological disorder in which the body's immune system erroneously attacks the peripheral nerves, causing muscle weakness and, if left untreated, paralysis.
Long COVID-19: a term that refers to a range of new, returning, or ongoing symptoms that persist beyond the initial phase of a SARS-CoV-2 infection.
Molecular mimicry: the process in which an immune response against a foreign antigen is inadvertently also directed against a self-antigen that closely resembles the triggering foreign antigen.
Receptor-binding domain (RBD): the part of a binding protein (e.g., in SARS-CoV-2 S protein) used to anchor the protein to its receptor.
Renin–angiotensin system (RAS): a system that is critical in the physiological regulation of (among others) neural, gut, cardiovascular, blood pressure, and kidney functions, as well as fluid and salt balance. It involves the enzyme renin which catalyzes the production of angiotensin I.

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universal property of carrier nanoparticles, as specific modifications in their chemistry can retain immunogenicity with minimal liver involvement [43,45]. In line with a plausible systemic distribution of the antigen, it was found that the S protein circulates in the plasma of the BNT162b2 or mRNA-1273 vaccine recipients as early as day 1 after the first vaccine injection [46]. Reportedly, antigen clearance is correlated with the production of antigen-specific immunoglobulins or may remain in the circulation (e.g., in exosomes) for longer periods [47,48], providing one reasonable explanation (among others) for the robust and durable systemic immune responses found in vaccinated recipients [49,50]. Therefore, there is likely to be an extensive range of expected interactions between free-floating S protein/subunits/peptide fragments and ACE2 circulating in the blood (or lymph), or ACE2 expressed in cells

Serological analysis: any analysis performed with blood serum, usually focusing on measuring antibody levels.
Syncytium: a cell with multiple nuclei resulting from multiple fusions of uninuclear cells.
Viremia: the detection of replication-competent viral particles in the bloodstream.

Key figure

Antigen expression–localization following cell transfection with spike (S) protein mRNA-containing lipid nanoparticles (LNPs) used in anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines

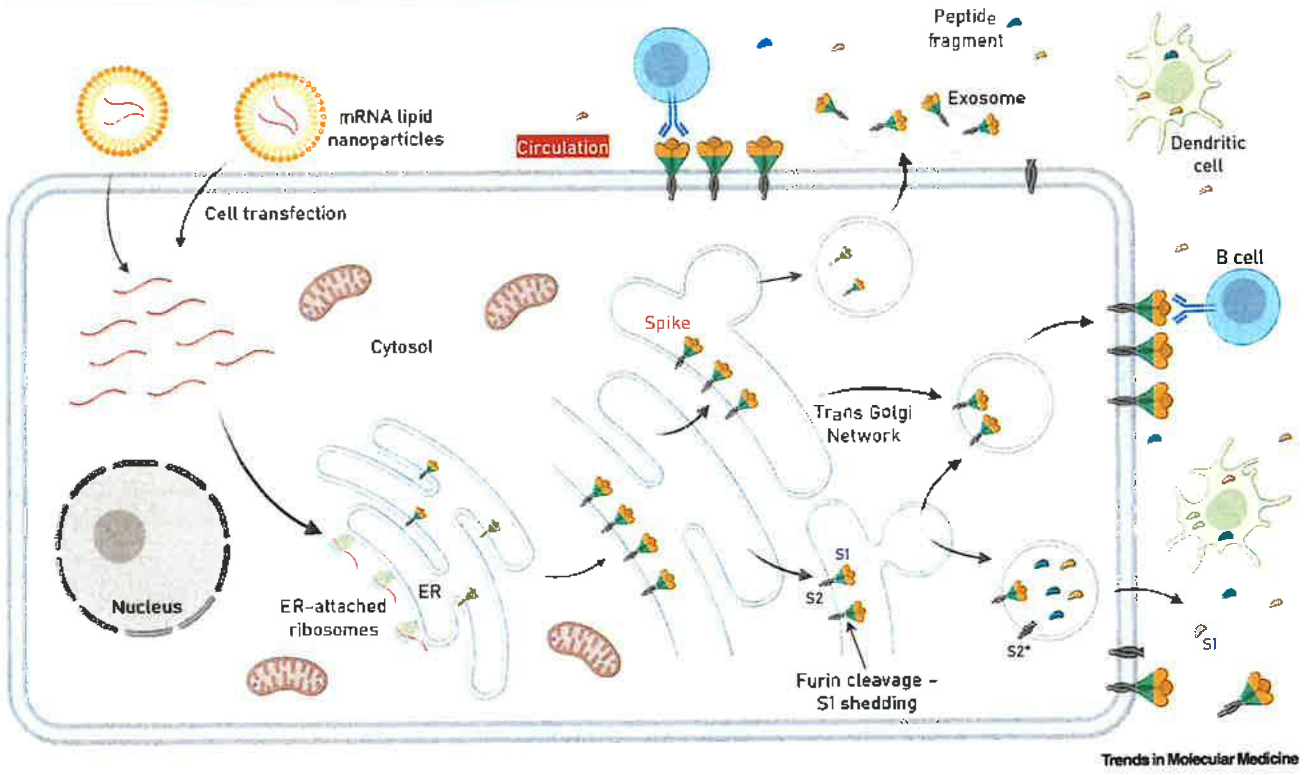

Figure 1. Following LNP internalization and mRNA release, the authentic viral signal peptide (as in the Pfizer–BioNTech and Moderna vaccines) drives antigen production in the lumen of the endoplasmic reticulum (ER) where it adopts its natural transmembrane localization via subunit 2 (S2) anchoring. After sorting in the trans Golgi network (TGN), S protein acquires its final position in the transfected human cell membrane, where S1 is exposed to the extracellular space (i.e., may face circulation). Although the extent of antigen expression per cell remains unknown, it is reasonable to assume that this process results in rather extended decoration of transfected cells with S protein. Furin-mediated proteolytic cleavage (as in SARS-CoV-2-infected cells) in the absence of a mutated S1/S2 furin cleavage site at the TGN may result in shedding of cleaved S1 and conversion of S2 into its postfusion structure (S2*). Antigen sorting and trafficking may also induce the release of S protein-containing exosomes. The events shown will occur in the apical and/or basolateral surfaces of polarized (e.g., epithelial) cells. The Pfizer–BioNTech and Moderna constructs do not contain a mutated S1/S2 furin cleavage site. Further research will clarify the impact of the S1/S2 subunits stabilizing D614G (or other) mutation or of a mutated furin cleavage site in antigen distribution, the immunogenicity of the vaccine, and induced adverse events (AEs). Also shown are dendritic cells (professional antigen-presenting cells, APCs) engulfing circulating antigens, and antibody-mediated binding of B cells to cell-anchored antigens.

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Box 2. Other types of COVID-19 vaccine

In viral vector vaccines, the S protein coding information is delivered via a replication-deficient adenoviral vector system that contains an encoding dsDNA. In this case, transcripts from adenoviral vectors are generated in the cell nucleus. Here, a major reported AE is immune thromboembolism (including cerebral venous sinus thrombosis) in various organs, probably through excessive innate immune system and endothelial activation [139]. Apart from the S protein itself, AEs can be also attributed to background expression of remaining adenoviral genes or to persisting adenovirus-vector DNA in a transcriptionally active form. Further concerns are the presence of other contaminant proteins, remnants of the vaccine production line, and to pre-existing antivector immunity [20]; this last issue does not apply to the recombinant ChAdOx1-S (Oxford–AstraZeneca) vaccine which employs a nonhuman adenovirus vector. More importantly, the infectious cycle of SARS-CoV-2 takes place exclusively in the cytoplasm, and thus there has been no evolutionary pressure against the presence of splice donor and acceptor sites in its genes. This is a major difference from mRNA vaccines that function in the cytoplasm, since various spliced transcripts from adenoviral vectors can be generated in the cell nucleus [56].

In protein subunit nanoparticle vaccines (e.g., NVX-CoV2373), the S protein is harvested in a cell culture system, purified, and delivered as a trimer via a nanoparticle assembly in an adjuvant. Although preliminary trials indicate that these vaccines can trigger robust immunity [139], reports on AEs are still scarce due to the limited amount of vaccination data.

Finally, in conventional vaccines, the whole virus is inactivated and inoculated using an appropriate adjuvant [26]. A significant benefit is that whereas in the previously discussed technologies the S protein is the sole source of immunogenic epitopes, in this case a wide repertoire of epitopes in other viral proteins is presented. Possible disadvantages include lower immunogenicity, production issues, AEs due to used adjuvant(s) (e.g., aluminum hydroxide), as well as issues that relate to incomplete inactivation of the virus. Given that these vaccines have not reached mass production, reports on possible AEs do not exist.

from various tissues/organs (Figure 2) [14–16]. This notion is further supported by the finding that in adenovirus-vectored vaccines (Box 2), the S protein produced upon vaccination has the native-like mimicry of SARS-CoV-2 S protein's receptor binding functionality and prefusion structure [51].

Additional interactions with human proteins in the circulation, or even the presentation to the immune system of S protein antigenic epitopes [52] mimicking human proteins (molecular mimicry) may occur [53–56]. Reportedly, some of the near-germline SARS-CoV-2-NAbs against S **receptor-binding domain (RBD)** reacted with mammalian self-antigens [57], and SARS-CoV-2 S antagonizes innate antiviral immunity by targeting multiple pathways controlling interferon (IFN) production [58]. Also, a sustained elevation in T cell responses to SARS-CoV-2 mRNA vaccines has been found (data not yet peer-reviewed) in patients who suffer from chronic neurologic symptoms after acute SARS-CoV-2 infection as compared with healthy COVID-19 convalescents [59]. Given the reported (rare) neurological AEs following vaccination, it was suggested that further studies are needed to assess whether antibodies against the vaccine-produced antigens can cross-react with components of the peripheral nerves [34]. Further concerns include the possible development of anti-idiotype antibodies against vaccination-induced antibodies as a means of downregulation; anti-idiotype antibodies – apart from binding to the protective neutralizing SARS-CoV-2 antibodies – can also mirror the S protein itself and bind ACE2, possibly triggering a wide array of AEs [60]. Worth mentioning is a systems vaccinology approach (31 individuals) of the BNT162b2 vaccine (two doses) effects, where anticytokine antibodies were largely absent or were found at low levels (contrary to findings in acute COVID-19 [61,62]), while two individuals had anti-interleukin-21 (IL-21) autoantibodies, and two other individuals had anti-IL-1 antibodies [63]. In this context, anti-idiotypic antibodies can be particularly enhanced after frequent boosting doses that trigger very high titers of immunoglobulins [64]. Frequent boosting doses may also become a suboptimal approach as they can imprint serological responses toward the ancestral Wuhan-Hu-1 S protein, minimizing protection against novel viral S variants [65,66].

The potential interaction at a whole-organism level of the native-like S protein and/or subunits/peptide fragments with soluble or cell-membrane-attached ACE2 (Figure 2) can promote ACE2 internalization and degradation [67,68]. In support of this, soluble ACE2 induces receptor-mediated endocytosis of SARS-CoV-2 via interaction with proteins related to the RAS [69].

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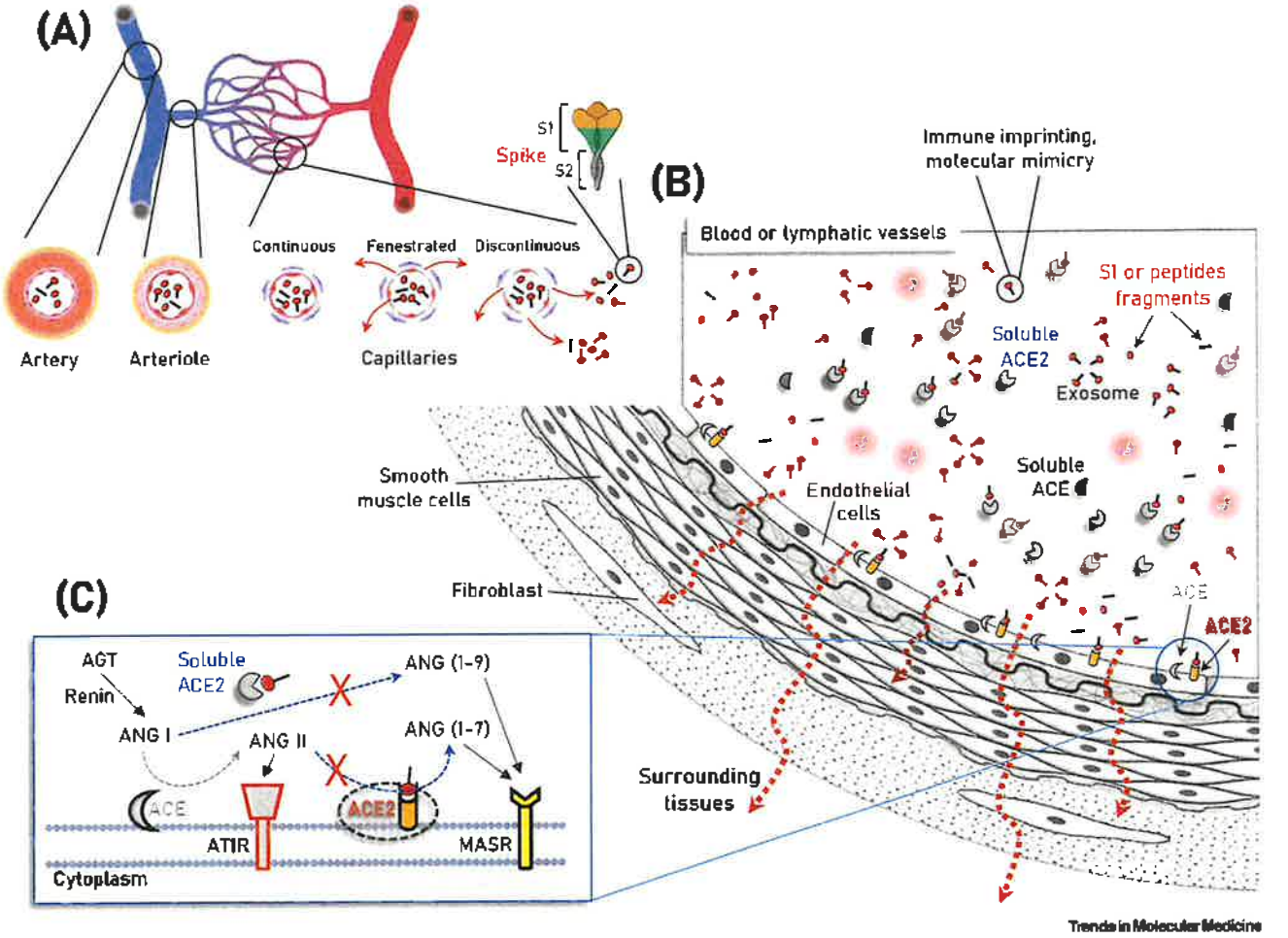

Figure 2. Schematic of the vasculature components showing vaccination-produced S protein/subunits/peptide fragments in the circulation, as well as soluble or endothelial cell membrane-attached angiotensin-converting enzyme 2 (ACE2). (A,B) Parallel to immune system activation, circulating S protein/subunits/peptide fragments (B) binding to ACE2 may occur not only to ACE2-expressing endothelial cells, but also in multiple cell types of the vasculature and surrounding tissues due to antigen diffusion (e.g., in fenestrated or discontinuous capillary beds) (A, red arrows). These series of molecular events are unlikely for any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related antigen in the absence of severe coronavirus disease 2019 (COVID-19), where SARS-CoV-2 is contained in the respiratory system. In (C) the two counteracting pathways of the renin–angiotensin system (RAS), namely the 'conventional' arm, that involves ACE which generates angiotensin II (ANG II) from angiotensin I (ANG I), and the ACE2 arm which hydrolyzes ANG II to generate angiotensin (1–7) [ANG (1–7)] or ANG I to generate angiotensin (1–9) [ANG (1–9)] are depicted. ANG II binding and activation of the ANG II type 1 receptor (AT1R) promotes inflammation, fibrotic remodeling, and vasoconstriction, whereas the ANG (1–7) and ANG (1–9) peptides binding to MAS receptor (MASR) activate antifibrotic, anti-inflammatory pathways and vasodilation. Additional modules of the RAS (i.e., renin and angiotensinogen, AGT) are also shown. Abbreviation: AT1R, angiotensin II type 1 receptor.

Prolonged loss or reduced ACE2 activity may result in extensive destabilization of the RAS which may then trigger vasoconstriction, enhanced inflammation, and/or thrombosis due to unopposed ACE and angiotensin-2 (ANG II)-mediated effects (Figure 2) [13]. Indeed, decreased ACE2 expression and/or activity contributes, among other things, to the development of ANG II-mediated hypertension in mice, indicating vasculature dysfunction [67]. The baseline expression levels of ACE2 in endothelial cells, or its induced expression levels upon stimulation from other tissue-resident cells, along with the potential of endothelial cells to shed ACE2 to the circulation, or their sensitivity to SARS-CoV-2 infection is debatable [70–73]. Nonetheless, even relatively low ACE2 expression levels in endothelial cells (e.g., compared to levels in epithelial cells) [15,16,70,71], along with the high expression levels of ACE2 in other cell types of the vasculature

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(e.g., heart fibroblasts/pericytes) [15,74], indicate that the vasculature can be sensitive to free-floating S protein or its subunits/peptide fragments (Figure 2). These effect(s), especially in capillary beds, and the prolonged antigen presence in the circulation [46–48], along with the systemic excessive immune response to the antigen, can then trigger sustained inflammation (discussed later) which can injure the endothelium, disrupting its antithrombogenic properties in multiple vascular beds.

The SARS-CoV-2 S protein-induced effects in mammalian cells or model organisms

Reportedly, intravenous (i.v.) injection of the S1 subunit in mice results in its localization in endothelia of mice brain microvessels showing colocalization with ACE2, caspase-3, IL-6, tumor necrosis factor α (TNF-α), and C5b-9; it was thus suggested that endothelial damage is a central part of SARS-CoV-2 pathology which may be induced by the S protein alone [7 . Also, the S1 subunit (or recombinant S1 RBD) impaired endothelial function via downregulation of *ACE2* [7 and induced degradation of junctional proteins that maintain endothelial barrier integrity in a mouse model of brain microvascular endothelial cells or cerebral arteries; this latter effect was more enhanced in endothelial cells from diabetic versus normal mice [77]. Similarly, the S1 subunit decreased microvascular transendothelial resistance and barrier function in cultured human pulmonary cells [7 . Further, S protein disrupted human cardiac pericytes function and triggered increased production of proapoptotic factors in pericytes, causing endothelial cells death [7 . In support of this, administration of the S protein promoted dysfunction of human endothelial cells as evidenced by, for example, increased expression of the von Willebrand factor [8 . Other reports indicate that S1 can directly induce coagulation by competitive binding to both soluble and cellular heparan sulfate/heparin (an anticoagulant) [81–8 , while cell-free hemoglobin, as a hypoxia counterbalance, cannot attenuate disruption of endothelial barrier function, oxidative stress, or inflammatory responses in human pulmonary arterial endothelial cells exposed to S1 [8 . Consistently, S protein binds fibrinogen (a blood coagulation factor), and S protein virions have been found to enhance fibrin-mediated microglia activation (data not yet peer-reviewed) and induce fibrinogen-dependent lung pathology in mice [8 , while S1 binding to platelets' ACE2 triggers their aggregation [84]. Interestingly, both the ChAdOx1 (AstraZeneca) and BNT162b2 vaccines can elicit antiplatelet factor 4 (anti-PF4) antibody production even in recipients without clinical manifestation of thrombosis [8 .

Intriguingly, the S protein increases human cell **syncytium** formation [88,89], triggering pyroptosis of syncytia formed by fusion of S and ACE2-expressing cells [90]. Also, in cells or mouse experimental models, it was shown that S removes lipids from model membranes and interferes with the capacity of high-density lipoprotein to exchange lipids [91], inhibits DNA damage repair processes [92], and induces Snail-mediated epithelial–mesenchymal transition marker changes and lung metastasis in a breast cancer mouse model [93].

In support of the possibility that there is a wide range of S protein binders, $A\beta_{1-42}$ (the 42 amino acid form of amyloid β in cerebrospinal fluid) was found to bind with high affinity to the S1 subunit and ACE2 [94]. $A\beta_{1-42}$ strengthened the binding of S1 to ACE2 and increased viral entry and production of IL-6 in a SARS-CoV-2 pseudovirus infection mouse model. Data from this surrogate mouse model with IV inoculation of $A\beta_{1-42}$ showed that the clearance of $A\beta_{1-42}$ in the blood was dampened in the presence of the extracellular domain of the S protein trimers [94]. Given the wide ACE2 expression in human brain [95], a study of particular interest showed that IV-injected radioiodinated S1 (I-S1) readily crossed by adsorptive transcytosis the blood–brain barrier in male mice, was taken up by brain regions, and entered the parenchymal brain space. I-S1 was also taken up by the lung, spleen, kidney, and liver; intranasally administered I-S1 also entered the brain, although at lower levels than after i.v. administration [96]. Similarly, S1 was found to disrupt the blood–brain barrier integrity at a 3D blood–brain barrier microfluidic

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model [97]. In support of this, biodistribution studies of the mRNA–LNP platform by Moderna in Sprague Dawley rats revealed the presence of low levels of mRNA in the brain, indicating that the mRNA–LNPs can cross the blood–brain barrier [22].

Finally, it was recently reported that human T cells express ACE2 at levels sufficient to interact with the S protein [98], while it had been shown previously that SARS-CoV-2 uses CD4 to infect T helper lymphocytes, and that S promotes a proinflammatory activation profile on the most potent antigen-presenting cells (APCs) (i.e., human dendritic cells) [99]. If these observations are confirmed, they may explain a SARS-CoV-2 vaccination-mediated AE, namely, reactivation of varicella zoster virus [100,101].

S protein-induced proinflammatory responses and unique gene expression signatures following vaccination

Reportedly, S protein (apart from the LNP–mRNA platform discussed earlier) mediates proinflammatory and/or injury (of different etiology) responses in various human cell types [102–104], and ACE2-mediated infection of human bronchial epithelial cells with S protein pseudovirions induced inflammation and apoptosis [105]. Also, S protein promoted an inflammatory cytokine IL-6/IL-6R-induced trans signaling response and alarmin secretion in human endothelial cells, along with increased oxidative stress, induction of inflammatory paracrine senescence, and higher levels of leucocyte adhesion [106]. Other reports indicate that S protein triggers an inflammatory response signature in human corneal epithelial cells [107], increases oxidative stress and DNA ds breaks in human peripheral-blood mononuclear cells (PBMCs) postvaccination [108], and binds to lipopolysaccharide, boosting its proinflammatory activity [109,110]. Furthermore, S protein induces neuroinflammation and caspase-1 activation in BV-2 microglia cells [111] and blocks neuronal firing in sensory neurons [112]. The S protein-induced systemic inflammation may proceed via TLR2-dependent activation of the nuclear factor κB (NF-κB) pathway [113], while structure-based computational models showed that S protein exhibits a high-affinity motif for binding T cell receptors (TCRs), and may form a ternary complex with histocompatibility complex class II molecules; indeed, analysis of the TCR repertoire in COVID-19 patients showed that those with severe hyperinflammatory disease exhibit TCR skewing consistent with superantigen (S protein) activation [114]. In *in vivo* mouse models, S protein activated macrophages and contributed to induction of acute lung inflammation [115], while intratracheal instillation of the S1 subunit in transgenic mice overexpressing human ACE2 induced severe COVID-19-like acute lung injury and inflammation. These effects were milder in wild-type mice, indicating the phenotype dependence on human ACE2 expression [78]. Consistently, the S1 subunit has been found to act as a PAMP that, via pattern recognition receptor engagement, induces viral infection-independent neuroinflammation in adult rats [116].

These observations correlate with the finding of a systemic inflammatory signature after the first BNT162b2 vaccination which was accompanied by TNF-α and IL-6 upregulation after the second dose [117]; these effects may also relate to a proinflammatory action of the mRNA–LNP platform (see earlier). In a thorough systems vaccinology study of the BNT162b2 mRNA vaccine effects, younger participants tended to have greater changes in monocyte and inflammatory modules 1 day after the second dose, whereas older individuals had increased expression of B and T cell modules. Moreover, single-cell transcriptomics analysis at the same time point revealed the emergence of a unique myeloid cell cluster out of 18 cell clusters identified in total. This cell cluster does not represent myeloid-derived suppressor cells, it expressed IFN-stimulated genes and was not found in COVID-19 infection; also, it was similar to an epigenetically reprogrammed monocyte population found in the blood of donors being vaccinated with two doses of an influenza vaccine [63]. Whether epigenetic reprogramming underlies the enhanced

Clinician's corner

Given the plethora of existing data on the available mRNA vaccines, a major 'known' is that in the short-term mRNA vaccines are well tolerated by the recipient, and that they can induce a robust immune response and therefore provide prolonged protection against severe COVID-19 (including emerging variants of concern); thus, vaccination remains a major tool for mitigating the COVID-19 pandemic and saving thousands of lives.

It is well established that the risk for severe COVID-19 increases with age or pre-existing comorbidities. Given the 'unknowns' discussed herein, boosting doses in healthy children and even adolescents should be delivered only if the benefit–risk profile is clearly established.

Multidisciplinary clinical and basic research aiming at understanding the cellular–molecular basis of the COVID-19 mRNA vaccine-induced AEs – along with active pharmacovigilance and long-term recording in the clinical setting of reported AEs in vaccinated recipients – are critical components for improving vaccines, guaranteeing safety, maintaining trust, and directing health policies.

The technology of the mRNA vaccines will continue to evolve as it opens up a whole new era of novel applications for large-scale development of new vaccines against various infectious and other diseases, including cancer.

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IFN-induced gene response in C8 cells after secondary BNT162b2 vaccination remains to be clarified. Finally, a comparison between the BNT162b2 vaccine-induced gene expression signatures at day 7 post-prime (d7PP) and post-boost (d7PB) doses and that of other vaccine types (e.g., inactivated or live-attenuated vaccines) exhibited weak correlation both between d7PP and d7PB as well as with other vaccines [63]. These findings suggest the evolution of novel genomic responses after the second dose and, more importantly, the unique biology of mRNA vaccines versus other more conventional platforms. Of particular interest is also the report of a cytokine release syndrome (CRS) – an extremely rare immune-related AE of immune checkpoint inhibitors – post-BTN162b2 vaccination in a patient with colorectal cancer on longstanding anti-programmed death 1 (PD-1) monotherapy; the anti-PD1 blockade-mediated CRS was evidenced by increased inflammatory markers, thrombocytopenia, elevated cytokine levels, and steroid responsiveness [118]. These proinflammatory effects could be particularly pronounced in the elderly, since recent data revealed that senescent cells become hyperinflammatory in response to the S1 subunit, followed by increased expression of viral entry proteins and reduced antiviral gene expression in nonsenescent cells through a paracrine mechanism [119].

The need to investigate the molecular basis of vaccination-induced AEs

Anti-SARS-CoV-2 mRNA vaccines induce durable and robust systemic immunity, and thus their contribution in mitigating the COVID-19 pandemic and saving thousands of lives is beyond doubt. This technology has several advantages over conventional vaccines [120] and opens a whole new era for the development of novel vaccines against various infectious and other diseases, including cancer. Based on currently available molecular insights (mostly in cell-based assays and model organisms), we hypothesize that the rare AEs reported following vaccination with S protein-encoding mRNA vaccines may relate to the nature and binding profile of the systemically circulating antigen(s) (Figures 1 and 2), although the contribution of the LNPs and/or the delivered mRNA is likely also significant [24,26,41]. Therefore, the possibility of subclinical organ dysfunction in vaccinated recipients which could increase the risk, for example, of future (cardio)vascular or inflammatory diseases should be thoroughly investigated. Given that severe COVID-19 correlates with older age, hypertension, diabetes, and/or cardiovascular disease, which all share a variable degree of ACE2 signaling deregulation, additional ACE2 downregulation induced by vaccination may further amplify an unbalanced RAS. Regarding localization of LNPs in the liver and consequent antigen expression, it is worth mentioning that the liver is continuously exposed to a multitude of self and foreign antigens and can mount efficient immune responses against pathogens as it hosts convectional APCs (e.g., dendritic cells, B cells, and Kupfer cells). Additional liver cell types – such as liver sinusoidal endothelial cells, hepatic stellate cells, and hepatocytes – also have the capacity to act as APCs [121]. It is plausible, though as yet unproven, that as the S protein is produced in liver cells, both conventional and unconventional APCs may prime adaptive but also innate immune responses in the liver's immunological niche. Despite the liver's major tolerogenic role [122], the sustained expression of S protein-related antigens (Figure 1) can potentially skew the immune response towards autoimmune-like tissue damage, as in the observed cases of autoimmune hepatitis following vaccination [123,124]. It therefore merits further investigation whether LNPs can transfect any other nonimmunological body tissues bearing cells that can act as unconventional APCs, thus inducing a sustained immune response but also a self-response, as in cases of chronic viral infections [125].

Concluding remarks

Although the benefit–risk profile remains strongly in favor of COVID-19 vaccination for the elderly and patients with age-related or other underlying diseases, an understanding of the molecular–cellular basis of the anti-SARS-CoV-2 mRNA vaccine-induced AEs is critical for the ongoing and future vaccination and booster campaigns. In parallel, the prospective pharmacovigilance

Outstanding questions

What are the localization pattern, transfection efficacy, and clearance rates of the mRNA vaccine LNPs in the human body?

Can we refine LNP chemistry towards retaining transfection efficacy and at the same time assuring on-demand tissue distribution?

Do the adverse inflammatory reactions noted postvaccination also relate – and if yes, to what extent – to LNPs and/or the mRNA used in mRNA vaccines?

What are the mechanistic details of antigen expression, processing, and cellular localization following cell transfection with the LNPs?

What would the impact be of excessive 'decoration' of nonprofessional antigen-presenting transfected human (e.g., liver) cells with transmembrane S protein?

Does the antigen or related subunits-peptide fragments leak into the circulation, and if so, in which form, at what concentration, and for how long? Is there any association with the vaccine-mediated immune responses?

Is the probable binding of the antigen to ACE2 in the vasculature accountable for the cardiovascular, metabolic, or other (e.g., inflammation-related) reported AEs?

Does the antigen cross the blood–brain barrier?

Is there any noteworthy molecular mimicry (especially of the major antigenic sites) between the S protein and the human proteome?

What is the profile of mucosal immunity induced by the mRNA COVID-19 vaccines?

It is the case that vaccination-mediated immunity (two doses) against the used ancestral antigen (Wuhan-Hu-1 S protein) wanes over time, or do we simply partially lose protection due to evolutionary leaps of the S protein (e.g., at the Omicron variant)? In that case, do we really need boosting doses with the same antigen?

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and long-term monitoring (clinical/biochemical) of vaccinated recipients versus matched controls should evolve in well-designed clinical trials. Moreover, the use of alternative chemistries for LNPs, and of S protein in its closed form (not prone to ACE2 binding) [126], along with the use of SARS-CoV-2 nucleocapsid protein or solely the S RDB, may be valuable alternatives for refined, next-generation mRNA vaccines. Finally, as we essentially do not know for how long and at what concentration the LNPs and the antigen(s) remain in human tissues or the circulation of poor vaccine responders, the elderly, or children (see Outstanding questions), and given the fact that cellular immunity likely persists despite reduced *in vitro* neutralizing titers [28], boosting doses should be delivered only where the benefit–risk profile is clearly established.

Does boosting, apart from raising antibody titers, also promote antibody diversification?

What would be the profile of immune responses and AEs following mRNA-guided expression of the S protein in its closed form (a form not prone to ACE2 binding)?

Overall, parallel to the ongoing research on the most challenging topics of SARS-CoV-2 biology, evolving dynamics and adaptation capacity to human species (i.e., transmission–infection rate and disease severity), the basic and clinical research (see Outstanding questions) aiming to understand the molecular–cellular basis of the rare AEs of the existing first-generation mRNA vaccines should be accelerated as an urgent and vital public health priority.

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Author contributions

I.P.T.: conceptualization, writing, and preparation of the figures. E.T., D.P., H.A., M.P., A.S., E.A., E.K. and M.A.D.: review, comments, and further additions. All authors contributed to discussions of the scope of this opinion article and approved the final revised version of the manuscript.

Declarations of interests

The authors declare no competing interests related to this opinion article.

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Review

'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA

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Abstract: The COVID-19 pandemic caused much illness, many deaths, and profound disruption to society. The production of 'safe and effective' vaccines was a key public health target. Sadly, unprecedented high rates of adverse events have overshadowed the benefits. This two-part narrative review presents evidence for the widespread harms of novel product COVID-19 mRNA and adenovectorDNA vaccines and is novel in attempting to provide a thorough overview of harms arising from the new technology in vaccines that relied on human cells producing a foreign antigen that has evidence of pathogenicity. This first paper explores peer-reviewed data counter to the 'safe and effective' narrative attached to these new technologies. Spike protein pathogenicity, termed 'spikeopathy', whether from the SARS-CoV-2 virus or produced by vaccine gene codes, akin to a 'synthetic virus', is increasingly understood in terms of molecular biology and pathophysiology. Pharmacokinetic transfection through body tissues distant from the injection site by lipid-nanoparticles or viral-vector carriers means that 'spikeopathy' can affect many organs. The inflammatory properties of the nanoparticles used to ferry mRNA; N1-methylpseudouridine employed to prolong synthetic mRNA function; the widespread biodistribution of the mRNA and DNA codes and translated spike proteins, and autoimmunity via human production of foreign proteins, contribute to harmful effects. This paper reviews autoimmune, cardiovascular, neurological, potential oncological effects, and autopsy evidence for spikeopathy. With many gene-based therapeutic technologies planned, a re-evaluation is necessary and timely.

Keywords: spike protein; pathology; transfection; biodistribution; lipid-nanoparticles; autopsy; inflammation; pharmacovigilance; COVID-19; mRNA vaccines

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1. Introduction

In this narrative review, we examine the solid evidence for a counter-narrative to the 'safe and effective' message that has accompanied the novel product COVID-19 vaccines, which were developed at 'warp speed' with great hope to end the pandemic. This evidence has accumulated and dampened the original optimism. The implications for the recognition of vaccine-related diagnoses and the need for therapeutics are significant for all health practitioners and many research scientists to consider.

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Key problem areas appear to be (1) the toxicity of the spike protein—both from the virus and also when produced by gene codes in the novel COVID-19 mRNA and adenovectorDNA vaccines [1,2], hence the novel term 'spikeopathy'; (2) inflammatory properties of certain lipid-nanoparticles used to ferry mRNA [3]; (3) N1-methylpseudouridine in the synthetic mRNA that causes long-lasting action [4]; (4) widespread biodistribution of the mRNA [5] and DNA [6,7] codes via the lipid-nanoparticle and the viral-vector carrier matrices, respectively and (5) the problem of human cells producing a foreign protein in our ribosomes that can engender autoimmunity [8,9].

The emergence of SARS-CoV-2 in late 2019, and the associated disease of COVID-19, declared by March 2020 as a global pandemic by the WHO, has caused much illness, and many deaths in the elderly and the at-risk, and seriously disrupted society. An umbrella literature review of publications between December 2019 and August 2021 revealed that the greatest risk of mortality due to COVID-19 was associated with cardiovascular disease, cerebrovascular disease, and chronic renal disease [10]. The production of safe and effective vaccines to halt the COVID-19 pandemic was one of the most important public health interventions. Many COVID-19 vaccines have been developed across the world. In non-Western nations, most vaccines have used traditional protein-based or inactivated virus technologies. The mRNA and adenovectorDNA vaccines have been produced by large pharmaceutical companies and favoured by regulators in most Western nations. It has been widely claimed that these vaccines have saved millions of lives. Sincere hopes have been held for this narrative. But this belief is largely founded on early Infection Fatality Rate (IFR) modelling estimates and Pfizer, Moderna, AstraZeneca and Janssen claims of efficacy, which have been undermined by new data.

Controversy has surrounded the use of the gene-based vaccines and this article explores the reason for this. To meet the widespread desire for 'safe and effective' vaccines, gene-based technology offers rapid speed of production. Hope has perhaps influenced much of the published literature as well as media narrative. A central issue has been growing evidence of pathogenic effects of the SARS-CoV-2 spike protein—whether as part of the virus or produced by genetic codes in the mRNA and adenovectorDNA vaccines.

The aim of this narrative review is to present a comprehensive account of the pathogenicity of the antigen, the biodistribution of the gene codes for the antigen throughout the body, their modified long-lasting nature particularly with the mRNA vaccines, and literature and data that show the adverse events that would be expected from such biodistribution and cellular production of a foreign antigen. The review presents a case of premature translation of experimental gene therapy technology to mass public vaccination and ethical and regulatory issues that need scrutiny and reform before the next pandemic.

Central to individual informed consent decisions and public health policy is the weighing of the risks of an illness versus the risks and potential benefits of an intervention. Given the risks of novel gene-based COVID-19 vaccines, were they worth it in light of the severity of SARS-CoV-2 infection? We address the risks of COVID-19 first.

2. COVID-19 Modelling Versus Real-World Data

It is apparent that the original Wuhan strain and early variants of SARS-CoV-2 in 2020 were more pathogenic than later variants. This is consistent with typical viral adaptive evolution to more infectious but less pathogenic strains, a natural phenomenon that is fortunate for humanity. The claim that the COVID-19 vaccines have saved many millions of lives is predicated on modelling based on case fatality rates (CFR) in China in February 2020 published by Verity et al. in *The Lancet* [11]. The authors estimated a CFR of 6.4% (5.7–7.2) in those aged over 60 years and "up to 13.4% (11.2–15.9) in those aged 80 years or older... with an overall infection fatality ratio for China of 0.66% (0.39–1.33)" (abstract). Fortunately, the virus mutated, and these modelling predictions did not materialise as the pandemic unfolded over the next three years.

The COVID-19 vaccines have saved lives from COVID-19, but it is not clear how many. The claim of millions of lives saved by COVID-19 gene-based vaccines was partly based

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on assumptions that the COVID-19 vaccines protected against infection and transmission, which was not the case because systemic immunity to respiratory viruses is not as effective as mucosal immunity from infection, and because of the continually evolving variants perhaps partly driven by adaptive evasion of vaccine-induced antibodies. Pfizer admitted that its phase 3 clinical trial [12] did not test for viral transmission [13].

However, presumptions of efficacy have been sustained by COVID-19 modellers, and reiterated by health authorities, medical publications, and the media. This is exhibited by Watson et al., (2022) in "Global impact of the first year of COVID-19 vaccination: a mathematical modelling study", published in *The Lancet Infectious Diseases* [14]. The authors estimate around 14.4 million lives saved related to vaccination benefits that include protection against infection and transmission, both now recognised to be unfounded. This suppositional estimate by Watson et al. persists as an accepted fact, whereas real-world infection fatality rate (IFR) data speak against the need for vaccination in the non-elderly.

Briefly, Roussel et al. in early 2020 presented a statistically significant analysis that likened the case fatality rate for SARS-CoV-2 to earlier coronaviruses and influenza-like illnesses: In OECD countries, the mortality rate for SARS-CoV-2 (1.3%) was not significantly different from that for common coronaviruses identified in public hospitals of Marseille, France (0.8%; $p = 0.11$) [15]. If modelling had been based on these data a few months after the initial Chinese data, different projections would have been made, more in line with eventual mortality statistics including in 2020 prior to any vaccine availability.

Ioannidis et al. in 2022 in a paper titled "Forecasting for COVID-19 has failed" critiqued the models that ignored the low IFRs to emerge in the first half of 2020 [16]. Ioannidis et al. noted:

> *"Failure in epidemic forecasting is an old problem. In fact, it is surprising that epidemic forecasting has retained much credibility among decision-makers, given its dubious track record. Modelling for swine flu predicted 3100–65,000 deaths in the UK (https://www.theguardian.com/uk/2009/jul/16/swine-flu-cases-rise-britain. (Accessed on 2 June 2020). Eventually, 457 deaths occurred (UK government, 2009)".* [16] (p. 425)

Ioannidis et al. then examined many US COVID-19 prediction models for deaths, hospitalisations, and ICU admissions, highlighting the extremely wide margins by which they failed to hit their targets. Ioannidis et al. continued:

> *"Despite these obvious failures, [COVID-19] epidemic forecasting continued to thrive, perhaps because vastly erroneous predictions typically lacked serious consequences... Upon acquiring solid evidence about the epidemiological features of new outbreaks, implausible, exaggerated forecasts (Ioannidis, 2020d) should be abandoned. Otherwise, they may cause more harm than the virus itself".* [16] (p. 428)

Societal narratives, once entrenched, become difficult to shift.

Accurate estimates of lives saved or lost as a result of the COVID-19 gene-based vaccines would have required long-term studies in vaccinated compared to unvaccinated individuals. Pfizer, Moderna, AstraZeneca and Janssen eventually vaccinated almost all placebo subjects and thus lost their control group. This was based on ethical principles given the fear of COVID-19 [17], but the loss to scientific integrity of only having short-term placebo-controlled trials was noted by the WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Evaluation (2020) [18].

To make up this deficit, one private organisation based in the UK, Control Group Cooperative [19], has collected data since the COVID-19 vaccination rollout, and is the only world-wide control group. Of this unvaccinated cohort 18,497 participated in a survey reporting COVID-19 positive testing and symptom severity between September 2021 and February 2022. A quarter (4636, 25.1%) reported experiencing symptomatic COVID-19 illness. Symptoms were reported as "mild" by 14.4%, "moderate" by 8.7% and "severe" by 2%. A further 560 reported asymptomatic illness and of the 5196 with COVID-19, only 74 (1.4%) reported attending hospital (as in- or out-patients) with 21 (0.4%) being hospitalised for longer than 1 week. As a self-reported survey, the limitations included deaths that may

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not have been reported; nonetheless, the cohort fared better than expected. The group was perhaps unusual in that 71% partook of some combination of vitamins C, D, quercetin, zinc and off-label ivermectin or hydroxychloroquine where available [20].

In this context, the Australian State Government (NSW) health data from November and December 2022 [21] (Figures 1 and 2) demonstrate that the unvaccinated are almost not represented in the hospitalisation data while the most vaccinated are over-represented. The proportion of unvaccinated in NSW was low at 3.2%; however, the proportion of unvaccinated with severe COVID-19 is lower than this in late 2022 at 2.9%. Even accounting for more COVID-19 vaccine boosters in the elderly and vulnerable, the data do not suggest significant efficacy against hospitalisation, ICU admission and death, at least after the emergence of the Omicron strain.

For weeks 51 and 52 of 2022, the NSW government data document nil hospitalisations and six deaths for unvaccinated persons, but 1415 hospitalisations and 82 deaths in known vaccinated persons. NSW Health no longer publishes vaccination status. These data do not support the premise that the vaccinations have 'saved millions of lives', but instead indicate correlations between more doses with severe COVID-19 illness warrants investigation. There has been an increase in all-cause mortality contemporaneous with the rollout of the COVID-19 gene-based vaccines and this warrants further research.

Mathematical models produce highly uncertain numbers that predict the future. These predictions can become politicised. To make sure predictions do not become adjuncts to a political cause, modellers, decision-makers and citizens need to establish the real-world facts that hold us all accountable.

If the COVID-19 vaccines are less efficacious than was originally hoped for and subsequently claimed, then the risk/benefit decision-making for individual informed consent and public health policy shifts. The degree of harm caused by the novel gene-based vaccine technology might then outweigh any benefits.

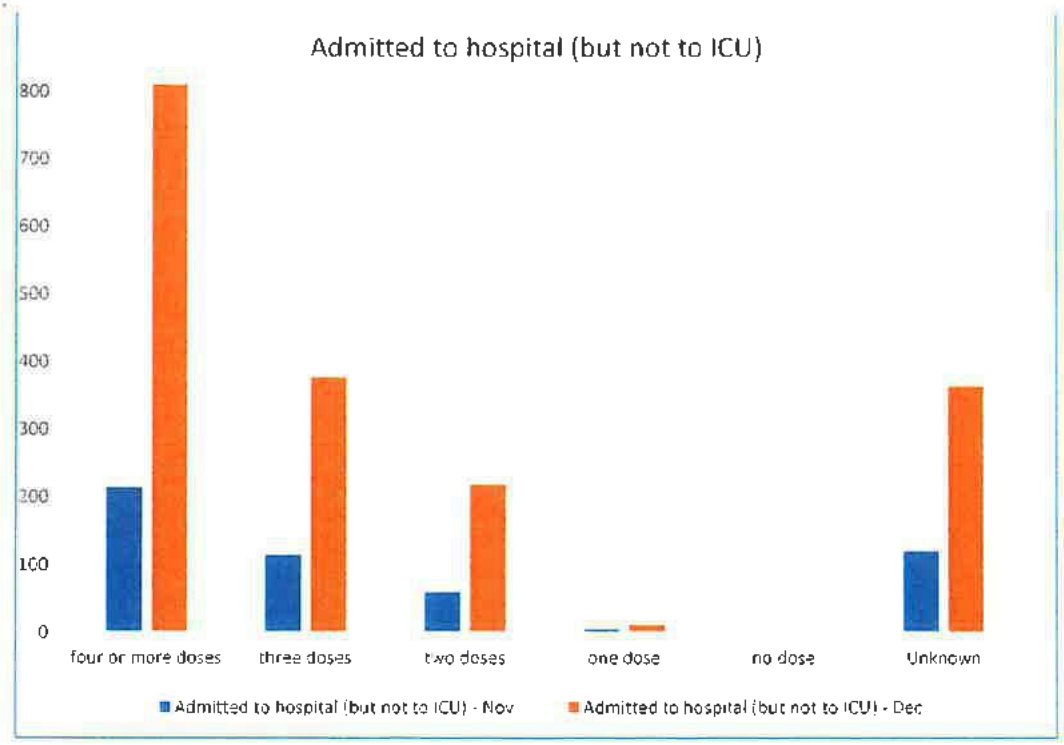

Figure 1. *Cont.*

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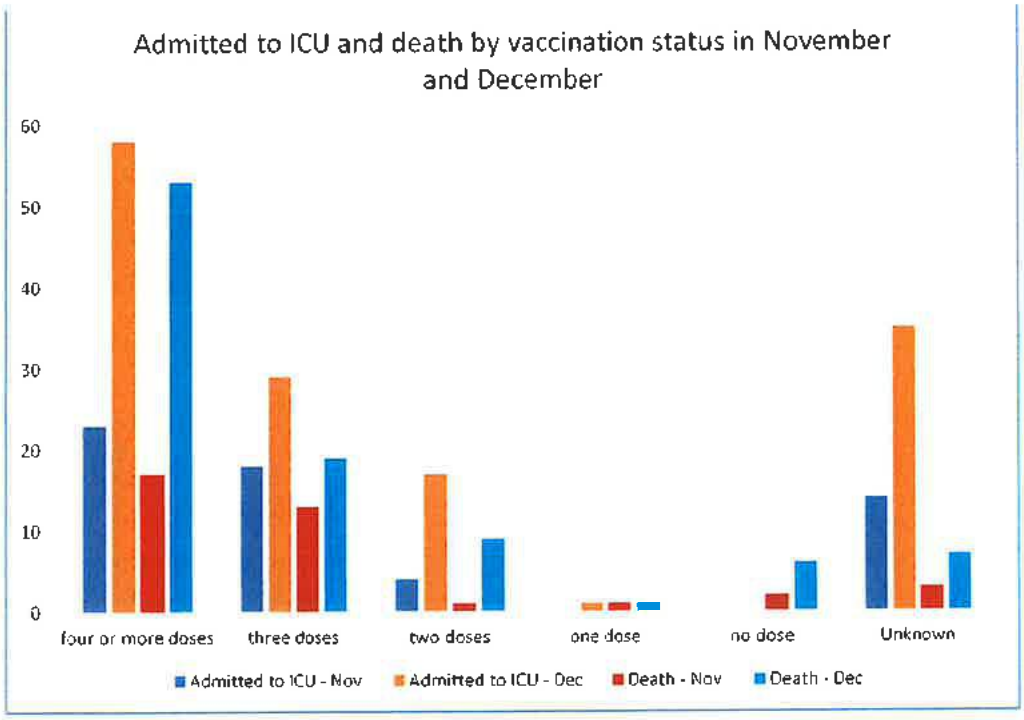

Figure 1. NSW Australia hospitalisations, ICU admissions and deaths last 6 weeks 2022 by vaccination status. NSW Health. Bar charts derived from the numbers in official government report excerpt of posted as Figure 2 [21].

NSW COVID-19 WEEKLY DATA OVERVIEW
www.health.nsw.gov.au/coronavirus
Epidemiological weeks 51 and 52, ending 31 December 2022

Table 1. People with a COVID-19 diagnosis in the previous 14 days who were admitted to hospital, admitted to ICU or reported as having died in the two weeks ending 31 December 2022

	Admitted to hospital (but not to ICU)	Admitted to ICU	Deaths
Gender			
Female	842	63	42
Indeterminate	1	0	0
Male	936	77	53
Age group (years)			
0-9	85	3	0
10-19	24	3	0
20-29	67	8	1
30-39	79	7	0
40-49	64	6	0
50-59	105	17	3
60-69	199	27	8
70-79	436	42	19
80-89	507	24	31
90+	213	3	33

Figure 2. *Cont.*

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Vaccination status*			
Four or more doses	810	58	53
Three doses	377	29	19
Two doses	218	17	9
One dose	10	1	1
No dose	0	0	6
Unknown	364	35	7
Total	1779	140	95

Excludes cases in correctional settings
*Vaccination status is determined by matching to Australian Immunisation Register (AIR) data. Name and date of birth need to be an exact match to that recorded in AIR for vaccination status to be determined. People with unknown vaccination status were those unable to be found in AIR. This may occur when names in AIR are different, for example shortened name or different spelling, to those used for the COVID-19 notification.

Figure 2. NSW Australia COVID-19 hospitalisations, ICU admissions, deaths, last 2 weeks 2022. NSW Health. From Table 1 of NSW Covid weekly data overview last 2 weeks 2022. Note that regional councils analysis of same data removed for space reasons. Used under Creative Commons Attribution 4.0 license. © State of New South Wales. For current information go to www.nsw.gov.au. [21].

3. Correspondence between TGA and Australian Senator Rennick

In Australia, the Therapeutic Goods Administration (TGA) provisionally approved the COVID-19 vaccines of Pfizer (Comirnaty, BNT162b2), Moderna (SPIKEVAX, mRNA-1273), AstraZeneca (Vaxzevria, ChAdOx1 nCOV-19) and Janssen (COVID-19 Vaccine, Ad26.COV2.S) in early 2021 [22] and in January 2022 added the protein-based lipid-nanoparticle embedded vaccine of Novavax (Nuvaxovid, NVX-CoV2373) [23].

On 16 December 2022, the Australian Department of Health advised by the TGA responded to Question 235 from 21 November 2022 by Senator Gerard Rennick (Liberal Party, Qld) in the Senate Community Affairs Committee Question on Notice SQ22-000609. Senator Rennick, whose parliamentary office has received numerous accounts of COVID-19 vaccine injuries from Australians, had asked whether the TGA's own report [5] that showed widely biodistributed high transfection and expression rates of the gene-based COVID-19 mRNA vaccines, was proof the vaccines were more pathogenic than the virus, implying more spike protein load on human cells [24].

The TGA replied:

> *"There is some confusion around the biochemistry and immunology here. Higher translation and expression rate is not associated with pathogenicity, rather it indicates better antigen (spike protein) expression. The expressed spike protein is not a pathogen and is not infectious. The spike protein is only one component of the coronavirus. It serves as an antigen to induce humoral and cellular immune responses against SARS-CoV-2 virus".* [24]

As Australian authors of this paper, we concur with the opinion of the TGA that the spike protein produced by the gene-based COVID-19 vaccines does act as an antigen to induce immune responses and is not a whole microorganism pathogen. However, the response by the TGA has missed the point of the question. We will summarise the evidence that the spike protein itself is independently bioactive and pathogenic. The spike protein has been directly related to both the pathophysiology that underlies COVID-19 viral illness and the serious adverse events from the COVID-19 vaccines that, via gene therapy mechanisms, induce human cells to produce the spike protein in substantial numbers.

In fact, the spike protein in the original SARS coronavirus 1 (SARS CoV-1) epidemic in 2003 was identified as a cause of lung injury for which the term 'severe acute respiratory syndrome' (SARS) was coined. It was thought to do this via action on angiotensin-converting enzyme 2 (ACE-2) receptors. SARS-CoV-1 (2003 virus) spike protein-driven downregulation of ACE-2 receptors led to lung oedema and acute pulmonary failure in mice as published in *Nature Medicine* [25].

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4. Narrative Review Methodology

We present here a narrative review of the literature that provides evidence for the toxicity and thus pathogenicity of the spike protein, independent of its role as a pathogenic determinant in SARS-CoV-2 infection. This is whether from the SARS-CoV-2 virus or produced by genetic code in human cells directly by mRNA (Pfizer and Moderna) or by mRNA derived from the adenovectorDNA (AstraZeneca and Janssen) COVID-19 vaccines.

We also review literature evidence for the toxicity and biodistribution profile of concern for the lipid-nanoparticle matrices for mRNA Moderna and Pfizer and protein-based Novavax COVID-19 vaccines; the modified nature of the synthetic mRNA which would explain prolonged mRNA persistence and spike protein production; the phenomenon of 'bad batch' variation in adverse event reports and relevant age-stratified risk/benefit considerations for COVID-19 vaccinations especially for paediatric and younger adult age cohorts.

These pharmacokinetic and pharmacodynamic aspects relate to the pathogenicity of the gene-based COVID-19 vaccines. In the context of the TGA's reply above, the pharmacokinetic biodistribution aspects of the gene-based COVID-19 vaccines are akin to an 'infectious' agent, in an invasive or blood-borne phase, as they distribute the pathogenic effects of the spike protein throughout the body.

This review presents evidence from the academic literature, as well as pharmacovigilance, and Pfizer clinical trial documents, via Freedom of Information (FOI) orders, to assist the TGA and other regulators and health authorities in reappraising the toxicity of the mRNA and adenovectorDNA produced spike proteins. A new era of pathology is emerging that could be termed "Spikeopathy". It is also vital to evaluate the potential for any new autoimmune phenomena driven by foreign antigen production caused by any new mRNA or DNA-based technology in the future.

Evidence for harm caused by 'spikeopathy', as well as other forms of pathophysiological damage, are reviewed by organ system, while a review of pharmacovigilance data will be the subject of a further paper.

The Key Points below summarise the information presented.

Key Points

- Highly safe and effective vaccines are central to combat infectious disease epidemics/pandemics.
- SARS-CoV-2 spike protein is pathogenic, whether from the virus or created from genetic code in mRNA and adenovectorDNA vaccines.
- Biodistribution rodent study data show lipid nanoparticles carry mRNA to all organs and cross blood-brain and blood-placenta barriers. Some of these tissues are likely to be impervious to viral infection; therefore, the biohazard is particularly from vaccination.
- Lipid-nanoparticles have inflammatory properties.
- The modification of mRNA with N1-methylpseudouridine for increased stability leads to the production of spike proteins for months. It is uncertain how many cells and from which organs mRNA spike proteins are produced, and therefore, the exact effective dose delivered per vaccine vial is unknown.
- The long-term fate of mRNA within cells is currently unknown.
- The mRNA and adenovectorDNA vaccines act as 'synthetic viruses'.
- In the young and healthy, and even in many older individuals with vulnerable co-morbidities, the encoding-based COVID-19 vaccines will likely transfect a far more diverse set of tissues than infection by the virus itself.
- Evidence suggests reverse transcription of mRNA into a DNA copy is possible. This further suggests the possibility of intergenerational transmission if germline cells incorporate the DNA copy into the host genome.
- Production of foreign proteins such as spike protein on cell surfaces can induce autoimmune responses and tissue damage. This has profoundly negative implications for any future mRNA-based drug or vaccine.

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- The spike protein exerts its pathophysiological effects ('spikeopathy') via several mechanisms that lead to inflammation, thrombogenesis, and endotheliitis-related tissue damage and prion-related dysregulation.
- Interaction of the vaccine-encoded spike protein with ACE-2, P53 and BRCA1 suggests a wide range of possible biological interference with oncological potential.
- Adverse event data from official pharmacovigilance databases, an FDA-Pfizer report obtained via FOI, show high rates and multiple organ systems affected: primarily neurological, cardiovascular, and reproductive.
- Pfizer and Moderna mRNA COVID-19 vaccines' clinical trial data independently interpreted has been peer-review and published to show an unfavourable risk/benefit, especially in the non-elderly. The risks for children clearly outweigh the benefits.
- Repeated COVID-19 vaccine booster doses appear to induce tolerance and may contribute to recurrent COVID-19 infection and 'long COVID'.
- The SARS-CoV-2 pandemic has revealed deficiencies in public health and medicines regulatory agencies.
- A root cause analysis is needed for what now appears a rushed response to an alarming infectious disease pandemic.
- Treatment modalities for 'spikeopathy'-related pathology in many organ systems, require urgent research and provision to millions of sufferers of long-term COVID-19 vaccine injuries.

5. Structure of SARS-CoV-2 Spike Protein

Cryo-EM electron microscopy revealed the structure of the spike protein at the outset of the pandemic [26]. The SARS-CoV-2 spike proteins protrude outwards from the cell wall of the virus and are in red in the schematic diagram in Figure 3 from Cuffari [27].

In the context of SARS-CoV-2 infection, the spike protein is a pathogenic determinant of cell invasion, consisting of two subunits: S1 at the distal end of the spike glycoprotein pointing outwards from the virus constructed of an N-terminal domain (NTD) and a trimer of three receptor binding domains (RBD), and S2 consisting primarily of a C-terminal region that forms the stalk of the spike protein and embeds proximally to the virus' envelope or membrane.

The virus uses the spike protein to bind with ACE-2 receptors on cell surfaces to enter the cells. For this to happen, the receptor binding domain (RBD) on the S1 subunit undergoes hinge-like extension from the 'down' to 'up' position to interact with the ACE-2 receptor.

Figure 4, from Wrapp et al. [26], shows one of the three 'trimer' RBDs in green in the 'up' position while the other two RBDs are 'down' and inaccessible to the attachment to ACE-2. The diagram on the left is the view of the spike protein in profile and on the right is a view of the S1 subunit or top of the trimeric spike protein from above.

5.1. *Does the Vaccine Produced Spike Protein Have Protective Closed RBDs?*

The SARS-CoV-2 virion carries spike protein in the form of trimers, predominantly in prefusion form. Prefusion spike protein trimers on each virus are found in various conformations, either closed with all three RBDs lying down at the top of the spike—or open, in which one or more of the RBDs protrude from the top of the spike. The receptor binding site (RBS) is largely inaccessible when the RBDs are in the down position. Spike protein contains a furin cleavage site, where it can be split into S1 and S2 subunits which facilitates infectivity. Serine protease is necessary to split the spike protein into S1 and S2 subunits which greatly increases infectivity via the ACE-2 receptor.

After interaction with the receptor, the spike protein undergoes a conformational rearrangement leading to exposure of the S2 subunit, insertion of the fusion peptide into the membrane of the target cell, and refolding of S2. This refolding pulls the fusion peptide and transmembrane domain of the spike protein together, drawing the target cell and viral membranes together and causing their fusion. As an analogy, imagine a bottle opener

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pulling the cork up from the bottle neck—but the cork is connected to a cell membrane that gets pulled up along with it [28].

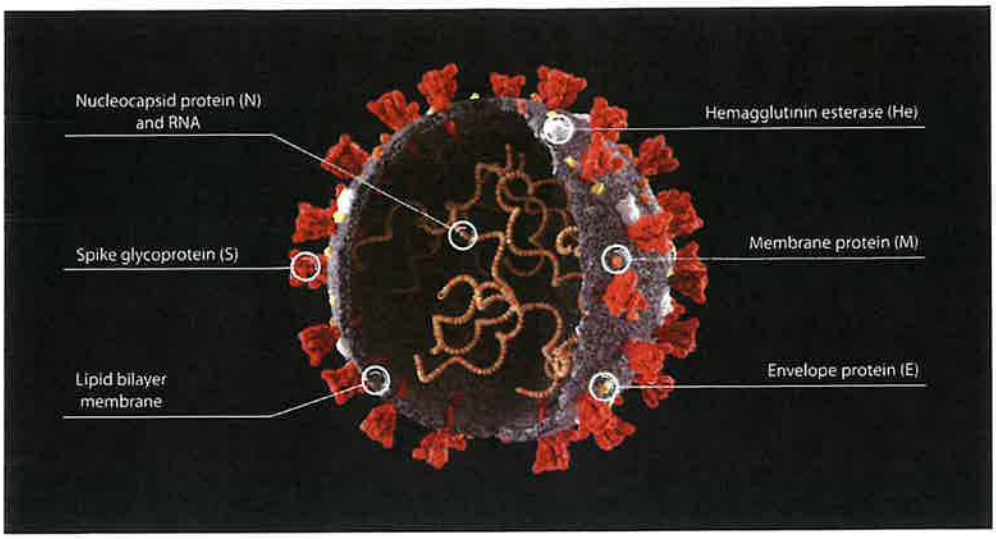

Figure 3. Diagram of various proteins of SARS-CoV-2 virus. Reprinted from *News-Medical.net* (accessed on 26 April 2023) Cuffari (2021): What are spike proteins? (*with permission, license from Shuttercock*). [27].

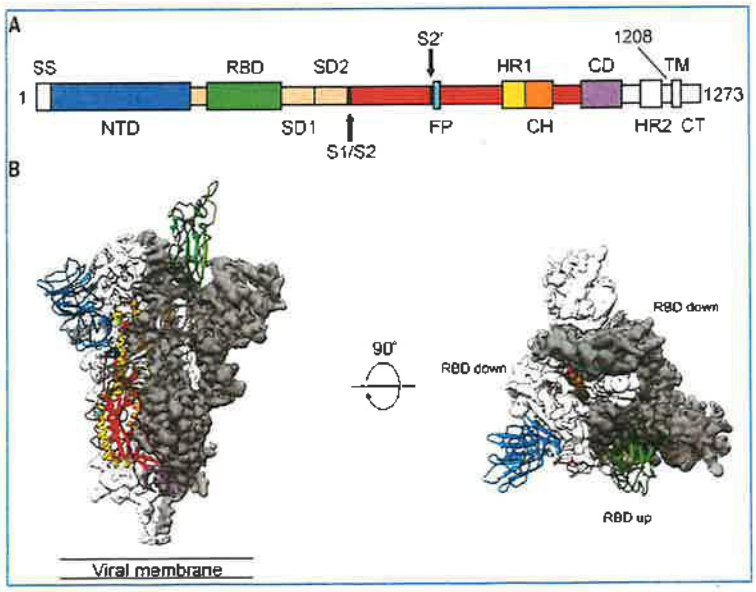

Figure 4. Structure of 2019-nCoV S in the prefusion conformation. (**A**) Schematic of 2019-nCoV S primary structure coloured by domain. Domains that were excluded from the ectodomain expression construct or could not be visualised in the final map are coloured white. SS, signal sequence; S2′, S2′ protease cleavage site; FP, fusion peptide; HR1, heptad repeat 1; CH, central helix; CD, connector domain; HR2, heptad repeat 2; TM, transmembrane domain; CT, cytoplasmic tail. Arrows denote protease cleavage sites. (**B**) Side and top views of the prefusion structure of the 2019-nCoV S protein with a single RBD in the up conformation. The two RBD down protomers are shown as cryo-EM density in either white or gray and the RBD up protomer is shown in ribbons coloured corresponding to the schematic in (**A**). Reprinted from [26] Figure 1, Copyright (2022) *with permission*.

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The commercially available vaccines in Australia rely on engineered mutations in the spike protein designed to stabilise the prefusion state and reduce the transition into the post-fusion form and therefore limit cleavage. Mutations include the replacement of two residues with a double proline (e.g., Pfizer/BioNTech, Moderna, Novavax, and Janssen), or mutations in the furin cleavage site for protease resistance (Janssen).

Given amassed data that suggest mRNA and adenovectorDNA-created spike proteins cause harm, these theoretical safeguards appear to have failed.

There are several possible reasons for the failure of this system. Since only the mRNA, not the full-length spike protein, gets injected with the lipid-nanoparticles, there is the possibility that the mRNA fragments are not full-length, due to suboptimal synthesis or degradation after manufacture. Spike protein could then be partially expressed as truncated spike protein with a conformation that allows cleavage into a peptide part and a functional S1 or S2 subunit.

Even with full protein code expression, some cleavage can still happen inside cells. No biological system is 100% effective, and the mutation is only supposed to reduce, not completely prevent cleavage into S1 and S2. The transport of spike proteins or subunits via exosomes, direct cell fusion and nanotube tunnels to other cells is still possible. Expression errors inside the cell could lead to spike proteins retaining certain functions. Contamination with replication-capable plasmid vectors leaves the option of mutation during replication or insertion into the genome.

The spike protein is not only toxic through binding of ACE-2 receptors, but it also has cytotoxic effects inside cells through interaction with cancer suppressor genes BRCA and P53 and mitochondrial damage, coagulopathies through direct contact with cellular proteins, and is neurotoxic through accumulation, with spread and reconfiguration of prion proteins into their pathologic form. The accumulation of spike protein inside cells could have toxic and apoptotic effects [29].

5.2. Toxin-Like Domain in the RBD

Another mechanism for pathogenicity has recently been demonstrated. The spike protein has been shown to also contain a 'toxin- like' domain in the RBD on S1, with sequence homology to Rabies Virus (RBC) and HIV glycoproteins, and neurotoxin NL-1, all of which bind to the α7 Nicotinic Acid Acetylcholine Receptors (α7 nAChR) of the cholinergic system [30]. Neurotoxin NL-1 is a neurotoxin, a type of snake venom, and similar to the archetypal bungarotoxin, a known inhibitor of the α7 nAChR, with high binding affinity. Snake venom three-finger neurotoxins (α-3FNTx) act on postsynaptic nicotinic acetylcholine receptors (nAChRs) at the neuromuscular junction (NMJ) to produce skeletal muscle paralysis and at specific nACHR at other sites [31], resulting in disturbances in the control of inflammation [32].

This spike toxin-like binding domain is a part of the RBD, adjacent to the ACE receptor binding site and has been demonstrated both in a computer-simulated study [32] and in electrophysiological studies, to bind preferentially to the α7 nAChR in nanomolar doses, similar to neurotoxins, such as bungarotoxin. The active peptide SCoV2P potentiates and inhibits acetylcholine (ACh)-induced α7 nAChR responses by a potential allosteric mechanism in nanomolar potencies and nicotine enhances these effects. At low doses, it potentiates and at higher doses, it inhibits nAChR function [33].

This binding model could provide logical explanations for the acute inflammatory disorder and other conditions in patients with COVID-19, long COVID, and vaccination injury, which may be linked to severe dysregulation of the central nervous system.

6. Reasons for Concern: Pharmacodynamic, Pharmacokinetic, and Pathophysiological

Pharmacokinetic and pharmacodynamic data give cause for concern about the conceptual design of the mRNA and adenovectorDNA COVID-19 vaccines and lay the groundwork for understanding the pathophysiology that is now being widely reported. There

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is uncontrolled biodistribution as well as durability and persistent bioavailability of the spike protein.

6.1. Gene-Based Vaccines Are Novel Experimental Technology

The unprecedented number of adverse events appears to be associated with the spike proteins produced by the gene-based technologies employed by Pfizer, Moderna, AstraZeneca, and Johnson and Johnson. Viral-vectorDNA technology is also employed in the Sputnik V and EpiVacCorona COVID-19 vaccines in Russia, iNCOVACC in India, and Convidecia in China. But the majority of COVID-19 vaccines, mostly made in non-Western countries, are traditional protein-based or inactivated virus non-genetic vaccines [34,35].

The gene-based COVID-19 vaccines fall into a special class of therapeutic agents defined by the FDA as "gene therapy products" [36], such that recipient cells produce antigens for transmembrane expression, or to leave the cell, to secondarily invoke an immune response. By design, therefore, by employing virus-like invasion and hijack of cellular transcription, both mRNA and adenovectorDNA gene-based vaccines cause non-immune cells to become de facto antigen-presenting cells, in their mode of immunogenicity. Therefore, these novel vaccine platforms risk tissue damage secondary to cytopathic autoimmune responses, raised against cells expressing foreign spike antigens.

Before the SARS-CoV-2 pandemic, the use of such technology was experimental and mostly restricted to making proteins for the therapy of metastatic cancer. No mRNA vaccines had ever been authorised for public usage prior to the COVID-19 pandemic [37] and viral-vectorDNA vaccines only had limited use for Ebola, Dengue, and Japanese encephalitis [38].

Documents obtained under a Freedom of Information (FOI) request reveal the mRNA COVID-19 vaccines were developed via the Trump Administration's "Operation Warp Speed" program under the auspices of the US Department of Defense. The gene technology vaccines were emergency "countermeasures" to a national security threat, which arguably the pandemic at first appeared to be in 2020. As such, many of the FDA's normal, protracted, and time-consuming safety testing and toxicology protocols were bypassed, in the rush to Emergency Use Authorisation status [39–41].

6.2. Wide Distribution of Lipid-Nanoparticle

Turni and Lefringhausen [42], in "COVID-19 vaccines—An Australian Review", note that the lipid-nanoparticle, the carrier for synthetic mRNA, is potentially inflammatory in its own right, crosses membranes and distributes widely in the body. It crosses both the blood-brain barrier and the blood-placenta barrier. They cite the EMA report on the Moderna vaccine "that mRNA could be detected in the brain following intramuscular administration at about 2% of the level found in plasma" (p. 491). They also cite research [43–45] that describes how and why lipid-nanoparticles easily traverse the blood-brain barrier.

A/Prof Byram Bridle, Canadian virologist-vaccinologist, obtained Pfizer rodent study biodistribution data from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) via a FOI request in 2021 [46]. Judicial Watch, a US independent watchdog foundation, obtained the same Pfizer study report via FOI lawsuit to the US Department of Health and Human Services after the FDA and CDC refused to comply [47]. A more recent FOI request to the Australian TGA (FOI reply 2389-6), reveals on page 45 of the TGA's "nonclinical evaluation report: BNT162b2 COVID-19 vaccine" that the same study was part of the TGA's evaluation in January 2021 prior to its provisional authorisation [5] (p. 45).

The Pfizer biodistribution study involved 63 Wistar Han rats of whom 42 (21 male, 21 female) were injected with the human equivalent of 50 µg mRNA per animal, and an additional 21 male rats were injected with the equivalent of a Moderna COVID-19 vaccine dose of 100 µg mRNA per animal. The mRNA coding for Luciferase was encapsulated in liquid nanoparticles containing radiolabelled cholesterol, injected into the gluteal muscle and monitored for 48 h. As indicated in Figure 5, the biodistribution data showed the

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lipid-nanoparticles, which were designed to pass easily through biological tissues and membranes, travel to all organs. By 48 h, 75% had left the injection site for elsewhere [5,47].

Table 4-2. Mean concentration of radioactivity (sexes combined) in tissue and blood following a single IM dose of 50 µg mRNA/rat

Sample	Total Lipid Concentration (µg lipid equiv/g (or mL))						
	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181
Adrenal glands	0.27	1.48	2.72	2.89	6.80	13.77	18.21
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687
Bone marrow (femur)	0.48	0.96	1.24	1.24	1.84	2.49	3.77
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112
Heart	0.28	1.03	1.40	0.99	0.79	0.45	0.55
Injection site	128.3	393.8	311.2	338.0	212.8	194.9	164.9
Kidneys	0.39	1.16	2.05	0.92	0.59	0.43	0.42
Large intestine	0.013	0.048	0.09	0.29	0.65	1.10	1.34
Liver	0.74	4.62	10.97	16.55	26.54	19.24	24.29
Lung	0.49	1.21	1.83	1.50	1.15	1.04	1.09
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.366
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.26
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253
Small intestine	0.030	0.221	0.476	0.879	1.279	1.302	1.472
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112
Spleen	0.33	2.47	7.73	10.30	22.09	20.08	23.35
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.000
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456
Whole blood	1.97	4.37	5.40	3.05	1.31	0.91	0.42
Plasma	3.96	8.13	8.90	6.50	2.36	1.78	0.81
Blood:plasma ratio	0.815	0.515	0.550	0.510	0.555	0.530	0.540

5

Although the highest levels went to the spleen and liver, where high cell turnover helps timely repair of any cytotoxic damage, the lipid-nanoparticle, and by implication the mRNA, went to seemingly all organs, particularly the ovaries and adrenal glands but also the brain, eyes, heart, testes, uterus, pituitary gland, spinal cord, thymus, bone marrow.

The Pfizer rat biodistribution study has been corroborated. Chinese researchers injected mice with lipid-nanoparticle-mRNA complexes (mRNA-LNPs) encoding the firefly luciferase gene and biodistribution from the injection site "became rapidly distributed throughout the body with a large presence in the liver" and the "non-linear relationship between the LNP exposure and the protein expression level varies in different tissues and organs" [48] (p. 114). Smaller mRNA-LNP complexes transfected further and relatively smaller amounts of mRNA in the liver and lymph nodes produced higher rates of encoded bioluminescent protein than at the injection site muscle. The authors stated:

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> *"The duration and kinetics of transgene expression are affected by the pharmacokinetics and biodistribution of the delivery systems. The pharmacokinetic-pharmacodynamic relationship of mRNA-LNPs is highly complex, making the prediction of gene expression and efficacy (pharmacodynamics) unlikely just based on LNP exposures in tissue (pharmacokinetics)".* [46] (pp. 112–113)

Effectively the lipid-nanoparticle, and presumably its mRNA payload, distributes throughout the whole body and gene expression varies unpredictably [5,46,48].

6.3. *Long-lasting Pseudouridine mRNA*

Natural messenger RNA is highly unstable, so the synthetic mRNA that codes for spike protein in Moderna and Pfizer COVID-19 vaccines has been stabilised by replacement of uridine with N1-methylpseudouridine [37]. This intervention is now known to make the synthetic mRNA excessively stable over a prolonged period [49]. Fertig et al. [50] found the lipid-nanoparticle and contained mRNA were still circulating in blood plasma 15 days post-vaccination. Recent research found the mRNA in blood plasma at 28 days post-vaccination [51]. Also, the S1 subunit was found recirculating in picomolar amounts along with full spike protein in a Brigham and Women's Hospital study of 13 nurses vaccinated with the Moderna COVID-19 mRNA vaccine to about 42–72 h [52].

Röltgen et al. [53] found persistence for the full 60 days duration of their study of both mRNA and free spike proteins in the cytoplasm and nuclei of germinal cells in axillary lymph nodes ipsilateral to deltoid muscle injection site. Spike protein persisted in 96% of vaccinees blood up to 2 days post-vaccination and was still present in 63% of vaccinees 1 week after the first dose. After the second dose, the detection of spike protein "is impeded . . . likely due to . . . anti-spike antibodies" (p. 1037). However, as shown earlier the modified RNA molecules are extraordinarily stable, and as long as they persist inside the cell, and the cell is not attacked and killed by the immune system, intracellular ribosomal spike protein production will persist. No studies have determined the stability of the vaccine-induced spike protein, but free spike protein has been found circulating up to 19 days post-vaccination in the plasma of young individuals with post-vaccine myocarditis [54].

The implications of Röltgen et al. [53] findings have been elaborated in detail in a blogpost by Jikomes [55] as indicative of danger, whereas a blogpost by Yong [56] argues the prolonged presence of mRNA and spike proteins is not dangerous. However, Yong concedes the persistence was unexpected. Health regulatory authorities had assured clinicians and the public early in the COVID-19 vaccine rollout that the persistence of mRNA spike protein production would be brief and localised to the deltoid. This is clearly not the case and the biological implications of persistent translation of spike protein within multiple tissue types warrant investigation.

The findings of these studies are consistent with the 14-day half-life for the mRNA-LNP in the Japanese Ministry of Health Pfizer rat biodistribution study [46] and are summarised in Table 1.

Cells that take up mRNA from the mRNA vaccines package some of the mRNA with ionizable cationic lipids into small lipid particles that are released as exosomes [59]. Other research has found spike proteins persist in circulating exosomes for at least four months after Pfizer COVID-19 vaccination [57]. This shows spike protein endurance, like mRNA endurance, is long-lasting in vivo. Varicella zoster virus (VZV) reactivation as shingles is the most common cutaneous adverse event after COVID-19 mRNA vaccination, and a case has been reported in which spike protein was detected in skin lesions 3 months after vaccination [58]. These authors postulated that:

> *"mRNA COVID-19 vaccination might induce persistent VZV reactivation through perturbing the immune system, although it remained elusive whether the expressed spike protein played a pathogenic role".* [58] (abstract)

Several possible ways for COVID-19 vaccines to perturb the immune system are hypothesised by the authors—via the lipid-nanoparticles, N1-methylpseudouridine in

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mRNA, the spike protein (particularly the S1 subunit), antibody-dependent enhancement and overwhelming antigenic stimulus [58]. Our review of a large and growing literature reveals these concerns to have an evidentiary basis, and there to be a pathogenic role for the spike protein.

Table 1. Studies demonstrating persistence of vector-based vaccine constituents and/or derivative spike protein.

Author	Constituents/Tissue Type/Assay Technique	Duration Measured
Animal		
Pfizer (Japanese MoH) 2020 [46]	Radiolabelled LNP in plasma and tissues	140 h–14 days
Human		
Ogata et al. (2021) [52]	Spike protein and S1 subunit (assay)	3 days
Bansal et al. (2021) [57]	Spike Protein	4 months
Fertig et al. (2022) [50]	LNPs and mRNA	15 days
Röltgen et al. (2022) [53]	mRNA and Spike Protein in ipsilateral lymph nodes; 2–7 days post dose in blood	60 days
Yamamoto et al. (2022) [58]	Spike Protein in skin	3 months
Yonker et al. (2023) [54]	Spike Protein in blood	1–19 days *in cases of myocarditis*
Castruita et al. (2023) [51]	mRNA in plasma	28 days

6.4. *Nanoparticle Toxicology*

Wang et al. showed in 2018 that even small amounts of nanoparticles taken up via lungs or skin can lead to cytotoxic effects [60]. When ingested, nanoparticles target predominantly the mesenteric lymph nodes, liver, and spleen, while when injected as a drug carrier, they can pass any barrier and translocate to the brain, ovaries, and testis, mainly after phagocytosis by macrophages which help distribute them across the body. Reproductive toxicity effects beyond the scope of this review.

The molecular mechanisms involved in nanoparticle toxicity to the reproductive system are not fully understood, but possible mechanisms include oxidative stress, apoptosis, inflammation, and genotoxicity through induction of reactive oxygen species (ROS), causing damage at the molecular and genetic levels which results in cytotoxicity and DNA damage.

Of particular concern in mRNA-LNP complexes are the two propriety functional excipients, ALC-0315 and ALC-0159, never before used in a medicinal product and not registered in either the European Pharmacopoeia or in the European C&L inventory [61]. A question in the European Parliament in December 2021 noted that "Echelon, the manufacturer of these nanoparticles, specifies they are 'for research only and not for human use'". The reply on behalf of the European Commission was that the excipient "in Comirnaty has been demonstrated to be appropriate . . . in compliance with the relevant EMA scientific guidelines and standards" [62]. Despite this reassurance, the presence of electrolytes in the preparation and manual dilution before inoculation raises serious questions about the stability of the resulting suspension and the polydispersity index of the nanomaterials contained in it, factors that can be hypothesised as the root causes of numerous post-vaccination adverse effects.

A nanoparticle in solution forms a colloidal system whose stability prevents the aggregation of particles through electrostatic repulsion. The parameter used to calculate colloidal stability is the Zeta potential, which refers to the potential generated by a double layer of electric charges. When the potential is low, attractive forces prevail over repulsive and more

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aggregates will form. The stability of a colloidal biphasic system is a precarious balance dependent upon ratios, processing methods, correct temperatures, and the presence of electrolytes [63]. After dilution with sodium chloride solution, the final ratio in Comirnaty is 2.61 mg of electrolytes versus only 0.48 mg of ALC-0315 + ALC-0159. This can only lead to a drastic reduction in the Zeta potential, with predictable aggregation, agglomeration, and, finally, flocculation. One can postulate the damage caused by aggregation of nanoparticles in capillaries throughout the body.

Should the colloidal suspension stay stable enough to disperse in lymph and blood, the nanoparticles as well as their toxic load will distribute across the body, cross blood-brain, blood-placental and other biological barriers and likely cause cell death and inflammation wherever they accumulate. Additionally, the elimination of toxic nanoparticles from the body is not straightforward. Particles of 5.5 nm or less can be excreted after glomerular filtration in the kidneys via the urinary tract. Larger particles could in theory be broken down going through the hepatobiliary tract, however, tend to be bound by, e.g., Kupffer cells, the resident macrophages, which slows down their processing considerably [64]. The mRNA-LNP complexes are around 100 nm in size and well above the size which allows their elimination via the kidneys. This would account for their accumulation in the liver and the observed liver toxicity.

6.5. Lipid-Nanoparticles Are Pro-Inflammatory

The lipid-nanoparticles used in the COVID-19 vaccines have been found to induce significant inflammatory cytokine secretion and macrophage inflammatory proteins with cell death [43]. Ndeupen et al. [43] note this pro-inflammatory effect of the lipid-nanoparticles would increase the vaccine adjuvant immunogenicity of the COVID-19 mRNA vaccines and add to the adverse events. The authors did not consider the widespread biodistribution of the lipid-nanoparticle, and therefore the potential for wide-ranging serious COVID-19 vaccine adverse effects across organs and systems.

Trougakis et al. [65] reviewing literature on adverse events from COVID-19 mRNA vaccines, noted the risk of spike protein-driven pathology, which they termed the "spike hypothesis". However, Trougakis and colleagues also reviewed evidence of lipid-nanoparticles' pro-inflammatory properties from animal model studies. These include "activating Toll-like receptors, excessive neutrophil infiltration, activation of diverse inflammatory pathways, and production of various inflammatory cytokines and chemokines" [65] (p. 544).

Hence, even if one were to change the antigen expressed there would likely still be adverse events. Halma et al. [66] point to the changes made to the mRNA and the ingredients of the lipid-nanoparticles, especially the addition of polyethylene glycol (PEG), that made it both more resistant to degradation and helped it to evade the immune system with lipid-nanoparticles helping biodistribution and bioaccumulation. Bioaccumulation can lead to blockage of small blood and lymphatic vessels. Biodistribution means that cell death and inflammation could occur in all organs including the brain, placenta, and testes, as has been seen with the COVID-19 mRNA vaccine [5,44–46].

PEG is known to cause anaphylactic reactions in some people, which is stated as a known adverse event in the vaccine patient information leaflet. Beside lipid-nanoparticle-encapsulated mRNA being highly inflammatory, antibodies against the spike protein damage cells and tissue that produce the spike protein. Regardless of which antigen is produced, damage to cells will occur in an autoimmune reaction [67].

Mechanisms involved in autoimmune damage to cells producing an endogenous protein include the development of cross-reactivity to the endogenous protein [68], immune-mediated toxicity [69], and immune tolerance due to switching to IgG4 [70]. Switching to an IgG4 immune response has consequences for cancer susceptibility [71], pregnancy [72] and IgG4-related diseases, which are chronic inflammatory conditions [73].

Another risk, and problematic with prior vaccines against coronaviruses both in the human and veterinary field, is the risk of antibody-dependent enhancement [66].

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6.6. *Novavax COVID-19 Vaccine Toxicity and Novel Lipid-Nanoparticle Technology*

That lipid-nanoparticle biodistribution makes an important contribution to adverse events is further suggested by adverse event reports from the protein-based Novavax COVID-19 vaccine Nuvaxovid. It has the novel technology of a lipid-nanoparticle matrix which could potentially increase biodistribution of the unmodified spike protein, with intact furin cleavage and receptor binding domain sites. In response to a query about biodistribution studies, Novavax replied in mid-2021 that "a pharmacokinetic/pharmacodynamic study has not been performed on the Novavax COVID-19 vaccine" (personal communication Novavax-Parry, 30 July 2021).

Myocarditis adverse events have been reported for the Novavax COVID-19 vaccine in several nations including New Zealand, where the regulator has released an "Alert Communication" on myocarditis [74]. This suggests a pathogenic amount of spike proteins from the Novavax COVID-19 vaccine can on occasion reach the heart. Overall, the adverse event reports from the Novavax COVID-19 vaccine are less than from the gene-based vaccines, which would be consistent with a dose-response effect for spike proteins. However, the lipid-nanoparticle matrix itself may be responsible for some of the myocarditis reports.

6.7. *AstraZeneca COVID-19 Vaccine Biodistribution Data*

In October 2022 a FOI request (MHRA IR07151D) obtained AstraZeneca documents that had been submitted to the British MHRA. According to the AstraZeneca "Nonclinical Overview" dated 21 December 2020, the rationale for initially not performing biodistribution studies on the AstraZeneca adenovirusDNA COVID-19 vaccine was that prior studies on viral vector vaccines showed minimal spread from the deltoid muscle and axillary lymph nodes to distal organs [75]:

> *"The biodistribution of AZD1222 following intramuscular administration is expected to be similar to that of AdCh63, confined to the site of injection and draining lymph nodes".* [75] (p. 13)

However, a later AstraZeneca "Nonclinical Overview" dated 26 April 2021, which included new mouse biodistribution studies on the company's COVID-19 vaccine did reveal biodistribution to distal organs [6]:

> *"The highest levels of AZD1222 vector DNA (103 to 107 copies/µg DNA) were observed in the intramuscular administration sites and sciatic nerve (close proximity to the administration sites) on Day 2. Lower levels of AZD1222 vector DNA (<LLOQ to 10^4 copies/µg DNA) were observed in the bone marrow, liver, spleen and lung on Day 2. The levels of AZD1222 and the number of tissues with detectable levels of AZD1222 vector DNA decreased from Day 2 to 29, indicating elimination".* [6] (p. 14)

The document stressed that the viral-vector itself was not replicating as an adenovirus, but that misses the point of protein production of a toxic foreign antigen in bodily organs. Although this suggests lesser quantities of the viral-vectorDNA COVID-19 vaccines are widely biodistributed than with the lipid-nanoparticle carried modified mRNA COVID-19 vaccines, the capacity of the adenovectorDNA vaccines to produce significant quantities of spike proteins remains. An autopsy series of three cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) with cerebral thrombosis related to the AstraZeneca COVID-19 vaccine found spike proteins in thrombosis and cerebral vein walls [7]. The authors state in the abstract:

> *"SARS-CoV-2 spike protein was detected within the thrombus and in the adjacent vessel wall. Data indicate that neutrophils and complement activation associated with antispike immunity triggered by the vaccine are probably involved in the disease process."*

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6.8. Traditional COVID-19 Vaccines Not Contributing High Adverse Event Reports

Traditional vaccine technology COVID-19 vaccines are mostly available in non-Western nations [35]. These include inactivated virus vaccine technologies such as Covaxin manufactured by Bharat Biotech [76] in India, and CoronaVac made by Sinovac [77] in China.

There are also traditional recombinant protein-based COVID-19 vaccines such as Spikogen, jointly developed by Australian and Iranian-based companies [78–80]. In Spikogen the spike protein antigen has been modified with the removal of furin cleavage site and RBD to reduce cell adhesion and entry and thus to reduce potential toxicity. A Spikogen phase 3 clinical trial in Iran involving 16,876 participants met its primary efficacy endpoint with greater than 60% protection against infection during a particularly widespread wave in Iran of the delta variant of SARS-CoV-2 [81,82]. Spikogen is on the market in Iran and recognised for travel to some nations including New Zealand, having been used for 8 million doses with no serious systemic adverse event reports to Iranian pharmacovigilance to date.

Traditional COVID-19 vaccines have not produced the high rates of adverse event reports that characterise the gene-based COVID-19 vaccines. This is further evidence that the risk is in the body-wide biodistribution and prolonged production of spike proteins. It points to pathogenicity of the spike protein and, given the evidence described above, also the lipid-nanoparticle carrier matrix.

6.9. Autoimmune Risk of Foreign Antigens Presented by the Body's Own Cells

As described above, evidence shows the spike protein to be innately toxic. Even if it were non-toxic in its own right, by virtue of its foreignness, spike protein could still produce pathophysiological damage through autoimmune responses. A straightforward consequence of a foreign protein. The lipid-nanoparticle matrix permits widespread biodistribution of mRNA gene codes to cells in most or all organs. The subsequent expression of the spike protein on cell surfaces, and as a soluble protein within the organs and blood stream, induces T-cell destruction of cells and tissues and B-cell antibodies. The latter may also cause immune complex deposition further damaging tissues via type III hypersensitivity.

Tissue damage, therefore, can be caused by the spike protein via autoimmune reactions, even if it is 'non-toxic'. While this is of minor consequence in a muscle such as the deltoid, it causes serious and fatal adverse events when occurring in critical organs such as the brain, ovaries, and heart. The method of delivery—mRNA gene therapy via lipid-nanoparticles that traverse biological membranes—is a core problem and a key reason why this technology has never been commercially marketed, until now.

The fact Moderna and other big pharmaceutical companies plan large-scale mRNA vaccine manufacture for many other diseases, in the absence of a full and detailed inquiry, is, therefore, deeply troubling.

6.10. Pathophysiology of Virus and Vaccine Spike Protein

The natural course of new pandemic/epidemic viruses is to become more infectious and less pathogenic with time. This has demonstrably been the case with SARS-CoV-2 where the original Wuhan strain and subsequent alpha and other early variants were quite pathogenic, the delta variant spread more easily but was somewhat less pathogenic, and the various omicron subvariants have been highly infectious but even less pathogenic in illness severity. In particular, the omicron subvariants have targeted the upper respiratory tract rather than the lower respiratory tract, leading to less systemic penetration of the virus and the spike protein [83].

On the other hand, the mRNA and adenovectorDNA vaccines cause human cells to manufacture a slightly modified version of the original Wuhan strain spike protein. Some "bivalent" booster doses add genetic code for omicron variant spike protein [84,85]. If an individual suffers wide biodistribution of this genetic code, many more spike proteins can be produced systemically than generally occurs with the natural virus. This is more

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likely for anyone who is young and healthy. The elderly and those with comorbidities have a greater risk of serious SARS-CoV-2 viral infection deep in the lungs and systemically, whereas the young and healthy tend to rid themselves of the virus in the upper respiratory mucosa. Therefore, in the young and healthy the encoding-based COVID-19 vaccines will transfect a far more diverse set of tissues than infection by the virus itself.

Many studies have demonstrated the spike protein is toxic. In "Understanding the Pharmacology of COVID-19 mRNA Vaccines: Playing Dice with the Spike?", Cosentino and Marino (2022) reviewed the evidence for the toxicity of the spike protein [86]. They argued that the COVID-19 mRNA vaccines should rightly be described as "prodrugs" as they meet the dictionary definition: "a pharmacologically inactive substance that is converted in the body (as by enzymatic action) into a pharmacologically active drug". This occurs via the mRNA action in ribosomes to cause the synthesis of the spike protein [86] (p. 3).

Cosentino and Marino (2022) reviewed the evidence for widespread biodistribution of the mRNA and concluded that "evidence strongly supports the possible link between inappropriate expression of S protein in sensitive tissues and subsequent tissue damage" [86] (p. 2).

They reviewed the literature on the pharmacology and pathophysiological effects of the spike protein on bodily tissues, which include [86] (p. 4–5):

- Binding to ACE-2 receptors as a "potential trigger for platelet aggregation, thrombosis and inflammation, as well as for hypertension and other cardiovascular disease".
- Disruption of CD147 transmembrane glycoprotein which interferes with cardiac pericyte and erythrocyte function may result in myocarditis, haemolytic anaemia, blood hyperviscosity, and possibly neurodegenerative processes.
- Binding to Toll-like receptors 2 and 4 (TLR2, TLR4), with theoretical pathogenic effects via increased inflammatory cytokine cascades, due to (1) activation of Nuclear Factor kappa B (NF-κB pathway) and deficient macrophage immune function via TLR2, and (2) lung damage, myocarditis and multiorgan injury via TLR4, that had yet to be properly investigated by the world's research community.
- Binding to the high affinity oestrogen receptor alpha (ER alpha) is possibly responsible for the menstrual irregularities commonly observed after COVID-19 vaccination and raising concerns of potential involvement in breast cancer.
- Spike protein S2 subunit specifically interacts with proteins p53 BP1 and BRCA1. The p53 BP1 is a well-established tumour suppressor; the BRCA1 is frequently mutated both in breast cancer and in prostate cancer [87].

Cosentino and Marino noted that these "potential toxicological issues" were not "taken into consideration in the studies that led to the marketing authorisation, precisely because . . . these products were treated as conventional vaccines", when in fact they are gene insertions acting as prodrugs [86] (p. 5).

In vitro research found the receptor binding domain (RBD) of the spike protein (the S1 unit) was the most active agent to trigger a pro-inflammatory response from dendritic cells [88].

Further in vitro research with human pulmonary artery muscle and endothelial cells treated with full-length spike protein or the RBD alone, found in this case the RBD to be relatively inert, but the full-length spike protein to induce enlargement of the pulmonary vessel cells via phosphorylation of protein MEK (mitogen-activated protein kinase kinase) [89]. This was found to also be the case in vivo when intratracheal administration of the S1 unit/RBD into transgenic mice with human ACE-2 on their cells showed a dramatic increase in inflammatory cytokines in bronchial lavage fluid from mice who received the spike protein S1 unit, whereas this was minimal for control mice (intratracheal saline) and mild and late for whole spike protein administered mice, indicating the cleaving of the S1 (RBD) unit increases the ACE-2 associated pathology [90].

Injection of mice, bred to have human-like ACE-2 receptors with spike protein S1/RBD unit was found to induce COVID-19-like acute pulmonary pathology, indicating it is the spike protein, unless modified as in the Australin-Iranian vaccine Spikogen [78,79],

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that is a cytotoxin primarily responsible for the severity of the SARS-CoV-2 respiratory infection [86]. This, in retrospect, means it has been a particularly poor choice for vaccine development purposes.

In a preprint, McKernan et al. [91] quantify the pharmacokinetics of the mRNA vaccines as creating greater numbers of spike proteins than the SARS-CoV-2 virus, and more systemically in most people not prone to overwhelming COVID-19 viral infection:

> *"The pharmacokinetics of injection are different from an infection; 30–100 µg per injection (90–300 µg for those boosted) of Spike mRNA equates to 13 trillion to 40 trillion mRNA molecules injected in a few seconds with each injection. The pharmacokinetics of this bolus injection differs from that of viral replication that occurs over the course of a few days. If each of these mRNAs can produce 10–100 spike proteins and you have 30–40 trillion cells, there may be a far greater systemic quantity and a much longer duration of spike protein exposure through the vaccination route than natural infection".* [91] (p.12)

Human tissue production of antigens means that the dose is likely to vary between individuals. This will be for reasons of individual genetics and physiology, the tissues exposed to the code, batch and vial variability of the product and manner of transportation, refrigeration, and administration. In terms of the toxicological principle ***dosis sola facit venenum*** (the dose makes the poison), this aspect on its own casts doubt on the safety of mRNA and viral vector DNA vaccines.

Around the time the COVID-19 vaccines were released to the public, researchers at the Salk Institute found that the SARS-CoV-2 virus relies upon the spike protein binding to ACE-2 receptors on host cells to gain cell entry [92]. ACE-2 is protective in the cardiovascular system, and SARS-CoV-2 spike protein promotes lung injury through a decrease in the level of ACE-2. The Salk Institute team showed that the spike protein alone can damage vascular endothelial cells by downregulation of ACE-2, inhibition of endothelial nitric oxide synthase (eNOS), impairment of mitochondrial function and direct impairment of endothelial function.

6.11. Disruption of the Nicotinic Cholinergic Anti-Inflammatory Pathway

High doses of the toxin-like spike protein binding domain (RBD) inhibit acetylcholine (ACh)-induced α7 nAChR responses. Inhibition of these α7 nACHRs has profound effects [33]. The nicotinic cholinergic system has been labelled the 'Cholinergic Anti-inflammatory Pathway' (CAP), as the activation of these receptors controls inflammation and their inhibition results in uncontrolled inflammation. The CAP forms a multi-faceted network, with distribution in neuronal and non-neuronal cells, and diverse functions throughout the body. In addition to the nervous system, α7 nAChRs are expressed in non-neuronal cells such as lymphocytes, monocytes, macrophages, dendritic cells, adipocytes, keratinocytes, endothelial cells, and epithelial cells of the intestine and lung. With such widespread distribution, nAChRs could be implicated in the pathophysiology of severe COVID-19 via mechanisms, both through and independent of the cholinergic anti-inflammatory pathway [32].

The modulation of inflammatory and immune response by the CNS through the vagus nerve is based on bi-directional communication between the immune and nervous systems. Afferent vagus nerve fibres, located in nucleus tractus solitarius, provide sensory input to the CNS about the inflammatory status that can result in the transmission of efferent signals, originating from the dorsal motor nucleus, to control the inflammatory response. Such a response is rapid and localised, unlike the diffusible anti-inflammatory network, which is slow, distributed, non-integrated and dependent on concentration gradients [32].

Activated via the vagal nerve release of ACh, nACHRs are found in the immune system on T-cells, B-cells, macrophages, monocytes, neutrophils and mast cells and act to reduce inflammation, including the reduction of proinflammatory cytokines, such as IL-6, while promoting anti-inflammatory cytokines such as IL-4 [93]. Dysregulation of nAChR by SARS-CoV-2 could also suppress the counterbalance to the sympathetic nervous system

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and thus promote the central sympathetic drive and the development of the sympathetic-driven cytokine storm [94]. In turn, the sympathetic storm triggers oxidative stress and hyperinflammation by increasing the generation of reactive oxygen species (ROS) and the release of pro-inflammatory cytokines.

NAChR are also found in the respiratory tract. Subtype α3β4 nAChR support cilia function and mucociliary clearance, and α7 nAChR stimulation is anti-inflammatory. Hence, the inhibition of both these receptor types, as spike protein is able to do, would contribute significantly to the lung pathology seen in both acute COVID-19 and long COVID [95].

SARS-CoV-2 infection-induced stress and suppression of the cholinergic pathways via nAChR inhibition may also activate the sympathetic nervous system (SNS) leading to neuro-hormonal stimulation and activation of pro-inflammatory cytokines with further development of a sympathetic storm. Sympathetic over-activation in COVID-19 is correlated with an increase in capillary pulmonary leakage, alveolar damage, and the development of acute respiratory distress syndrome. Furthermore, SARS-CoV-2 can spread through pulmonary mechanoreceptors and chemoreceptors to the medullary respiratory centre in a retrograde manner resulting in sudden respiratory failure as a result of nAChR inhibition in the parasympathetic medullary centres [96].

Once someone is infected with SARS-CoV-2, the immune system is mobilised. As the virus replicates, cell and viral debris or virions may interact with the nAChRs to block the cholinergic anti-inflammatory pathway. If the initial immune response is not enough to combat the viral invasion at an early stage, the extensive and prolonged replication of the virus will eventually disrupt the cholinergic anti-inflammatory pathway and seriously compromise the ability to control and regulate the immune response. The uncontrolled action of pro-inflammatory cytokines will result in the development of cytokine storm, with acute lung injury and acute respiratory distress syndrome (ARDS), coagulation disturbances and multiorgan failure. Based on this hypothesis, COVID-19 appears to eventually become a disease of the nicotinic cholinergic system [92].

This same mechanism can explain both the breadth and severity of symptoms experienced in long COVID and in COVID-19 vaccine injuries. The former shows failure to clear spike protein and virus, with uncontrolled immune activation and sequelae [97], and in the latter vaccine injuries, where spike protein overwhelms the system and is produced for months, there is increased load with each subsequent injection. This also provides a mechanism for possible interventions with α7 nAChR agonists and positive allosteric modulators (PAMS).

7. Evidence of 'Spikeopathy'—Spike Protein Pathogenicity

The spike protein of SARS-CoV-2 has turned out to be pathogenic. The term "spikopathy" has been coined [98] as its pathological effects, like tuberculosis, appear to be legion, widespread in body organs, and induce a myriad of known diseases and syndromes. The term is spelled "spikeopathy" by others on the internet and we have chosen that spelling.

Figure 6 shows the FDA was aware of this potential before the public release of the gene-based COVID-19 vaccines. It is the 16th slide from a PowerPoint presentation of the "Vaccines and Related Biological Products Advisory Committee (VRBPAC) 22 October 2020, Meeting" [99]. What is striking is the predictive accuracy of these mostly neurological, cardiovascular, and autoimmune "possible adverse events" with those reported to VAERS and other global vaccine injury databases.

The website www.react19.org lists as of June 2023 over 3400 published papers and case reports of COVID-19 vaccine harms under over twenty organ system and syndrome headings [100]. Here, we will review some key organ systems in relation to the pathogenic effects of the COVID-19 mRNA and adenovectorDNA-produced spike proteins.

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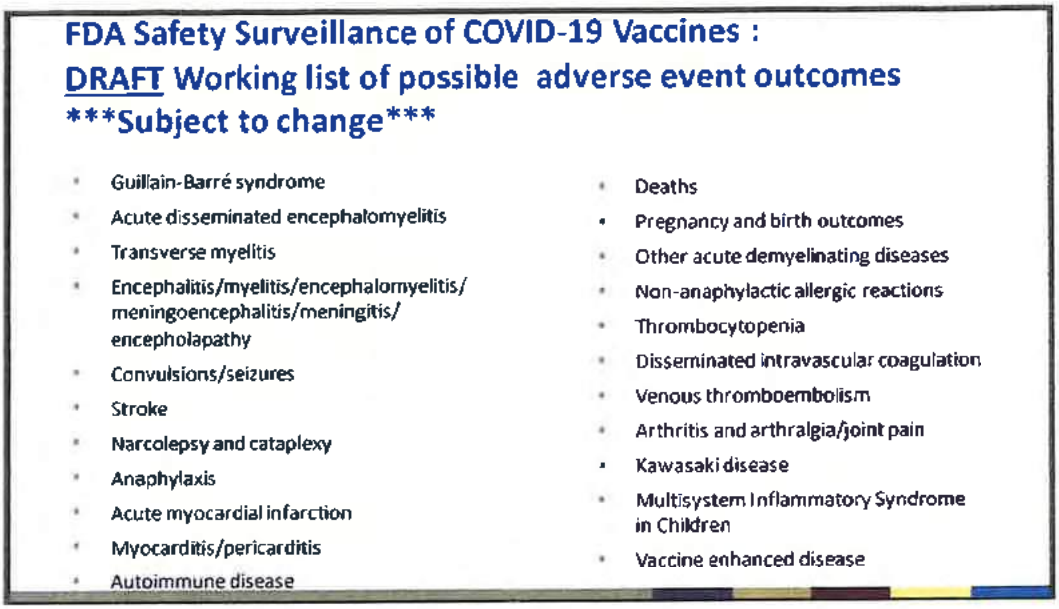

Figure 6. Slide 16 FDA's VRBPAC meeting, Oct. 2022 [99].

7.1. Cardiovascular Pathogenesis

Literature accumulates about the cardiovascular harms of COVID-19 vaccines. For example, as of June 2023 react19.org, under the heading "Cardiac", lists 432 peer-reviewed papers and case reports covering myocarditis, cardiomyopathy, myocardial infarction, hypertension, aortic dissection, postural orthostatic tachycardia syndrome (POTS), tachycardia, and conduction disturbance [100].

7.1.1. Myocarditis and Pericarditis

Reports of myocarditis and pericarditis are particularly numerous. Yonker et al. [54] found free spike proteins in the blood of 16 adolescents and young adults who developed post-vaccination myocarditis, but not in 45 post-vaccination age-matched controls without myocarditis. The authors examined immuno-profiles and free spike protein plasma concentrations in young subjects with myocarditis after vaccination with COVID-19 mRNA vaccines. Significantly elevated full-length free spike protein concentrations, unbound to antibodies, were found in the myocarditis patients compared with controls. Antibody profiles and T-cell responses were similar between subjects with myocarditis and carefully age-matched controls, but it may be reasoned that part of the variance seen with regard to myocarditis as a complication of mRNA vaccination, may be explained by the fact that some achieve greater transcription and secretion into the blood. This raises serious concern about the pathogenicity of free spike protein in such cases of myocarditis.

Avolio et al. [101] found the free SARS-CoV-2 spike protein, separated from the virus, could cause microvascular disease via several mechanisms, which include stimulation of cardiac pericytes to engage in pro-inflammatory cytokine production via CD147 receptor binding. Further evidence for the pathogenicity of spike protein is from mouse studies where spike protein-induced cardiac fibrosis and myocardial contractile impairment may underlie COVID-19-related cardiomyopathy [102].

The possibility that COVID-19 vaccine-associated myocarditis, as opposed to the hypersensitivity myocarditis seen with agents such as the smallpox vaccine, is in fact autoimmune, is considered by Baumeier and colleagues [103] in a series describing 15 cases with endomyocardial biopsies (EMB), a study is discussed in a later section of this paper. Like other studies and case reports, lymphocytic infiltration was seen in

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association with intracardiac spike expression (although the authors did not specifically refer to lipid-nanoparticle biodistribution characteristics).

Barmada et al. [104], in a recent study from Yale in light of the findings of Yonker et al. [54] and Baumeier et al. [103] consider whether spike-induced molecular mimicry is the driver of autoimmune myocardial attack. They effectively exclude this possibility in a serum study by employing REAP, a "rapid extracellular antigen profiling screen" for autoantibodies. They additionally postulate "cytokinopathy", with reference to serum cytokine profiles and other markers of inflammation in a subgroup, but do not report blood concentrations of spike protein, or obtain myocardial tissue.

From the above, although much laboratory study remains to be conducted regarding the myocardial inflammation seen prominently after mRNA vaccinations, it appears that spike protein plays a role. Whilst molecular mimicry is not the reason, direct toxic effects of spike protein may be implicated, in addition to the reaction of the immune system to the presence of spike protein, either expressed in or deposited in the myocardium. That myocarditis is precipitated by spikeopathy is further indicated in that the adenovectorDNA COVID-19 vaccines of both AstraZeneca and Johnson & Johnson, as well as the Novavax protein-based lipid-nanoparticle embedded vaccine, have been reported as causative [105,106].

How common is COVID-19 vaccine-induced myocarditis and pericarditis? As a baseline, a study published on 7 January 2020, the eve of the SARS-CoV-2 pandemic, reported: "viral myocarditis has an incidence rate of 10 to 22 per 100,000 individuals [107].

As to community epidemiological incidence, a review in the *New England Journal of Medicine* [108] noted that the annual incidence rate depended on the level of investigation:

> *"Before the COVID-19 pandemic, the estimated global incidence of myocarditis was 1 to 10 cases per 100,000 persons per year (12). The highest risk was among people between 20 and 40 years of age and among men; 6.1 cases per 100,000 men and 4.4 cases per 100,000 women. The increased use of cardiac MRI has led to a gradual rise in the reported incidence of myocarditis in the United States, from 9.5 to 14.4 cases per 100,000".* [108] (p. 1488)

Health authorities like the FDA, TGA and other regulators have claimed that post-COVID-19 vaccination myocarditis is very rare. An early study of 2.39 million Kaiser Permanente insured Californian adults who received at least one dose of a Pfizer or Moderna COVID-19 vaccine found only 15 cases of post-vaccine myocarditis, all males with a mean age of 25 years [109]. However, cases were based on physician reports to the Kaiser Permanente immunisation committee or hospitalised cases within 10 days of vaccination. Milder cases could have been missed; physicians might not always have reported cases to the committee.

A systematic review of pharmacovigilance reports to US VAERS, UK Yellow Card, and EU EudraVigilance databases up to March 16, 2022, found 18,204 submitted events of myocarditis and/or pericarditis, some fatal [110]. Given hundreds of millions of vaccine recipients, the authors noted this to be a rare event.

The FDA recognised the risk for myocarditis and pericarditis from the COVID-19 mRNA vaccines was real, especially in younger males after the second dose, but judged it to still be rare, and cited a VAERS-derived figure of 6.5 per 100,000 and up to 20 per 100,000 for adolescent boys [111]. The FDA did not calculate that pharmacovigilance databases, like its own FAERS (FDA Adverse Event Report System) and the CDC's VAERS, have a large under-reporting factor.

A common factor in this pharmacovigilance-derived estimate of the FDA, as well as those of others, is the failure to mention the perennial problem of underreporting in passive notification systems. Pharmacovigilance databases, like its own FAERS and the CDC's VAERS, are acknowledged to have large under-reporting factors. As to how large the under-reporting factor is, is a matter of debate.

Compounding the phenomenon of underreporting in the case of myocarditis, is that this diagnosis is difficult to make, and often depends on the availability of specialty

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units, cardiac MRI facilities and/or endomyocardial biopsy (EMB). The diagnosis can mimic myocardial infarction and thus can be misdiagnosed. In this regard, the paper by Baumeier et al. [103] (discussed later in this paper), noted that a third of those with histologically confirmed myocarditis, categorised as vaccine-associated on the basis of history and exclusion of other causative agents, did not have cardiac MRI evidence of myocarditis. Further, many cases of myocarditis are subclinical and may be missed in the acute phase. This does not mean, however, that a benign course is always expected since even minor fibrosis and scarring of the myocardium can create arrhythmogenic foci and may present later with serious and fatal arrhythmias, or else may eventually lead to heart failure (so-called inflammatory cardiomyopathy) [112]. Hence, it is rational to say that the exact frequency of vaccine-associated myocarditis is unknown: cases can be subclinical, missed, or misclassified and even specialised imaging may underdiagnose.

An indication of how common subclinical myocarditis, or at least myocardial involvement, might be comes from a prospective study in Thailand. Adolescents (n = 301) with no cardiac history had cardiac biomarkers (troponin-T, creatinine kinase-band (CK-MB)), ECG, echocardiography, and diary of cardiac symptoms at baseline and on days 3, 7 and 14 after the second dose of Pfizer mRNA COVID-19 vaccine [113]. Although there was no control group, the diary, physical examination, and ECG results are of concern: "tachycardia (7.64%), shortness of breath (6.64%), palpitation (4.32%), and hypertension (3.99%)" (p. 4). Fifty-four adolescents (18%) had abnormal ECGs. Troponin elevation occurred in five adolescents, echocardiography detected pericardial effusions in three adolescents, and signs of myopericarditis in one adolescent led to ICU admission. In total seven adolescents presented "with myopericarditis, subclinical myocarditis, and pericarditis after second dose vaccination" but apart from the adolescent hospitalised to intensive care, the other six cases were subclinical or mild and easily missed if it were not for this rigorous prospective study [113] (p. 8, Table 3).

While this methodologically excellent Thai study appears not to have been replicated in terms of a full manuscript, a conference abstract suggested comparable results, with a simpler methodology [114]. Of 777 healthcare workers from University Hospital Basel who received a COVID-19 booster vaccination in late 2021 to early 2022, evidence of cardiomyonecrosis (troponinemia) was detected in 22 (2.8%), with no cause other than a Moderna COVID-19 mRNA-1273 booster injection [114]. Although in a different population, receiving the second mRNA vaccine dose, the Thai study reported a rate of 2.3% for myocarditis or pericarditis. Given that billions of doses have been given to the human population, this would equate to 2300 cases per 100,000. As all cases were male the rate was 3.5% for male adolescents [113].

Although the public health authorities' narrative is that myocarditis from COVID-19 vaccines is mild and self-limiting, the evidence is that symptomatically while this might be the case, pathological changes in these young hearts are persistent. An Italian study followed 13 cases of post mRNA vaccine-induced myopericarditis, myocarditis or pericarditis, median age 15 years, for 12 weeks. Although overt symptoms in all but one case resolved, 12 of the 13 adolescents still had pericardial effusion and six of nine who had cardiac MRI scans had signs of "persistent, although decreased, myocardial injury" at the study end [115].

Subclinical myocarditis inducing cardiac fibrosis as foci for later arrhythmia under stress is a possible explanation for the epidemic of sudden deaths in youths and young to middle-aged adults since the advent of the COVID-19 vaccines [116,117]. This possibility was noted by the TGA early in the vaccine rollout [118]:

> *"Even apparently mild episodes of myocarditis may lead to long-term sequelae, such as arrhythmias. . . . the majority of cases of myocarditis and/or pericarditis after mRNA COVID-19 vaccines (both Pfizer and Moderna) analysed to date occurred in older adolescents and young adults (aged 16 to 30 years), with the highest risk in younger males within days after dose 2".* [118] (p. 8)

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7.1.2. Thrombotic Effects of Spike Proteins

Somewhat separate to the pathogenesis of myocarditis, COVID-19 vaccine-induced spike protein binding to ACE-2 receptors can trigger platelet aggregation, thrombosis, and inflammation, thereby leading to blood clots [119,120]. Angeli et al. [99] summarise the biochemical pathway to these pathophysiological effects:

> *"Free-floating Spike proteins released by the destroyed cells previously targeted by vaccines may interact with ACE-2 of other cells, thereby promoting ACE-2 internalisation and degradation (16,79). This mechanism may enhance the imbalance between Ang-II overactivity and Ang-1-7 deficiency through the loss of ACE-2 receptor activity, which may contribute to triggering inflammation, thrombosis, an increase in BP, and other adverse reactions ("Spike effect" of COVID-19 vaccines) (80,81). Moreover, the detrimental effects of other angiotensinases (POP and PRCP) deficiency on BP, thrombosis and inflammation are well supported".* [120] (p. 24)

The authors describe the mechanisms by which these clotting effects are more common in younger patients. Angiotensinases prolyl oligopeptidase (POP) and prolyl carboxypeptidases (PRCP) become deficient in older people with cardiovascular diseases and paradoxically this translates to less susceptibility to spike protein-induced cardiovascular pathogenesis, whereas with younger people the risk is increased:

> *"The relative deficiency of POP and PRCP among young and healthy subjects does not counterbalance ACE-2 internalisation, downregulation and malfunction due to free-floating Spike protein interactions, resulting in an increased risk of Ang-II accumulation, and adverse reactions ("Spike effect" of COVID-19 vaccines)".* [120] (p. 26)

They also propose that pre-existing immunity from SARS-CoV-2 infection or prior vaccination induces greater immune responses to spike protein production by cells, such as platelets, endothelial vascular cells or myocytes, leading to increased inflammation and thrombogenic activity. In Angeli et al. [119] they conclude:

Whereas Phase III vaccine trials generally excluded participants with previous immunisation, vaccination of huge populations in real life will inevitably include individuals with preexisting immunity. This might lead to excessively enhanced inflammatory and thrombotic reactions in occasional subjects. Further research is urgently needed in this area.

Live electron microscopy has shown free spike proteins trigger platelets to deform and coagulate via filopodia induction and the interaction of spike protein with platelet integrins to cause coagulopathy [121]. Early in the pandemic, mice transfused with transgenic human ACE-2 receptor platelets developed thrombi due to spike protein binding with the ACE-2 receptors on the platelets [1]. The authors noted:

> *"SARS-CoV-2 and its Spike protein directly stimulated platelets to facilitate the release of coagulation factors, the secretion of inflammatory factors, and the formation of leukocyte-platelet aggregates".* [1] (abstract)

The spike protein also was found to "competitively inhibit the bindings of antithrombin and heparin cofactor II to heparin/HS, causing abnormal increase in thrombin activity" [122]. In another mouse study, the spike protein was also found to "bind to the blood coagulation factor fibrinogen and induces structurally abnormal blood clots with heightened proinflammatory activity" and that "spike delays fibrinolysis" [123] (preprint).

French researchers at the Méditerranée Infection Institute in Marseille examined the effects of the spike proteins of the SARS-CoV-2 Wuhan, alpha, delta and omicron BA.1 variant on red blood cells (erythrocytes) in vitro and found the spike protein induced haemagglutination (clumping) of erythrocytes, the omicron BA.1 variant achieving this at lower concentrations down to 0.13 ng/μL, the earlier variants down to a concentration of 0.13 ng/μL. The mechanism of action was deduced via molecular modelling to be the positive charge on the spike protein reducing the natural electrostatic repulsion of negatively charged erythrocytes. Interestingly ivermectin when added to the in vitro solution bound strongly to the spike protein and prevented or reversed the haemagglutination depending

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on whether added pre or post the spike protein. The authors note the implications for treatment of vaccine adverse effects [124].

The plasma and internal membranes of other eukaryotic cells can be considered to function with anions and cations acting as a current loop to drive membrane potential on either side of the cell membrane [125,126]. The red blood cell's unique design is a toroid where currents also flow on the surface of the torus. If this static flow on the erythrocyte membrane surface is interrupted by a lack of separation between the negative surface membrane charge and the Stern layer, the zeta potential weakening leads to distortion of shape, decreased electric permittivity, increased viscosity, flocculation and rheological alterations [127]. When this surface current flow is static, with efficient separation of the positively charged Stern layer and negative surface membrane charges, the zeta potential is enhanced and the size, shape, proportion, and curvature of the erythrocyte transforms to the optimal shape. Erythrocytes must maintain a biconcave discoid shape in order to efficiently deliver oxygen (O_2) molecules and to uptake carbon dioxide (CO_2) molecules [128]. The interpolation of a positive spike protein into the negatively charged erythrocyte membrane can thus be expected to result in significant alterations in erythrocyte shape and function.

Thrombotic complications of COVID-19 vaccination involve many potential mechanisms, such as endothelial cell damage, immune response, dysregulation of the renin-angiotensin-aldosterone system, and thrombo-inflammation. Additionally, platelets contain acetylcholine and express α7nAchR. Acetylcholine acts as an endogenous inhibitor of platelet aggregation. Hematopoietic α7nAchR deficiency increases platelet activation and, in experimental studies, α7nAchR stimulation can diminish the pro-inflammatory state and modulate platelet reactiveness via increased levels of nitric oxide (NO). Inhibition of platelet nAChR by SARS-CoV-2 thus promotes platelet hyperreactivity and thrombosis which are hallmarks of COVID-19 and vaccine injury [129].

These mechanisms would explain clotting to both the virus and the spike proteins produced by the gene-based COVID-19 vaccines. It also suggests that public health policies that negated natural immunity and mandated COVID-19 vaccination, and booster programs, put the young and non-elderly population at greater risk. To illustrate these increased risks of harms, blindness cases have been reported to pharmacovigilance databases and a recent large study of retinal vascular occlusion diagnoses in the United States from January 1, 2020, to December 31, 2022, found COVID-19 vaccinated individuals with Moderna, Pfizer or AstraZeneca COVID-19 vaccines had a 2.19 hazard ratio increased risk compared with unvaccinated Americans [130].

7.1.3. Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

In contrast to the spike protein's role in myopericarditis and thrombogenesis as described above, the syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) seen with the adenovectorDNA vaccines of AstraZeneca and Johnson & Johnson, as well as the adenovectorDNA Russian Sputnik V vaccine [131], is a rare condition mediated by anti-PF4 platelet antibodies. It appears unrelated to the spike protein, and other components of the adenovectorDNA technology are being investigated [132]. It is odd that these vaccines have been mostly withdrawn from markets, whereas the mRNA COVID-19 vaccines with similar issues, albeit by different pathophysiological mechanisms, have not.

In addition to the presence of anti-PF4 antibodies in the pathogenesis of VITT, numerous authors have discussed the evidence for the role of NETosis (neutrophil extracellular traps) as a basis for thrombilia observed in adenoviral vector vaccines, independent of spike proteinaemia [133,134]. Interestingly, Talotta and Robertson discuss the possibility that NETosis may also play a part in the thrombophilic consequence of mRNA vaccines, noting for example that naked RNA, if escaping the confines of the LNP vector and leaked into the bloodstream, can act as a trigger for NETosis [135].

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7.2. Autoimmune Disease

In 2020, prior to the launch of the vaccines, Lyons-Weiler suggested that more than one-third of COVID-19 proteins, the spike protein included, show problematic homology with key proteins in the human immune system. Thus, there is potential for autoimmune reactions against these proteins [8]. Vojdani et al. [9] cited Lyons-Weiler and went further in their testing, performing epitope mapping and applied monoclonal anti-SARS-CoV-2 spike protein and nucleoprotein antibodies to 55 human tissue antigens in vitro. They discovered that SARS-CoV-2 antibodies reacted with 28 of the tissue antigens, thus likely playing "a role in the multi-system disease process of COVID-19" (abstract) and may precipitate or exacerbate autoimmune diseases. Their paper was submitted in October 2020 and they noted historical precedents for vaccines causing autoimmune-related disorders and expressed concern that "an insufficiently vetted vaccine might mean trading freedom from COVID-19 to an autoimmune assault in the future" (p. 2).

Vojdani and colleagues found the 28 antigens had molecular mimicry/shared homology and reactivity with:

> *"Gut and barrier proteins, gastrointestinal system cells, thyroid, nervous system, heart, joint, skin, muscle, mitochondria, and liver diseases".* [9] (p. 5)

Khavinson et al. in a paper titled "Homology between SARS-CoV-2 and human proteins" found more than two dozen heptamers and octamers, homologous with human proteins, some of which fuse to extended lengths along the length of the SARS-CoV-2 spike protein [136]. They noted that given the "structural similarity, a part of the immune response will be directed against the proteins of the host organism" (p.1).

Kelleni reports on the potential risk of vaccines to induce autoimmune diseases such as thrombocytopenia, myocarditis and immune-induced thrombosis and thromboembolism, all potentially fatal and possible causes of sudden death [137].

Most recently, a group from Saudi Arabia has found clear clinical emergence of autoimmune disease after COVID-19 vaccination. A series of exclusively new-onset autoimmune diseases are described after COVID-19 vaccination. The average time between vaccination and new onset disease was 7 days. Cases included vasculitis, neurological disease, systemic lupus erythematosus, inflammatory arthritis, and a case of Sjogren's syndrome [138]. A systematic review by Rodríguez et al. documented 928 cases from 464 published reports of new or relapses of autoimmune disease following COVID-19 vaccination [139]. The authors noted:

> *"The most common disease associated with new-onset events following vaccination were immune thrombocytopenia, myocarditis, and Guillain-Barré syndrome. In contrast, immune thrombocytopenia, psoriasis, IgA nephropathy, and systemic lupus erythematosus were the most common illnesses associated with relapsing episodes".* [139] (abstract)

Since Rodríguez et al.'s review, further peer-reviewed case reports keep appearing. A small sample includes autoimmune dermatological and vascular disorders attributed to the COVID-19 vaccines including IgA pemphigus where the "likely cause" was the AstraZeneca COVID-19 vaccine [140]; autoimmune bullous disease with IgG and IgM autoantibodies against epidermal basement membrane zone after mRNA COVID-19 vaccine [141]; polyarteritis nodosa in a 32-year-old male with "limb pain, fever, pulmonary embolism, and multiple subcutaneous nodules and haematomas" following the COVID-19 vaccine [142].

Autoimmune-related thyroid and renal case reports include that of Graves' disease following the second dose of the Pfizer COVID-19 vaccine [143] and "rapidly progressive IgA nephropathy" following the third dose of the Moderna COVID-19 vaccine [144]. A 78-year-old woman developed IgG4-related sialadenitis and autoimmune pancreatitis following her second Pfizer COVID-19 vaccine, the authors concluded: "the use of mRNA vaccines requires more studies regarding their effects on the human immune system" [145] (p. 1550).

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A 23-year-old woman suffered an ocular autoimmune reaction in the form of granulomatous anterior uveitis following her third Pfizer COVID-19 vaccine 15 days earlier [146]. The authors commented:

> *"Autoimmune reaction in the uveal tissue via molecular mimicry as a result of an adaptive humoral and poly-specific cellular immune response against epitopes may be the potential mechanism for post-vaccine uveitis in this patient"*. (p. 1034)

A case report of hepatitis-associated aplastic anaemia (HAAA) following COVID-19 vaccination in a 15-year-old girl from Japan [147] cited Talotta [148] and postulated:

> *"The pathogenic mechanisms by which mRNA vaccination triggers the development of autoimmune disease remains unclear. mRNA vaccination triggers potential cross-reactivity between antibodies against the spike protein and self-antigens and may also activate immune responses, leading to the production of interferon I and other pro-inflammatory cytokines and chemokines"*. [148] (p. 3)

Repeated antigenic stimulation of immunity, as occurs with the gene-based COVID-19 vaccines' prolonged production of spike proteins, repeated booster doses and recurrent SARS-CoV-2 infections, has seen a rise in IgG4 levels over 480-fold above normal levels [149,150]. This IgG class shift can be associated with serious disease pathology relating to sudden cardiac death [151,152].

It has also been associated with Mikulicz syndrome with systemic involvement, pancreato-hepatobiliary disease, head/neck disease, retroperitoneal fibrosis/aortitis [153–156], as well as lymphadenopathy, sialadenitis, dacryoadenitis, autoimmune pancreatitis, periaortitis/retroperitoneal fibrosis, prostatitis, sclerosing cholangitis, sinusitis, inflammatory pseudotumour, mediastinal fibrosis, skin involvement, sclerosing thyroiditis, hypophysitis, orchitis and colitis [157–160].

These widespread autoimmune and pro-inflammatory effects of spike protein and potentially lipid-nanoparticles illustrate 'spikeopathy' to be another 'great mimicker' akin to tuberculosis, which makes the diagnosis of the underlying aetiology difficult [161].

7.3. Neurological Disorders

The most common group of adverse events reported from the gene-based COVID-19 vaccines to pharmacovigilance databases, including Pfizer's own post-marketing research [162,163] is not cardiovascular but neurological. Neurological symptoms and cognitive deterioration with accelerated neurodegenerative disease are a feature of acute COVID-19, vaccination injuries and to some degree, long COVID [164].

As the lipid-nanoparticle carrier of the mRNA to make spike proteins crosses the blood-brain barrier, direct neurotoxic effects are possible [43]. Loss of blood-brain-barrier (BBB) impermeability has been demonstrated post-COVID-19 vaccination [165], and spike protein S1 can cross the BBB and translocate into the brain parenchyma [166,167]. Cell culture in vitro experiment of brain endothelial cells (a component of the BBB) showed the S1 subunit (RBD) bound to ACE-2 of endothelial cells to traverse the BBB. The S1 subunit correlated with mitochondrial impairment and also entered cell nuclei; the authors postulated that it could disrupt gene expression [168].

7.3.1. Neurovascular and Neuroimmunological Aspects

To some degree, the pathophysiology is likely to be via vascular and autoimmune pathology in the central and peripheral nervous system. The spike protein has been found in in vitro human cell cultures to dysregulate brain vascular pericytes by increasing ACE-2 expression leading to these cells lining the cerebral vasculature and adopting a "contractile and myofibogenic phenotype" as well as a "potent inflammatory response" worsened by hypoxia [169].

In further mouse experiments infusion of spike protein into brains led to TLR4-mediated neuroinflammation and hippocampal microgliosis with associated memory dysfunction. It was noted in humans that cognitive dysfunction post-COVID-19 was more

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likely with a particular TLR4 genotype [170]. This replicated similar mouse experimentation finding that infusion of the S1 subunit (RBD) to mice hippocampus induced cell death and glial activation and the mice exhibited cognitive deficits and anxiety-like behaviour [171].

Tillman et al., (2023) [172] described how the co-expression of the S1 and S2 subunits of the SARS-CoV-2 spike protein, via a helical motif in the spike neck, causes profound down-regulation of functional α7 nAChR, which "is implicated in neuropsychiatric diseases and disrupts the cholinergic anti-inflammatory pathway" (p. 689). German researchers [173] (preprint) autopsied mice that had been intravenously injected with the S1 unit of the spike protein and examined skulls from human autopsies. They found the S1 unit binding to cells in most organs, including ovaries and testes. In the brain they found the presence of S1 associated with differential expression of proteins, following the known expression of ACE-2 receptors, in the skull marrow, meninges and brain parenchyma compared to controls. S1 was seen in diverse regions of the brain, including the channels connecting skull marrow to the meninges (SMC) in both mice and humans. This suggests that in addition to the distribution of the S1 protein through phagocytic cells or direct extravasation from blood vessels, it could use these channels as pathways through the skull. The S1 protein accumulated in the marrow of tibia and femur as well as the spinal cord.

Using human proteomics data, the authors found dysregulation of both complement and coagulation cascades concurring with known coagulopathies following injection. Neutrophil-related pathways were dysregulated, some proteins upregulated, and other proteins downregulated. Among the upregulated ones were proteins associated with inflammation, such as interferon-gamma (IFN-γ) and IFN-γ induced the protein C-X-C motif chemokine ligand 10 (CXCL10). Other protein changes were involved in neutrophil extracellular traps (NETosis) formation, neutrophil degranulation, and phosphatidylinositol 3-kinase/protein kinase B (PI3K-AKT) pathways. In the meninges, upregulated proteins were also associated with platelet activation, signalling, and aggregation. In the brain's cerebral cortex, there were altered levels of ribosomal protein and dysregulation of neurodegeneration pathways. The plasma cytokines levels and plasma IL-6 were increased three days after injecting spike S1.

In addition to experimentally injecting mice with the S1 unit of spike protein, they autopsied 34 patients who died from non-COVID-19 illnesses and found 10 of them had persisting spike proteins in their skulls and noted these might be involved in long COVID symptoms via their spread via the meninges into the brain parenchyma. In summary, the spike protein accumulates in various regions of the brain, persists there even after death, and causes activation of microglia, blocking of α7 nAChR and dysregulation of coagulation- and neutrophil-related pathways as well as upregulation of inflammatory proteins, all of which are connected to memory loss, inflammation of the brain and cell death [173].

Of note SARS-CoV-2 viral infection, especially the earlier variants, can cause loss of smell and thus shows neurotoxicity to the olfactory nerve. Mechanisms of neurotoxic action of the virus and the gene-based COVID-19 vaccines are subject to ongoing research.

Olajide et al. [174] proposed that the SARS-CoV-2 spike glycoprotein induces neuroinflammation via its effects on microglia by:

> *"Induction of neuroinflammation by this protein in the microglia is mediated through activation of NF-κB and p38 MAPK, possibly as a result of TLR4 activation."* [174] (Abstract, p. 445)

> *"Activation of BV-2 microglia by S1 resulted in the increased release of TNF-α, IL-6 and IL-1β, which are hallmarks of neuroinflammation. Activation of neuroinflammatory processes by the spike S1 protein was further confirmed by results showing increased iNOS-mediated production of NO by the protein in microglia. Elevated iNOS/NO has been previously linked to a wide range of CNS disorders including Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy and migraine".* [174] (p. 452–453)

In a cell culture in vitro experiment, spike protein has been implicated in increasing expression of alpha-synuclein (α-Syn), an aggregation-prone protein that is further implicated

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in the pathogenesis of Lewy bodies which are hallmark lesions in brains of patients with Parkinson's Disease, Lewy body dementia and other neurodegenerative diseases [175].

Winkler et al. [176] caused mild respiratory COVID-19 in a mouse model expressing human ACE-2 in trachea and lung by exposure to SARS-CoV-2 intranasally. They detected no SARSCoV-2 in the brain but found signs of neuroinflammation as well as elevated levels of chemokines in cerebrospinal fluid and serum. These changes led to activation of microglia in subcortical and hippocampal white-matter regions. Microglia are commonly referred to as the macrophages of the central nervous system and maintain neuronal networks by removing dendritic spines and synapses during neuronal development. When activated in the mouse model, however, they transitioned to a neurotoxic state which in subcortical white matter led to loss of both oligodendrocyte precursors and mature oligodendrocytes.

Additionally, myelin and myelinated axons decreased for at least 7 weeks after infection, impacting the structure and function of neuronal networks. Demyelinating diseases are some of the known adverse effects of the mRNA injections. In the hippocampus, the activation of microglia was associated with inhibited neurogenesis, which could explain impaired memory formation in patients. The activation of microglia appeared to be mediated by persistently elevated levels of a molecule called C-C motif chemokine 11 (CCL11). CCL11 has been associated with ageing and with inhibition of neurogenesis [177,178], as well as allergies and the recruitment of eosinophils [179].

Fernández-Castañeda et al. [180] investigated the effects of mild respiratory SARS-CoV-2 infection in a mouse model. They detected changes in neuroinflammatory cytokines and chemokines, including the protein CCL11 in the cerebrospinal fluid and serum over a period of 7 weeks after initiation of infection. They also observed changes specific to the brain regions of the subcortical white matter, with microglia activation and subsequent loss of oligodendrocytes, oligodendrocyte-precursor cells, and myelin.

Other authors have found CCL11 protein increases the proportion of CD4 + CD25 + Foxp3+ Treg cells, the expression of CCR3 and Foxp3, and the release of IL2 and TGFβ1 in non-tumour-associated CD4+ T cells via the STAT5 signalling pathway [60]. Regulatory T-cells are immunosuppressive and shift an immune response towards immune tolerance. This concurs with a German group [149] who showed that vaccination with mRNA-LNP complexes causes a general shift in antibodies from inflammatory IgG1 and IgG3 to IgG4, which is associated with Treg cells and immune tolerance and occurs after the second vaccination. The proportion of spike-specific IgG antibodies that were IgG4 rose from 0.04% shortly after the second dose to 19.27% late after the third vaccine dose. Demonstrative of the tolerance effect, a large Cleveland Clinic study of staff has found increasing IgG4 with subsequent booster doses correlates with increased susceptibility to SARS-CoV-2 infection [181].

Chemokines like the eotaxin CCL11 (eotaxin-1) are produced locally from epithelial, mesenchymal, and endothelial cells and are crucial for directing migration and priming of eosinophils or mediator secretion once they reach the airways [182,183]. Eosinophils secrete a range of proinflammatory granule basic proteins that include major basic protein, eosinophilic cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase [184].

Another study looked at the toxin-like domain of the RBG on S1, which binds to α7 nAChR, increasing levels of IL-1b and TNFα in the brain and impaired episodic memory in mice [178]. As discussed above, the blocking of this receptor with the spike protein could cause very high levels of inflammation since it regulates pro-inflammatory cytokine production.

The nAChR is highly expressed in the hippocampus, cortex and several limbic regions, and is involved in cognition, sensory information processing, attention, working memory, and reward pathways. Reduction in α7 in the brain, particularly in the hippocampus, has been reported in Alzheimer's disease patients. In addition to binding the α7 nACHR in a manner similar to a neurotoxin, the spike protein has been demonstrated to be amy-

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loidogenic [185]. It is known that amyloid β (Aβ) peptides of Alzheimer's disease bind to the nAChRs with picomolar affinity, and that snake α-neurotoxins competitively inhibit this [186]. Amyloid has long been known to bind to nAChR receptors, as has spike protein. Computerised in silico modelling of the binding mechanism to amyloid demonstrates similarity to that of snake venom and thus it has been proposed that the interaction with AChR enables the conformational change of amyloid such that it then blocks channel opening and similar to snake venom, at low concentrations initially activates, but then slows and blocks AChR channel function. Low concentrations (picomolar) of soluble Aβ peptides in the brain of healthy people play physiological roles, whereas in Alzheimer's disease, concentrations increase to the nanomole range and trigger the formation of insoluble plaques, a major neuropathologic hallmark of Alzheimer's [187].

7.3.2. Prion Formation and Neurodegenerative Effects

Neurodegenerative diseases such as Alzheimer's, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) are all associated with misfolded proteins that accumulate in plaques and Lewy bodies. These proteins, which are termed amyloidogenic, have also been labelled as "prion-like". Prion-like C-terminal domain of TDP-43 and α-synuclein interact synergistically to generate neurotoxic hybrid fibrils [188]. Thus at least two mechanisms exist by which spike protein, via α7 nAChR, may contribute to neurodegenerative disorders: direct inhibition and secondary amyloidogenic inhibition.

The SARS-CoV-2 spike protein receptor binding domain has prion-like properties, is the only coronavirus with such properties, and has enhanced virion binding affinity to the ACE-2 receptor and thus increased human infectivity and transmissibility [189]. The full spike protein with intact receptor binding domain (RBD) S1 subunit, if it crosses the BBB, therefore has prion-like properties that warrant further research into possible pathogenic effects.

Additionally, the mRNA or adenovectorDNA vaccines include protein sequences that can induce TDP-43 and FUS (proteins involved in RNA/DNA binding and RNA regulation) to aggregate into prion configuration. This could potentially lead to neurodegenerative conditions, such as Alzheimer's disease [190,191]. The connection with neurodegenerative disease is the ability of the spike protein to interact with heparin-binding, amyloid-forming proteins [192]. Though speculative, these considerations are supported by a case report of prion disease due to vaccination [193]. In an in vitro experiment, spike protein was proteolyzed into smaller segments by neutrophil elastase, some of which exhibited amyloidogenic properties [185].

Certain primary sequences in sialoglycoproteins in neurons in the brain, enable these proteins to adopt a range of alternative structures capable of conformational self-replication via templating copies of the same protein. This conversion into what is termed prions typically radically alters the protein function, often becoming transmissible [194]. Prions thus consist of the misfolded, amyloidogenic isoform of prion protein.

Prion diseases, such as Creutzfeldt-Jakob disease (CJD) are fatal neurodegenerative disorders caused as a result of vacuolation and spongiform neuropathologic changes with rapid neurodegeneration and activation of astrocytes and microglia [195]. Neuronal accumulation of misfolded proteins is involved in the pathogenesis of other neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease [196,197]. Infectious prion diseases may also induce nonspecific neurocognitive effects [198].

CJD cases have also been documented post-COVID-19 vaccination; one as early as 5 days post-vaccine [199] and another dying at 6 months [200]. In Australia dementia deaths for January–February 2022 were increased 27.2% above the 2017–2021 baseline (which included the first COVID-19 wave) for the same months, with an ongoing increased dementia mortality rate since then [201,202].

Neurological symptoms are commonly noted post-COVID-19, in 'long Covid' and post mRNA vaccination, raising the possibility of prion involvement.

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Potential mechanisms by which mRNA COVID-19 vaccination could produce prions and trigger neurodegenerative processes include: RNA binding proteins like TAR DNA binding protein (TDP-43) and Fused in Sarcoma (FUS) can be activated to form disease-causing prions; TDP-43 dimers bind UG-rich RNA or TG-rich DNA and are resistant to degradation [203] and binding to these RNA sequences when the proteins are cytoplasmic may cause misfolding leading to prion formation [204]. It is, therefore, concerning that the Pfizer vaccine uses a unique RNA nucleoside 1-methyl-3'-pseudouridylyl (Ψ) and that multiple uracil motifs have been found in the vaccine mRNA [191].

In addition to uracil sequences in the mRNA which may bind proteins and precipitate misfolding, prion-like domains in the RBD of the S1 subunit of the spike protein have been identified in silico. SARS-CoV-2 is the only coronavirus with such a domain, conferring a 10- to 20-fold higher affinity for ACE-2 receptor compared to SARS-CoV-1 in addition to its prion potential [189].

Further, spike protein RBD has several heparin-binding sites that can interact with heparin and heparin-binding amyloid-forming proteins, suggesting that this peptide is prone to act as functional amyloid and form toxic aggregates [205]. The S1 protein has been demonstrated to bind stably to aggregation-prone proteins Aβ, α-synuclein, tau, prions, and TDP-43 and thus could initiate aggregation of these proteins and subsequent neurodegeneration [192].

Researchers also identified a 'glycine zipper' motif within the S1 subunit linked to susceptibility to misfolding and thus prion formation. It is characterised by a pattern of two glycine residues spaced by three intervening amino acids, represented as GxxxG. The GxxxG motif is a common feature of transmembrane proteins, and the glycines play an essential role in cross-linking α-helices in the protein [206]. Prion proteins become toxic when the α-helices misfold as β-sheets, and the protein is then impaired in its ability to enter the membrane [207]. Amyloid-β precursor protein (APP) has four GxxxG motifs: the glycine plays a central role in the misfolding of amyloid-β linked to Alzheimer's disease [208]. The SARS-CoV-2 spike protein is a transmembrane protein that contains five GxxxG motifs in its sequence (see uniprot.org/uniprot/P0DTC2), one within the RBD and thus it is plausible that it could behave as a prion [209].

Another proposed mechanism is the spontaneous induction of prions and prion-like proteins via the effects of Reactive Oxygen Species (ROS). Excess ROS formation and presumed compromised mitochondrial function with cognitive dysfunction is a feature of both acute severe COVID-19, long COVID [198] and spikeopathy. Under situations of stress, TDP-43, FUS, and other RNA-binding proteins translocate from the nucleus to the cytoplasm and associate with stress granules [210,211]. When the stress dissipates, the stress granules disaggregate, and the RNA-binding proteins return to the nucleus. Enhanced environmental stress with excess ROS (for example, exposure to toxins, traumatic injury, viral infection) could cause loss of normative proteosome functioning and restoration of normal conformation, increasing the likelihood for RNA-binding proteins to inappropriately aggregate [212,213].

Similar is the effect of neuroinflammation, particularly astrocyte activation. Animal studies demonstrate the accelerated transition from pre-clinical to clinical stages of prion disease in settings of co-infection, with neuroinflammation, elevated pro-inflammatory cytokines, and enhanced activation of A1 reactive astrocytes [214]. TNF and C1q from activated microglia further activate A1 astrocytes [215] that are thought to be neurotoxic by mediating neuronal damage and serving as foci for prion propagation [216]. Non-neutralising antibodies after vaccination against spike protein peptides in mice have also been demonstrated to activate glial cells and astrocytes [217], consistent with this proposed mechanism of activated astrocytes, prion formation and cognitive dysfunction.

Seneff and colleagues, in an extensive narrative review of potential pathophysiological mechanisms of the spike protein in neurodegenerative diseases, describe "the spike protein's contributions, via its prion-like properties, to neuroinflammation and neurodegenerative diseases; to clotting disorders within the vasculature; to further disease risk due

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to suppressed prion protein regulation in the context of widely prevalent insulin resistance" and "explain why these prion-like characteristics are more relevant to vaccine-related mRNA-induced spike proteins than natural infection with SARS-CoV-2" [29] (abstract p.1). Key findings they reviewed included:

- Spike-induced endotheliitis disturbs the blood-brain barrier and exacerbates Alzheimer's disease via the interaction of the spike protein with amyloid β or hyperphosphorylated tau [164].
- Studies have shown that autoantibodies in the globular C-terminal domain can cause an aggressive form of Creutzfeldt Jakob Disease (CJD) by interfering with the transport of the prion protein into the endoplasmic reticulum [218].
- The spike protein itself, which is also an RNA-binding protein, may facilitate the reverse transcription of spike protein mRNA into DNA, mediated by LINE-1. Neurons actively express LINE-1 in association with neurodegenerative diseases [219,220].
- Cells that take up mRNA from the lipid nanoparticles in mRNA vaccines package up some of the mRNAs, together with the ionizable cationic lipids, into small lipid particles released as exosomes that can be shipped around the body [59,221]. For example, an immune cell in the spleen could ship intact mRNA code for the spike protein to the brain along the vagus nerve, whereupon a neuron or microglial cell could begin to synthesise spike protein.
- Micro RNA (miRNA) are small bits of active RNA code, capable of active control of cell function, including embryogenesis and apoptosis. miR-146a is found in exosomes released by immune cells and is on the list of miRNAs whose expression levels are altered in association with COVID-19 [222]. Exosomes that reach the brain stem deliver not only spike protein but potentially also intact mRNA and miRNA molecules, including miR-146a which is associated with both viral infection and prion diseases in the brain [223,224].
- Spike protein itself induces sharp TNF-α upregulation and causes cognitive issues which could indicate that it upregulates prion protein (PrP) expression in the brain. An increase in prion glycoprotein (PrP^C) numbers can lead to prion conformation misfolding and generate prions and prion-related diseases [225,226].
- Spike protein has been shown to induce senescence in transfected cells [227]. Further, it has been proposed that the mRNA COVID-19 vaccines can induce premature senescence via syncytia formation in exposed immune cells, due primarily to their lipid content (ionizable lipids, cholesterol and the phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)) [228]. In vitro molecular studies show that macromolecular crowding can facilitate the conversion of native PrP into the neurotoxic soluble β oligomer configuration [229].

7.3.3. Dysautonomia

Another key feature of COVID-19 infection or vaccination is dysautonomia (DSN), a neurological disorder of autonomic nervous system (ANS) function, with widespread effects on the heart, bladder, sweat glands, pupils, intestines, and other autonomic systems. Both the sympathetic (SNS) and parasympathetic nervous system (PSNS) are affected, with the potential for a sympathetic storm and abnormal autonomic responses that include excess sweating, exercise intolerance, insomnia, resting tachycardia, postural hypotension, fatigue, urinary and bowel dysfunction. The neuroinvasive nature of SARS-CoV-2 results in neurological complications such as DSN [96] and suggests either direct autonomic neuronal injury or indirect immune-mediated mechanisms, as would occur with α7 nAChR inhibition. Inhibition of nAChR by SARS-CoV-2 may lead to the inhibition of PSNS and exaggeration of SNS with subsequent progression of cytokine storm [94].

Another neurological dysfunction related to COVID-19 is anosmia, a common symptom of COVID-19 and also prodromal for Parkinson's disease. The olfactory bulb has a rich network of nAChRs, and α7 nAChRs may also be expressed on the olfactory axon terminals. This may facilitate CNS infection through anterograde transport along the olfactory nerve.

This is Exhibit " J " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

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PR21-0225617

OPEN SOURCE INVESTIGATION REPORT
(OFFICER NOTES INCLUDED)

Prepared by Detective [redacted]
Cyber Support Services
December 10, 2021

Disclaimer

Any website related hyperlinks (URLs) contained in this document are not viewable from an offline location. In order to access the link, Internet connectivity is required. The links are only listed as a record of where the author of this report obtained the information, media and associated comments.

This report contains screen captures conducted by the author using SnagIt software. The screen captures are true representations of how the Internet based content appeared on the author's computer screen or mobile phone at the time the content was captured. It is unknown if visiting these URLs at a later time will results in the same matter being viewed as online content can be deleted or altered at anytime by the owner of that content. There were no alterations or modifications to the screen captures except as noted by the author.

Depending on the method of capture, the filename of the screen capture will be the date and time of the capture followed by a brief description of what the screen shot is of [2019-10-21_8-32-50-screenshot_descriptor]. The filename of a downloaded video will be the original file name obtained from the source.

The original screen captures were archived by the author in their original format and are available to the Court should they be required as evidence.

[redacted]

I, Detective Constable Turczak #3321 of the Peel Regional Police am a member of the Cyber Support Services (CSS) unit since July 21, 2019.

On December 9, 2021, at approximately 2:18pm, CSS unit received a request from Constable Bird #3115 requesting a Twitter history of two accounts for a period of May 15 – November 30, 2021.

Below is the original officer request to Cyber Support Services unit.

Disclaimer Acknowledged: Yes
Occurrence Number: PR210225617
Request Date: Thursday, December 09, 2021
Requested By: Bird, Jeff
Requested By Badge #: 3115
Lead Investigator/OIC: Bird, Jeff
Lead Investigator/OIC Badge #: 3115
Requesting Area: Fraud Bureau
Phone Extension: 3342
Type of Occurrence: ID Fraud
Incident Information: On May 28th 2021 unknown parties created a website in the name of the victim in order to ruin, defame and tarnish his character
What information are you looking for ?: Seeking Twitter history of the suspects between the time period of May 15th to Nov 30th 2021

Glen PYLE @glenpyle
Scott WEESE @weese_scott

Victim Information: Byram BRIDLE
Victim Location: Guelph Ontario
Suspect Information: Glen PYLE, Scott WEESE
Suspect Location: U/K

Software Used

The following software was used to view, capture and/or download data contained in this report.

Software	Version
Google Chrome (web browser)	96.0.46664.93
TechSmith SnagIT	2019.1.6

Officer notes and Findings

December 9, 2021

At 3:54pm, I review the CSS request that was submitted by Constable Bird #3115 as well as PRP general report.

Utilizing the website Twitter.com, I go directly to the account that was provided in the CSS request (glenpyle) and take a screenshot (Image 1) of the account and obtain details summarized below.

Twitter Account Details

- Name: **Glen PYLE**
- Username: **glenpyle**
- User ID: **408776066**
- Profile URL: **https://twitter.com/glenpyle**

Source: https://twitter.com/glenpyle

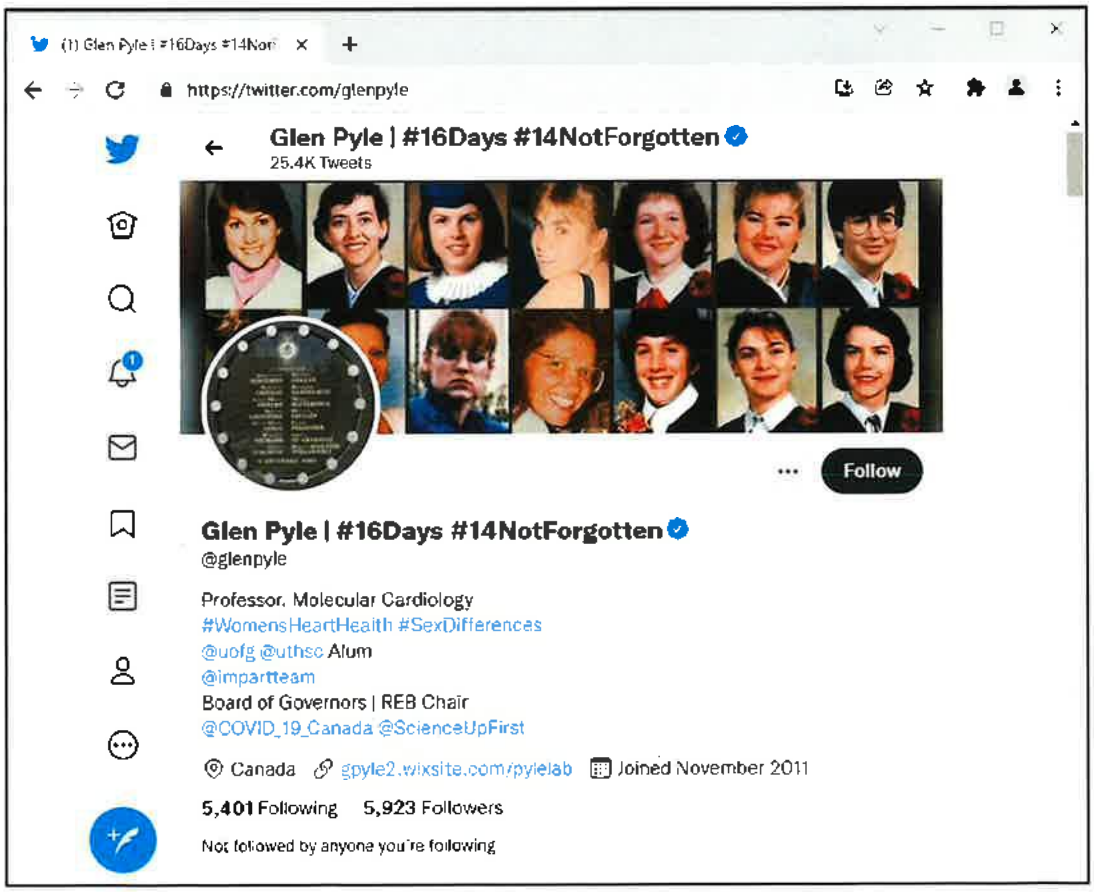


Image 1. Screen captured on December 9, 2021 at 4:09pm

I proceed the same way to obtain information on the second Twitter account (weese_scott). I take a screenshot (Image 2) of the account and obtain details summarized below

Twitter Account Details

- Name: **Scott WEESE**
- Username: **weese_scott**
- User ID: **1141022739421126658**
- Profile URL: **https://twitter.com/weese_scott**

Source: https://twitter.com/weese_scott

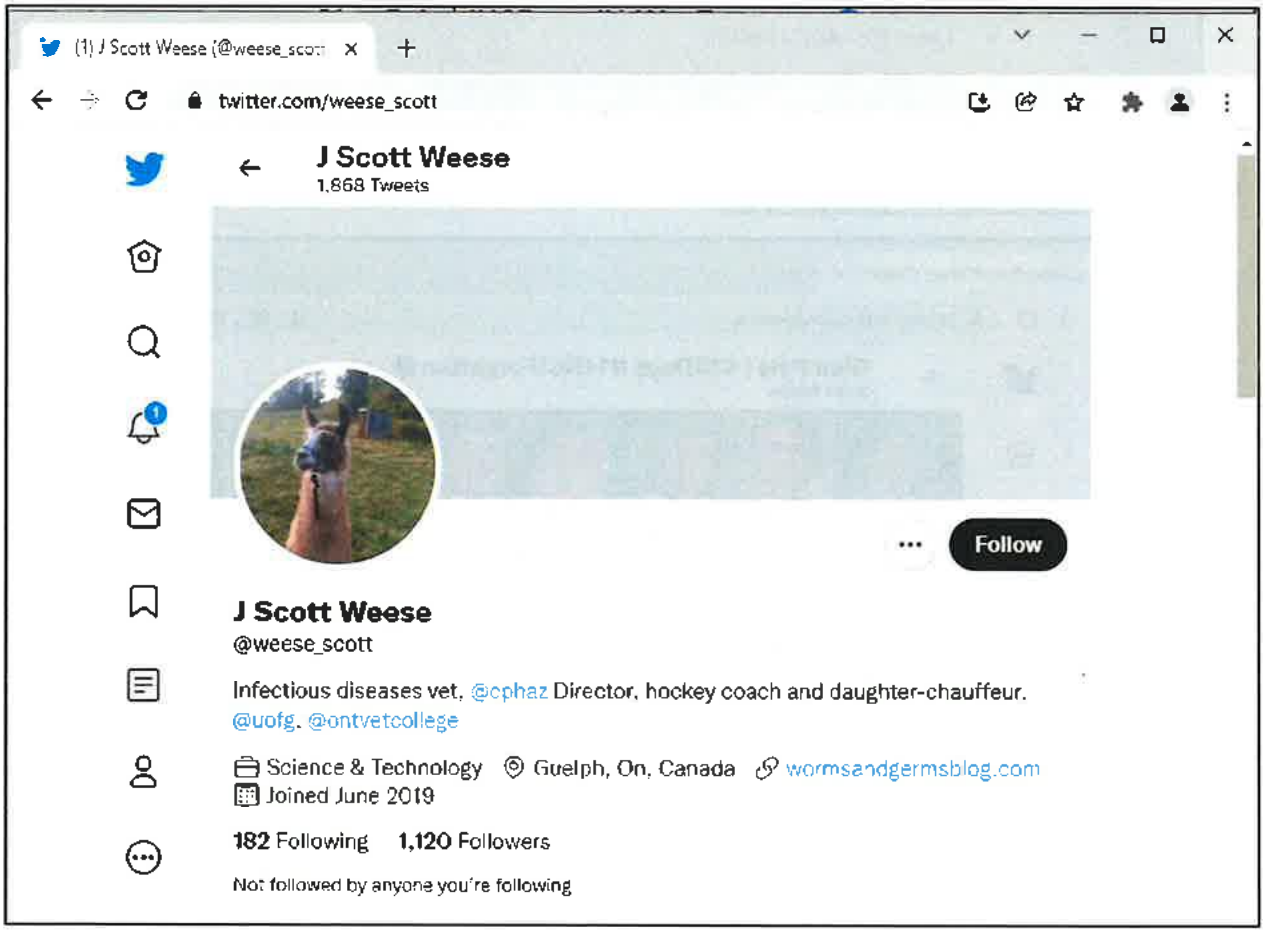
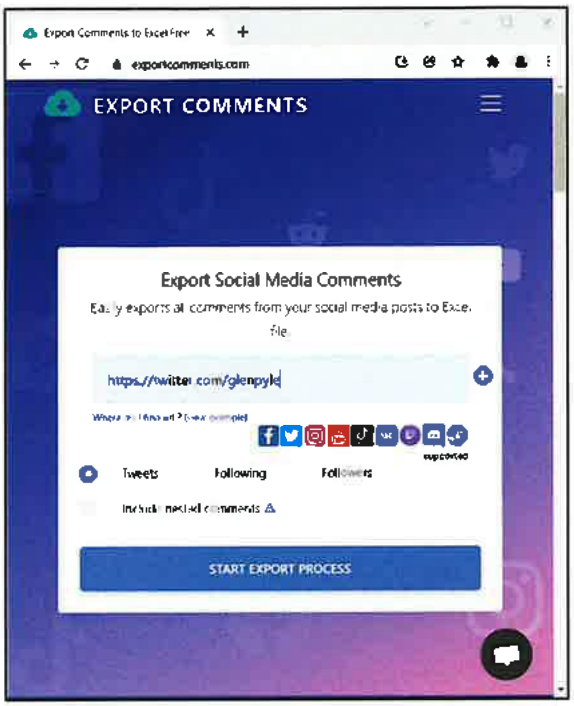


Image 2. Screen captured on December 9, 2021 at 4:10pm

At 4:57pm, I go to exportcomments.com website, enter in the URL of each Twitter account (shown below) in the export box and export tweets posted by each Twitter account.



I then download the Excel files and filter by requested date range of May 15 – November30, 2021. Below are links to Excel files containing filtered tweet history for each Twitter account.

- Click HERE for **glenpyle**
- Click HERE for **weese_scott**

Lastly, I examine both Excel files and check that the data exported matches what I observe on the Twitter website for each account. Random tweets were selected from each Excel file and located on the Twitter accounts without any discrepancies (date and content match). Note that "nested comments" which are comments within comments are not included in either export as exportcomments.com was unable to export those for technical reasons.

ONTARIO COURT OF JUSTICE
(Central West Region)

INFORMATION AND AFFIDAVIT

IN THE MATTER OF an application for a Production Order for transcripts held at North Shore HR Consultant Inc. pursuant to section 487.014 of the Criminal Code

IN THE MATTER OF an application for a Production Order for subscriber information of Alexpierson.ca held at Go Get Canada Domain Registrar Ltd pursuant to section 487.014 of the Criminal Code

INFORMATION

I, [redacted] of the Region of Peel, in the Province of Ontario, am a Peace Officer employed by the Peel Regional Police and hold the rank of Constable. I have personal knowledge of the facts hereinafter deposed to except where same are stated to be based upon information and belief.

I am aware of my obligations as an affiant under R v Araju, [2000] 2 SCR 992: namely, that I am obliged to submit an affidavit that sets out the facts fully, frankly and fairly for an authorizing judge or justice in order that he or she can make an assessment of whether these rise to the standard required in the legal test for the authorization.

I MAKE OATH AND SAY AS FOLLOWS:

THAT there are reasonable grounds to believe that an offence against the Criminal Code has been committed, namely:

That Scott WEESE on June 23rd 2021 at the University of Guelph did fraudulently personate Alex PIERSON with the intent to cause disadvantage to Alex PIERSON contrary to section 403(1)(C) of the Criminal Code of Canada.

And furthermore that

That Scott WEESE et al, knowing that Dr Byram BRIDLE is harassed or being reckless as to whether Dr Byram BRIDLE is harassed did without lawful authority repeatedly communicate directly or indirectly with Dr Byram BRIDLE thereby causing Dr Byram BRIDLE to reasonably, in all circumstances, fear for his safety. Contrary to Section 264 (2) (b) of the Criminal Code of Canada.

THAT IT IS PROPOSED THAT North Shore HR Consulting Inc. located at 521 George St N, Peterborough, ON produce the following:

- All transcripts of the witness recordings made in relation to the University of Guelph's investigation of Dr Byram Bridle.

And furthermore

THAT IT IS PROPOSED THAT Go Get Canada Domain Registrar Ltd (namecheap.com) located at 4600 East Washington Street Suite 305. Phoenix, AZ 85034. USA produce the following:

- Detailed account information to include but not limited to first name, last name, date of birth, address, email address, phone number, registration information, IP addresses used to create/maintain/access the account and payment details for domain name **Alexpierson.ca**

IT IS PROPOSED THAT the execution of this Production order will take place on the **4th of May 2022** when Detective Constable [redacted] or his designate by electronic mail deliver the production order to Nick Duley nick@northshorehr.ca of North Shore HR Consulting Inc. and to Legal@namecheap.com for Namecheap.com

IT IS FURTHER PROPOSED THAT the requested records be produced within 30 business days of the execution of the Production Order

IT IS FURTHER PROPOSED THAT upon completion of the request that Constable Bird #3115, be advised via telephone (905)453-2121 ext. 3342 or email at 3115@peelpolice.ca and that the records be sent via courier or electronically 3115@peelpolice.ca to associated to the address of 180 Derry Rd, Mississauga, Ont L5T 2Y5.

THAT the facts being relied upon to justify my belief that the person(s) who is/are the subject of this order has possession or control of the requested records together with the particulars of the offence are as follows

I, [redacted] am a Police Officer with the Peel Regional Police and have been so employed since August 2006. I have experience with the Criminal Investigation Bureau, and the Homicide and Missing Persons Bureau, Neighborhood Policing Unit and Uniform Patrol. I am currently assigned to the Fraud Bureau. As a member of the Fraud Bureau, it is my responsibility to investigate Fraud related offences occurring in the Region of Peel and elsewhere. **I believe that the contents of this affidavit are true.**

Investigative Sources

In this Information, I will be referring to several acronyms for computerized police information networks or police and government agencies I have become familiar with because of my police experience. The following definitions will apply to these acronyms:

Twitter- is an American microblogging and social networking service on which users post and interact with messages known as "tweets". Registered users can post, like, and retweet tweets, but unregistered users can only read those that are publicly available. Users interact with Twitter through browser or mobile frontend software, or programmatically via its APIs.

SUMMARY

On June 30, 2021, the complainant, Dr. Byram Bridle, on the counsel of his lawyer, attended the Peel Regional Police Fraud Bureau, located at 180 Derry Road East, in the city of Mississauga, in order to file a report based upon Identity Fraud/impersonation, which has caused ongoing negative ramifications on his medical career and personal life. As a result of this appointment, the following information was obtained:

For the past fourteen years, Dr. Bridle, has been employed as an Associate Professor of Viral Immunology at the University of Guelph, in Ontario, Canada. Dr. Bridle is a tenured faculty member, who directs a team of eight scientists in research and medical grant submissions.

As a Virologist, Dr. Bridle, has a high degree of expertise, with regard to overall vaccine application used to combat community illness. Due to his knowledge base and experience level, he has recently been summoned to speak at numerous media events concerning the response to the pandemic. Specifically, on these platforms he has outlined his general concerns with adverse effects of the Covid vaccine, especially in young people. It should be noted, Dr. Bridle, has only offered his medical opinion, of which is supported by current peer-reviewed scientific documents, as well as other physicians. Moreover, Dr. Bridle, has stated he is in favour of vaccines, and other well established medical interventions, however, he also advocates for a more balanced approach, further data collection and open debate of the pandemic policies in place.

Due to, Dr. Bridles's, recent speaking engagements, he has amassed a following as a scientist and public figure. As of recent, a website in the name of "ByramBridle.com" and other unauthorized online profiles (twitter "Not Dr. Byram Bridle") were generated by unknown persons(s) with the intent of publically discrediting and impersonating Dr. Bridle. These sites have utilized Dr. Bridle's good name and professional standing to damage and cause disadvantage to career and personal life. As a result, this has had a detrimental effect on his scientific research, funding and overall well-being. For these reasons, Dr. Bridle, believes he is being unfairly targeted, due to his forthright approach to the pandemic.

Through further investigation by a US based cyber company employed by Dr. Bridle, it has been revealed that the defamatory websites (Byrambridle.com) are operating out of a system (withheldforprivacy.com) based in Iceland.

The introduction and promotion of the "byrambridle.com" was a conscious endeavour to dismantle the reputation of Dr Bridle, which left him vulnerable in securing much needed funding for further research, his research teams survival and subsequently his family life balance.

Since the introduction of the website Byrambridle.com, Dr. Byram Bridle's reputation as a credible immunologist has been openly questioned which in turn has caused many government-funding organizations to distance themselves from him and his work thus causing a distinct disadvantage to his career.

It is the writer's belief that WEESE being a colleague at the University would have knowledge on how to tarnish one in a similar position, being BRIDLE, by directly targeting their reputation, causing immediate professional and personal harm in addition to monetary loss.

On July 23rd 2021, University of Guelph contacted North Shore HR consulting Inc. , a firm to conduct an Investigation into an on campus incident on July 21st 2021.

On November 30th 2021 North Shore found BRIDLE to be in violation of Workplace Harassment Prevention Policy Article 42 of the Collective Agreement

On September 22nd 2021 Ontario Justice of the Peace JANAND reviewed and authorized the production order seeking email records from University of Guelph, namely IP addresses for the time of May 27th to June 2nd 2021.

On October 12 2021, Ontario Justice of the Peace BUTANY-GOYAL granted authorization of emails related to gpyle@uoguelph.ca. from the University of Guelph encompassing the time period of May 27th to June 2nd 2021

On November 9th, the writer came in receipt of the emails, reviewed and learned that WEESE played a role in setting up the website and promoting an ongoing character assault against BRIDLE.

It is the writer belief that WEESE, PYLE and others colluded to target and defame, discredit and smear BRIDLE and Alex PIERSON in order to ruin their reputation and careers due to different views in regards to the COVID-19.

It should be noted, this application is not in reference to valid or invalid scientific hypothesis but rather a deliberate course of action commenced with the intent to utilize Dr. Bridle's identity to discredit his professional standing in the scientific community. Therefore, I believe the offence of Identity Fraud contrary to section 403 (1) C of the C.C. has materialized.

BACKGROUND TO THE INVESTIGATION

1) On June 30 2021, Dr Bridle attended 180 Derry Road for a video interview regarding the report peel Police report PR2102256170. I made notes during the interview and learned the following:

    a. BRIDLE is a viral Immunologist with University of Guelph.

    b. BRDILES expertise is in the field of vaccines i.e. (Covid-19).

    c. BRIDLE submits approximately 10 proposals a year to private and government organizations seeking funding for his research and is successful on 2 to 3. Monetary grants range from thousands to hundreds of thousands of dollars.

d. Funding is crucial for the day to day operational of the research lab and personnel.

e. BRIDLE states that funding criteria is based off three specific points
   i. premise of the paper
   ii. the school/research team
   iii. The reputation of the author

f. BRIDLE states that, "reputation" is a very important criteria in this matter.

g. Months prior to May 27 2021 BRIDLE had appeared as an expert on multiple media outlets in Canada and throughout the US of A.

h. BRIDLE has received funding for the research of Covid-19 vaccine by federal and provincial governments.

i. On May 27 2021, BRIDLE attended the radio show by Alex PEIRSON and BRIDLE stated that he has comes across evidence regarding the vaccine distribution throughout the body and therefore young people and females should not be taking the vaccine until further studies are completed.

j. The Alex Pierson radio show was 8 minutes in duration.

k. Due to time constraints was not asked what evidence nor to further explain his findings.

l. BRIDLE was in possession of PFZIER documents via Freedom of Information explaining the bio-distribution of the vaccine on young male/females.

m. On May 28 or 29 2021, learned about the website Byrambridle.com defaming his character and wrongly misrepresenting his science.

n. BRIDLE is aware that colleagues Dr PYLE and Dr WEESE have been openly against him.

o. BRIDLE has no social media and therefore is not up to date on what is being said and relies on others to share information

p. BRDILE is aware of David FISMAN (@dfisman) promoting the website Byrambridle.com.

q. BRIDLE is extremely bothered how FISMAN tweeted out that BRIDLE'S parents refused to get the vaccine. This is private information and FISMAN's tweet is unprofessional.

r. BRIDLE is aware of the twitter handle "@Notbyrambridle"

s. BRIDLE has advised that the Terry Fox foundation has expressed concern about the recent social media posting and have cautiously distanced themselves from him and his research

t. BRIDLE advises that the Terry Fox foundation have consistently provided funding to him and his research for many years.

u. BRIDLE is under lots of stress as he doesn't understand why his colleagues are unable to civilly debate his research and recent findings.

v. BRIDLE has stated that debates are very common and encourages that scientist debate/discuss their research with others.

w. BRIDLE is concerned for his welfare, career and the overall well-being of his family as they all are being unfairly targeted.

2) On May 1 2021, Peel Police Cyber unit conducted a search on the website Byrambridle.com. I made notes and learned the following:

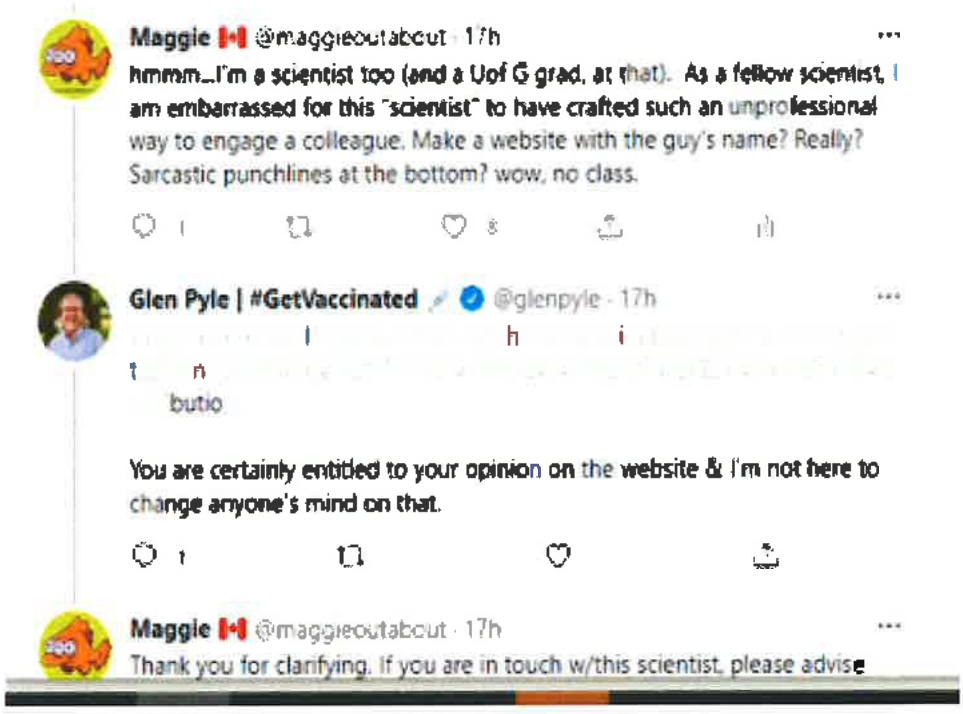
a. The website domain is associated to the company Withheldforprivacy.com based in Iceland.
b. Withheldforprivacy.com does not hold any information of its subscribers and instead refer them to the domain registrar of Namecheap.com
c. Namecheap.com have stated that all the information is private and will consult with the subscriber if served with judicial authorization before/if they choose to reply.

3) On May 28 2021, a website by the name of ByramBridle.com was posted and promoted on the social media by FISMAN via Twitter handle @DFisman. It shall be noted, Byram Bridle did not authorize this site nor did he provide consent to the websites operation.

4) On the same above thread a party by the name of @Maggieoutabout replies to @DFISMAN questioning the validity of the Byrambridle.com:

5) In response to @maggieoutabout Dr Glen Pyle using the twitter name @glenpyle replies:

6) At this point, @glenpyle and @maggieoutabout further engage in a back and forth on Twitter:



7) On July 6th 2021 I spoke with [redacted] who is @Maggieoutabout and reviewed her tweets and I learned the following:

a. She is a University of Guelph Grad and studied Toxicology.

b. Knows Dr BRIDLE via the Canadian Covid Care Alliance.

c. Observed the tweet made by FISMAN introducing the Byrambridle.com website.

d. Created the twitter handle @Maggieoutabout.

e. Believed the actions of the fake BRIDLE account have vilified the character of BRIDLE.

f. Believes that Dr PYLE may have knowledge of the originator of the fraudulent BRIDLE account.

g. And shared the following letter submitted by University of Guelph staff Dr PYLE and Dr WEESE.

i. _____

8) On August 25th 2021 I reviewed emails from BRIDLE (bbridle@uoguelph.ca) dated May 28th 2021 sent to University of Guelph personnel advising of his knowledge about the website Byrambridle.com.

a. "It has been brought to my attention that a smear campaign has been launched against me because I answered a question about COVID-19 vaccines that was posed to me by a radio show host. Everything I said is backed up by peer-reviewed scientific articles. Of course, however, I had no way to show these references in the context of a radio interview. FYI, this libelous website was set-up... http://byrambridle.com/"

". Of incredible concern was this tweet that was forwarded to me...

https://twitter.com/glenpyle/status/1398810510234206210

b. I demand to know what Glen's role is in this. Did he condone this? Was he part of this? He certainly knows who made the website and did not speak out

against it. The website also uses an article that Glen wrote to try to slam me. I will wait to see if this can be handled internally.

9) On August 25 2021, I reviewed emails with BRIDLE sent to University of Guelph personnel and advising of his knowledge about the website Byrambridle.com.

   a. "I just received this... https://twitter.com/DFisman/status/1398756044004802565 Glen Pyle is all over this. He seems to be loving the bashing I am taking. He even states embarrassment when correcting someone to note that I am from OVC, not OAC. Is David Fisman the one who made the website?"

10) On August 25th 2021, Dr Bridle (bbridle@uoguelph.ca) shared email communication with himself and Dr PYLE (gpyle@uoguelph.ca). These emails are in response of BRIDLE learning of the website in his name defaming his character. I have taken excerpts from the email and noted them below.

   a. "Can you please explain your role in the smear campaign against me? Who is the scientist that made the website to slander me? I need this information now! ...or are you going to continue to revel in the harm being caused to a colleague that you are embarrassed about? If I do not receive a reply from you by noon on Monday, I will contact the police to see if they can get the information from you " sent on: Sunday, May 30, 2021 4:10 AM

   b. " I was just sent even more tweets from you that slam my interview. This is absolutely disgusting. You do realize don't you that I could not possibly show the scientific basis for my statements on a radio show, right? Since you are 'just down the hall from me' why don't you drop by sometime for a real scientific debate. You are obviously the local expert on COVID-19 vaccines, not me. If you have issues, why not talk to me directly? Why, instead, are you slamming me behind my back and in public forums?" 2021-05-30 4:24 AM (GMT-05:00)

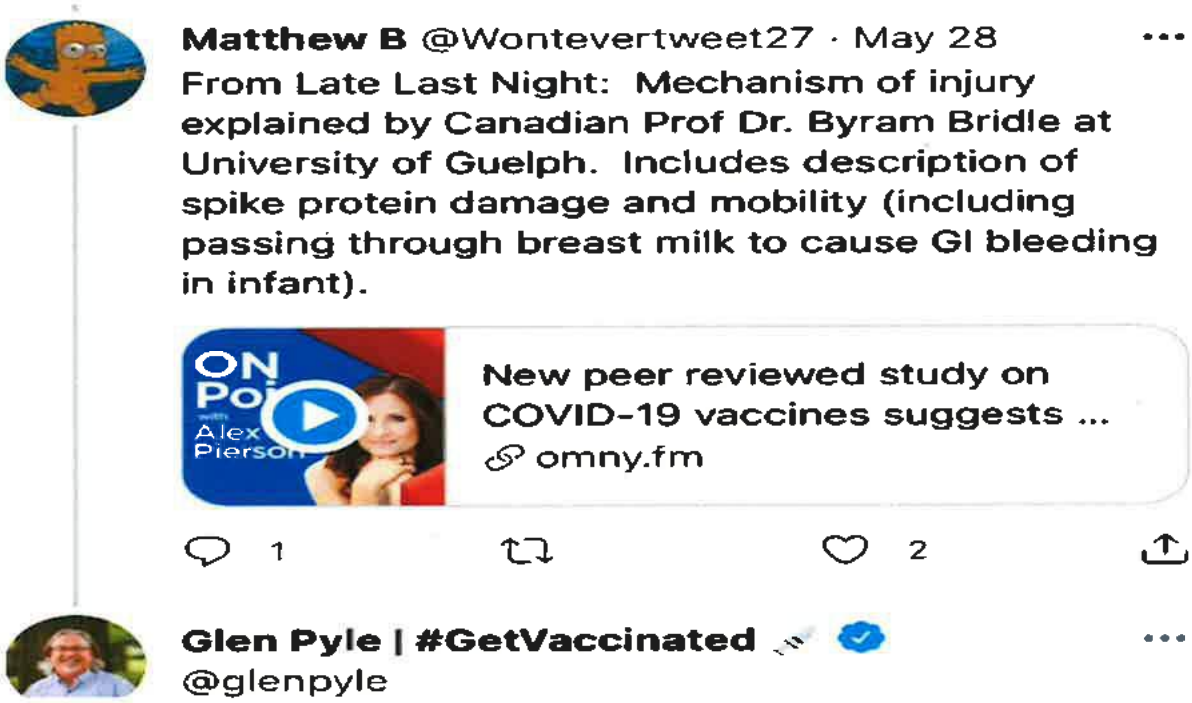
11) At this time, PYLE (gpyle@uoguelph.ca responds to BRIDLE (bbridle@uoguelph.ca with the following email sent on May 30th 2021 at 11am

a. "I am not slamming you behind your back. As you note, it is a public forum and I am presenting data from studies."

At 1pm, PYLE gpyle@uoguelph.ca pens a lengthy letter to BRIDLE bbridle@uoguelph.ca explaining his role and disassociated himself of the website:

b. "Second, I don't know who made the website. You've mentioned you are not on social media so you may not be aware that some people chose to remain anonymous. The website was flagged to me and that was the info I was given. Others tried to tag it to Dr Fisman and someone mentioned a hacker. I simply clarified that my understanding was this was not the case. I think you can appreciate that had someone been mistakenly linked to material they didn't create, that could create stress for them"

12) On September 01st 2021, I captured post on twitter of PYLE using his Twitter handle @glenplye posting a number of tweets calling BRIDLE assertions as "misinformation" in direct response to the tweet promoted the link to the Alex PIERSON radio show: dated on May 28 2021:



Glen Pyle | #GetVaccinated
@glenpyle

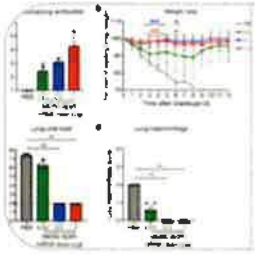
Replying to @Wontevertweet27 @Aly_Meek and @WesternU

No, this is a hypothesis, and nothing is reviewed or published. A few points:

1. Claims the first access to biodistribution studies. In fact EMA reported these data last year & updated in Feb 2021.

ROGERS 4:51 PM mobile.twitter.com 73%

2. Spike protein causes damage. It does. But the vaccine spike protein is engineered to stay in the pre-fusion form (nature.com/articles/s4158...). This prevents it from fully binding.



SARS-CoV-2 mRNA vaccine design enabled by prototype ...
nature.com

1 1 10

Glen Pyle | #GetVaccinated · May 28

3. Spike protein gets in the blood. In small amounts yes. Concentration around 0.3 pM. Kd of ACE2 binding is ~1.5 nM.

This means the concentration in blood is 5-fold less than needed to bind ACE2. And that doesn't even consider engineering to limit binding.

13) On August 25th 2021, I reviewed emails forwarded by BRIDLE regarding tweets distributed by @Dfisman and linked to @glenplye dated on May 30 2021:

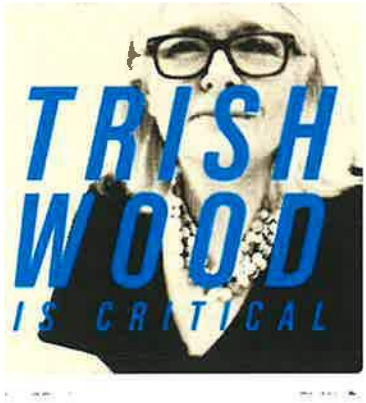
a.

14) On Sept 2 2021, I reviewed emails sent by BRIDLE bbridle@uoguelph.ca capturing his communication with PYLE gpyle@uoguelph.ca and University of Guelph staff. On June 22 2021, BRIDLE emails staff clarifying his position:

a. BRIDLE encourages them to read his report "Children and Covid-19 Vaccine" explaining his concerns with Children receiving experimental covid-19 vaccines.
b. References that Dr Robert MALONE, the inventor of the mRNA vaccine technology clearly supports BRIDLE interpretations of the science is 100% and identifies a link supporting it:

https://podcasts.apple.com/ng/podcast/mrna-inventor-robert-malone-backs-up-byram-bridle-on/id1513237951?i=1000526212312

(When you click on the link, you get taken to this webpage)



mRNA TECH INVENTOR ROBERT MALONE BACKS UP PROF. BYRAM BRIDLE

Trish Wood is Critical

News Commentary

Listen on Apple Podcasts ↗

In an explosive interview, impeccably credentialed Malone and Bridle go after critics trying to silence anyone who raises issues about vaccine safety. They explore spike proteins, dosing errors, the coercion of children, the attack on podcaster Bret Weinstein, and the absence of risk-benefit ratios — the bedrock of ethical medicine. Also on the episode: Canadian docs Donald Welsh and Jean Marc Benoit who are collecting information and boldly speaking out.

c. BRDILE references a link from the website of the World Health Organization (WHO) corroborated this concerns with Children and vaccination"

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice

" Children should not be vaccinated for the moment." ...because "Children and adolescents tend to have milder disease compared to adults, so unless they are part of a group at higher risk of severe COVID-19, it is less urgent to vaccinate them than older people, those with chronic health conditions and health workers. More evidence is needed on the use of the different COVID-

19 vaccines in children to be able to make general recommendations on vaccinating children against COVID-19."

d. BRIDLE addresses the allegations against him via the website Byrambridle.com and provides a link in which they can hear his response:

https://www.facebook.com/WhatsUpCanadians/videos/206400258023039

e. BRIDLE makes a passionate plea for University of Guelph Faculty et al via email:

"If anyone remains intent upon trying to defame me and harm my career, I kindly ask, out of respect, that you try to do so in a public forum where you and I can openly discuss the science in front of the public. We can get a moderator to facilitate the discussion. If not willing to do this, please refrain from disrespectful, cowardly behaviours. Definitely don't attempt to slander me if you are unwilling to invest the time into investigating the four sources of information that I listed above."

15) On September 2 2021, I reviewed the Guelph Police report 210721-437 authored by Sgt. Larry O'CONNELL of University Guelph Police. I made notes and learned the following:

a. On July 21 2021, at approximately 3:15pm Sgt. O'CONNELL responded to an allegation of harassment by PYLE against BRIDLE who claimed that BRIDLE confronted him in the parking lot yelling.

b. On July 22 2021 O'CONNELL responded to a complaint by Dr BIENZLE against BRIDLE because of an email received with the attachment of "Children and Covid-19 Vaccine".

c. On the same date, Associate Professor Andrew PEREGRINE and BIENZLE were confronted by BRIDLE in the hallway wherein BRIDLE was "yelling and using unprofessional language" and due to the actions of BRDILE, they contacted campus Police.

d. O'CONNEL took a formal report capturing the sides of all parties involved and advised that no safety issues were at jeopardy and that upon the direction of Guelph administration, an external company (North Shore investigations) will review the matter.

16) On September 7 2021, I reviewed a letter, which was provided to me by [redacted] and disseminated by PYLE via his twitter handle @glenpyle on July 5 2021. I took an excerpt from the letter which summarizes the concerns of a selected few of the University of Guelph faculty towards BRIDLE:

https://twitter.com/glenpyle/status/1412170097897189383?s=20

> **Therefore, we wish to state publicly that as scientists, faculty, and/or staff of the University of Guelph we stand firmly against the continued spread of factually incorrect and misleading information that is being disseminated by Dr. Bridle. We have confidence that the SARS-CoV-2 vaccines approved for use in Canada are safe and effective, and we wish to reassure the public that as members of the University of Guelph community we fully support evidence-based public health, which includes vaccination against COVID-19.**

17) On September 2 2021 I spoke to Jeremy EDWARDS who had previously sent an email to BRIDLE on June 6th 2021 warning of the website Byrambridle.com and noted a few iterations that may lead one to believe that PYLE had posted the website and/or knew who did. I made notes and learned the following.

a. The Byrambridle.com website was first posted on May 29th 2021 (https://web.archive.org/web/20210529111831/http://byrambridle.com/) and under the heading "General Claims about the Spike Protein" the following paragraph was written:

> "Had he walked down the hall, and consulted with his colleagues **who have written extensively on this topic**, they could tell him that the data shows no significant amount of the vaccine enters the circulation"

(The area in bold is a link to an article written by Dr PYLE)

https://web.archive.org/web/20210512220241/https://www.science20.com/w_glen_pyle/the_thorny_problem_of_covid19_vaccines_and_spike_proteins-254373

The Thorny Problem Of COVID-19 Vaccines And Spike Proteins

By W. Glen Pyle | May 12th 2021 05:26 AM | Print | E-mail

b. Under the heading " Who is Alex Pierson" the unknown author writes "I don't know much about Alex".

c. On June 1st 2021 the Byrambridle.com website (https://web.archive.org/web/20210601005022/http://byrambridle.com/) was changed and the paragraph and PYLE link is removed for unknown reasons.

d. The 1st person singular is removed from the website.

e. When comparing the original website from May 29th to the June 1st 2021 there was only 1 edit.

f. From June 1st to present day there have been over 30 amendments

18) **September 22nd 2021 Ontario Justice of the Peace JANAND reviewed and authorized the production order seeking email records from University of Guelph, namely IP addresses for the time of May 27th to June 2nd 2021.**

19) On Friday October 8th 2021 the writer received the results of the production order from University of Guelph lawyer Hilary JARVIS, specifically IP addresses.

20) A review of the IP addresses submitted by the University of Guelph confirms that PYLE was in possession of a Rogers's device mobile or computer accessing his gpyle@uoguelph.ca address.

21) In order to prove the criminal offence of Identity Fraud sec. 403 (1) C of the C.C the emails from gpyle@uoguelph.ca interacting with others in order to create and edit the website byrambridle.com will be found within the University of Guelph Server.

22) It is noted that in conversation on September 8th 2021 with Stephen WILLEM, Chief Information Security officer of University of Guelph, that they are in possession of university personnel emails. It was the writer's intent to seek the emails in order to prove the offence.

23) On October 12 2021, Ontario Justice of the Peace BUTANY-GOYAL granted authorization of emails related to gpyle@uoguelph.ca.

24) On November 9 2021, I was in receipt of the emails in relation to gpyle@uoguelph.ca. Review of the emails failed to identify PYLE starting up the website; however, email evidence shows that PYLE is aware of who is behind the website, who created and may have openly contributed to it. Furthermore, what is captured and revealed is an outright colluded effort by FISMAN, Dr Scott WEESE and PYLE to promote a campaign of disinformation against BRIDLE.

25) To prove how PYLE was aware of who was behind and/or created the website, I captured an excerpt from an email between himself and a colleague Amy GREER agreer@uoguelph.ca . In this email, dated June 1st 2021 PYLE writes:

a. **" I can tell you confidentially that I believe the website was created by a student.** The phrasing on the initial version was the same as some of their tweets. I also recall one of their tweets saying "You should buy your domain name before someone smarter buys it first". That's been deleted"

GREER response

b. " I do think that the website has come from a student (or maybe students?). It is a boatload of research that seems to have been put together really quickly… (never underestimate a determined student(s) to get something done they feel strongly about). I am pretty sure it is not a student from my team (I think they would have likely asked me about it before making it public…but maybe not). **I am somewhat concerned about what it might mean for the student/students should their identity be made public**"

(What can't be overlooked is GREER openly stating to PYLE that there may be consequences if the student identities are revealed)

26) On November 15th 2021 I reviewed emails between PYLE and Charly MCKENNA mckennch@uoguelph.ca and learned the following:

a. On My 31st 2021 1255pm PYLE responds to MCKENNA who asked how are you doing?

"It's a fucking shit show. A faculty member is threatening lawsuits because some of us dared to critique the science he has been spreading. If you are on Twitter you'll know what I am talking about."

(The writer can confirm that the faculty member is BRIDLE)

b. May 31st 2021 145pm PYLE writes

"Just type Byram Bridle into Twitter"

c. May 31st 2021 7:52pm MCKEENA writes

Did you make that website?

d. May 31st 2021 817pm PYLE writes

"I did not. It's not hard to figure out who did though"

e. May 31st 2021 8:30pm MCKENNA writes

"Figured it was someone in the dept. but I'm not that great of a sleuth" .

27) On November 15th 2021 I reviewed the emails between Dr Scott WEESE _____ and PYLE. captured emails show PYLE venting to WEESE about BRIDLE threating to call police

a. May 30th 2021 1102am PYLE writes

"I received an email from him this morning that he will call the police to visit me on Monday, so I guess that is some drama.

b. May 30 2021, 1124a, WEESE writes

"Did you report this conduct to the Dean? I've talked to him before about Byram and he's sympathetic but also somewhat hand tied because of academic freedom and I think they're wary because he is such a complainer. However, threatening to call the police **based on very benign, evidence-based conduct by you is completely unacceptable"**

c. May 30 2021, 1129am WEESE writes

"Not surprising, unfortunately. I should ramp up what I'm saying so he can come after me at the same time.

If you need any support...moral, letter writing, sending the same statements...let me know. I'll be more than happy to do it."

d. May 30 2021 At 11:36am PYLE writes

"He copied the Dean, Shayan, Provost, President. Etc. They are aware"

e. May 30 1146a, WEESE writes

"What an idiot. Does he truly have no clue how he's viewed? This can't be a good longterm career move for someone that wants to be seen as a serious scientist.

I hope your day goes better. I haven't had any threats yet today from anyone (knock on wood) so it's a nice change. The ivermectin fan club seems to have moved on now, so it's back to just the ones that want to lynch the Science Table".

f. On May 31st 2021 AT 758am WEESE writes in reference to BRIDLES mailing list:

No, I'm not on his mailing list (although he sent me a whiny email and copied the Jeff, Shayan and Brandon. **No threat to call the police. I was a bit disappointed in that.) I assume there was lots of 'woe is me, people are being mean' in the newsletter, but it's useful to know what misinformation is being said to be ready for the next wave of questions.** There are a lot of people freaking out internationally about his statements about fertility risks, unfortunately.

Have you seen his affidavit for the Adam Skelly (Adamson BBQ) legal challenge? It's entertaining reading.

https://fearlesscanada.org/Skelly-vs-ROA/?fbclid=IwAR1Q4ESN5jha1FUm8gto6QuJtlwbLYNvD87gyHeruhimO7o2FNGRBTa9xpY

28) On November 15 2021, I reviewed emails between PYLE, David FISMAN, WEESE, GREER with USA today writer Daniel FUNKE. On June 2nd 2021, FUNKE reached out to FISMAN asking him to fact check BRIDLES comments on the Alex PEIERSON show. FISMAN replies and CC's PYLE and WEESE and invites them to contribute. FISMAN ends the email by promoting the fictitious website.

a. On June 2nd 2021 FISMAN CC's WEESE, GREER, PYLE and writes his interpretations of BRIDLES claims.

"Bridle is suggesting that a study that noted minuscule quantities of spike protein in blood after first dose represent a health hazard. That is poppycock: biologically implausible and not data based"

"As I don't have the ability to answer at greater length right now I have cc'd some colleagues from U of Guelph (all of whom are more knowledgeable than I am) who might be able to add to the conversation.

You may also want to check out https://byrambridle.com"

b. June 2nd PYLE writes

"The spike protein used in vaccines has been constructed to limit its ability to fully activate. This work was done by Drs. Jason McLellan and Barney Graham"

(https://cen.acs.org/pharmaceuticals/vaccines/tiny-tweak-behind-COVID-19/98/i38

c. June 2nd WEESE writes

"I don't have much to add unless you have other specific questions. The comments from Glen and David are great. I've never referred a fact checker to TikTok before but there's a great series of 11 videos debunking Byram's claims:

(The writer can confirm in earlier conversation with BRIDLE that the Tik-Tok video has refused BRIDLE's request to discuss the videos and to this date remain anonymous pg. 31 para. 38 sec s)

29) Since early in the year, WEESE using his twitter handle @weese.scott has openly targeted BRIDLE on this platform through name calling, shaming and taunting. An example of such tweets from early June 2021.

a.

b.


@dankddy111 · Jun 15
Breaking: Dr Byram Bridle's massive new 202 page report detailing all relevant research about vaccine safety concerns.
Spread it, post research here.
COVID-19 Vaccines and Children: A Scientist's Guide for Parents
smallpdf.com/result#r=b6a6f...
files.catbox.moe/mhg7u6.pdf
Smallpdf.com
smallpdf.com
12
128
168


J Scott Weese @weese_scott · Jun 17
Spreading it....

d.


Tweet
6
7
16
J Scott Weese @weese_scott · 15h
It seems like Bridle (surprise, surprise) misinterpreted a comment and (surprise, surprise) continues to spew misinformation about it.
I've seen nothing supporting it and how would the person he's accusing have access to Bridle's parents' info?
Just more misdirection.
1
Patti @booboobunster · 12h
I see your a collegue of Dr. Bridles. Are you in on the smear? And if so why? Is he not a credible scientist? And if not why are you all just coming forward now?
1
2
J Scott Weese
@weese_scott
Replying to @booboobunster @diana_c2021 and 3 others
What smear? Many people are simply pointing out all the flaws and misinterpretations.
His information is not credible, as has been pointed out by many people and groups, including the authors of the papers he cites as evidence.

d.

J Scott Weese @weese_scott · Jun 17

An far right politician, anti-vaxxer and guy who compared public health measures to the Holocaust walk into a press room...

I wish there was an actual joke in there. The real story's too sad/frustrating/maddening.

Misinformation kills. We need to address and remember that.

1 6

Show this thread

30)On September 30 2021, Rocco GALATI Law firm issued a cease and desist letter to WEESE and Jeff WICHTEL (See Appendix D) (Dean of University of Guelph) to stop the online harassment which has escalated in tone, tenor and frequency. On October 27th 2021 WEESE sent out the following tweet

a.

J Scott Weese @weese_scott · 18h

My seat belt works. How dare they make me be sober!

I wear a helmet. I'm cheated if I can't ride my bike down the middle of a busy road at night with no lights!

I'm being oppressed. Someone on some website told me so.

... twitter.com/JoostBroekers/...

Joost Broekers @JoostBroekers · 1d

Replying to @DrFedes

The vaccine works but you still need to wear a mask get tested and remain under restrictions...

How the vaccinated don't feel cheated is...

8

31)On May 10th FISMAN tweets out a link associating anti-vaxxers to Neo Nazis and white supremacy:

David Fisman @DFisman · May 10

A good read from @NoLore on close linkages between antivaxxers, antimaskers and neo-Nazis in Canada. Media need to start calling this for what it is. H/t @n_stiriya

J Scott Weese @weese_scott · Nov 10

Vaccines induce cancer recurrence (no evidence).
Vaccines are minimally effective (they're very good)
Ivermectin works (clear evidence it doesn't)
Various conspiracies.
...and more...

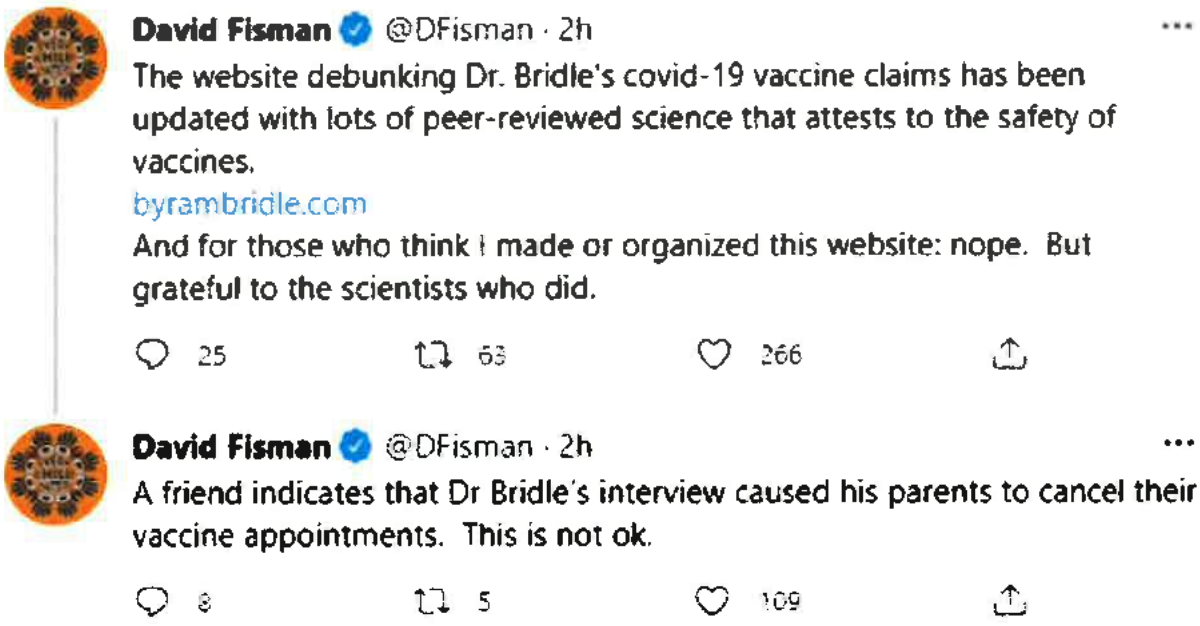
Veroos19 @Veroos19 · Nov 10

WHY ARE HIGHLY VACCINATED COUNTRIES EXPERIENCING COVID OUTBREAKS? - VACCINOLOGIST
bitchute.com/video/5-4O1pXV...

b. WEESE links the following BRIDLE image/article

32) WEESE co-authored and distributed the letter noted on pg. 27 para. 16, which is a link to an article, in which PYLE disseminated via twitter supported by the faculty of Guelph against BRIDLE.

33) Here is a tweet by FISMAN in late May of 2021, promoting the website and distributing private information about BRIDLES parents.



a.

(FISMAN mentions "grateful to the scientist who did")

34) On July 21 2021, an incident took place on campus and referenced on pg. 16 para. . On October 8th 2021, University of Guelph Police Sgt. O'CONNEL submitted his notes along with the complainants email

a. PYLE emails OCONNEL to register a complaint with police regarding BRIDLE'S behavior. In this email, PYLE CC'd the following faculty BIENZLE,WEESE,PEREGRI and WICHTEL

b. On July 22 2021 BIENZLE and PEREGREI email OCONNELL and CC'd WEESE,PYLE and WICHTEL

c. University Guelph Police attended and investigated the complaints and found no criminal wrongdoing by BRIDLE.

35) On September 24 2021, I received the notes from Officer BECKMANN who attended and investigated the matter with O'CONNEL. On September 28th 2021 I spoke with BECKMAN, made notes and learned the following

a. BECKMANN stated that the claim of harassment had no merit, BRIDLE was not a threat nor acted in an intimidating manner and therefore no reasonable grounds to believe that a criminal offence had occurred nor a safety plan is required

b. BECKMANN stated that PEREGRI and BIENZLE appeared bothered that BRIDLE would not be further investigated.

c. BECKMANN further stated that it was evident that there was a concentrated effort too purposely target BRIDLE

36)On November 15th 2021 WEESE submitted the following twitter post:

a.

← Tweet

J Scott Weese
@weese_scott

Hey @uofg.

Your logo is featured (again) on an antivax misinformation site: drbyrambridle.com

Time for clear statement.

Do you support this misinformation or not?

Silence indicates support. Time to act.

5:20 PM · Nov 15, 2021 · Twitter Web App

11 Retweets 3 Quote Tweets 57 Likes

b.

c. WEESE falsely spreading misinformation above.

(As noted below, on pg. 31 sec u. BRIDLE is aware of the site, approved it and he would never promote Anti-V position being an immunologist)

37) On November 16 2021, Dr Byram Bridle attended 180 Derry Rd for a video Interview. I made notes and learned the following:

a. BRIDLE is still working from home and relegated to online teaching once a month

b. BRIDLE still being investigated by North Shore investigations in relation to the July 21 2021 incident in which Campus Police found no wrongdoing.

c. BRIDLE is 100% in support for vaccines as it's his career and passion.

d. BRIDLE is aware of who WEESE is as they are with the Veterinary College at the University

e. BRIDLE has requested the school, campus police and Guelph Police to advise WEESE to stop to no avail

f. BRIDLE has no social media presence

g. BRIDLE is clearly frustrated as journalist and others take snippets of his conversations and promote that he is anti-vax

h. BRIDLE believes WEESE motivation is fueled by jealousy

i. BRIDLE has raised lots of money for the university

j. BRIDLE reiterates that all his beliefs are supported by science, has offered to debate all scientist and to date all have refused.

k. WEESE is a scientist at University of Guelph and work in the same department

l. BRIDLE stated that WEESE nor PYLE nor FISMAN could effectively discuss the science of vaccines, as it is not their field of expertise.

m. BRIDLE stated that WEESE would most likely refer to PYLE for scientific argument.

n. BRIDLE has testified before the superior court and multiple panels throughout the world as an expert

o. BRIDLE again reiterated that on May 27th 2021 Alex PIERSON radio show, he expressed more studies are required on youth and females.

p. BRIDLE stated that since May 27 myocarditis has been a cause of concern, as he noted on the radio show.

q. BRIDLE has received government funding for a Covid vaccine, recognized throughout the country as a leader in immunology and WEESE, PYLE and FISMAN don't come close to his level of science expertise.

r. BRIDLE has stated that WEESE operates a website called 'Worms and Germs" that promotes "Safe Pet Ownership". On July 5th 2021, WEESE submitted a link to the letter signed by faculty (88 signees)

s. BRIDLE has made multiple attempts to reach out to the creator of the Tik Tok videos that WEESE promoted and BRIDLE confirms that he has never received a response.

t. BRIDLE confirmed that in opposition to the letter posted on July 5th 2021, a co-worker Dr Mallard, drafted a letter, lobbied support among peers and others and garnered 8000 signatures worldwide.

u. BRIDLE stated that on October 21st 2021, a website bearing his name DrByramBridle.com was created and posted which fairly illustrated his work and science.

v. BRIDLE is well aware that the ongoing social media and reputation bashing and all out character assault will cause issue if ever a return to University of Guelph or any other University.

w. BRIDLE on November 9th 2021 wrote a 200 page document with 400 resources for public publication.

x. BRIDLE is concerned for himself and his family's safety, especially after the association to white supremacy and have even gone to the lengths of discussing safety plans if anything is to occur.

38) As per the University of Guelph website, Scott WEESE is listed as a:

a. Professor | DVM, DVSc Guelph; Dipl ACVIM

39) On November 30th 2021, I received the Investigative report authored by Nick DULEY of North Shore HR Consulting Inc. DULEY upon the request of University Guelph personnel Dean WHYCHTEL was asked to investigate the incident on July 21st and 22nd 2021 involving BRIDLE, PYLE, PEREGRINE and BIENZLE. The report does not capture BRIDLE's side of the events, who as per his lawyers was advised not to participate and therefore was in violation of the Workplace Harassment Prevention Policy and Article 42 of the Collective Agreement. I spoke with DULEY on December 1st to 9th 2021 and learned the following.

a) DULEY was contacted by WICHTEL to investigate the incident on July 21st to July 22nd 2021

b) The incident involved PYLE and BRIDLE on July 21st and PEREGRINE, BIENZLE and BRIDLE on July 22nd 2021

c) DULEY noted that he was provided a witness list by WICHTEL and other witnesses came about as the investigation proceeded.

d) DULEY noted that even though the Campus police investigated and found no criminal wrong doing, BRIDLE'S actions may have breached the University of Guelph's workplace harassment policy

e) DULEY advised that due to BRIDLE'S lack of participation, he was unable to get his side of the story and therefore was found in violation of the offence

f) DULEY was unable to advise on whether or not the promotion of a fictitious website by a University employee is breaching the University Policy.

g) DULEY was unable to comment if the actions of PYLE copying WEESE,WICHTEL,PEREGRINE and BIZENZLE on an email to Sgt O'CONNEL of Campus Police on July 21st 2021 a bit suspicious, considering the fact that none were present for the incident with him and BRIDLE.

h) DULEY was unable to comment if the actions on July 22 2021, by BIZENZLE copying the same parties on an email to Sgt O'CONNEL in relation to an incident with BRIDLE involving PEREGRINE and herself were suspicious.

i) DULEY advised that the interviews were conducted by Zoom or MS Teams, audio recordings were made and transcriptions prepared.

j) Duley advised that all his notes, transcripts (with appendices) recordings are held by University of Guelph personnel, namely Laurie ARNOTT

k) On December 2nd 2022, University of Guelph Legal representative Hilary JARVIS advised that that the North Shore Investigative file are in possession of the University.

40) On December 1st I reviewed the Investigative report from North Shore and learned the following:

a) The report contains 11 witness accounts in relation to the incident

b) The Dean and Witness 1 to 4 are identifiable as they provide testimony of the July incident that is reflected in the occurrence report and officer notes.

c) In review of Witness 1 (PYLE), he states to DULEY that he had no involvement with the website (byrambridle.com) and that he believed a junior scientist may have been involved and was protecting their identity from Dr BRDILE in fear of retaliation.

(as noted on page 20 para.*****, PYLE in communication with MCKENNA that he well aware of who made the website)

d) In review of the report, witness number 3 (WEESE) provides DULEY with supposed evidence of BRIDLE's emails and how he himself is being targeted. DULEY notes these emails within the report as appendix D, K, R and Q.

(Appendices notes above are emails to which BRIDLE sent to Witness 3)

e) During the interview of WEESE, he states that he has "received online threats, death threats and abuse by Dr Bridle supporters including "alt right groups... some of these individuals have said that WEESE is guilty of violating the Nuremberg Principles and that he should be hung for his role in human medical experimentation. Witness 3 described Dr Bridle as "one step away from QAnon and white supremacist groups" (pg. 21 of North Shore Investigative report)

(As per judicial authorization granted by Justice of the Peace CASSANO, University of Guelph provided 4 weeks of emails (1816) associated to WEESE (jsweese@uoguelph.ca) to the writer. A review of those emails indicate no threats, death threats nor mention of Nuremberg Trial were ever located nor communication from third parties connecting BRIDLE to Alt Right groups.

f) On page 21 of the Investigative report WEESE states that he was "ringleaders" of a group of faculty who had prepared and signed an open letter addressing misinformation that BRIDLE had been providing in the media

41) On March 15th 2022, I reviewed the cyber report conducted by D/C TURCZAK and ALLEN of the Cyber unit who were tasked to identify tweets of WEESE (@weese_scott) and PYLE (@glenpyle) from the period of May 5th 2021 to February 30th 2022. As noted above, tweets identified by WEESE to be offensive toward BRIDLE and it appears that WEESE is on a campaign against BRIDLE.

a) Between the periods of dates and noted above WEESE has tweeted BRIDLES name 58 times.

b) As noted on page 26, tweets, WEESE eludes that BRIDLE is associated to white supremacy

c) These tweets have ranged from professional to personal condemnations without provocation or retaliation from BRIDLE. It should be noted many of the Tweets are highly offensive in nature.

42) On February 22nd 2022 I interviewed Dr MALLARD who is a scientist at University of Guelph for the past 30 years and associate of BRIDLE, PYLE and WEESE.

a) Dr. Mallard is a Professor at the Ontario Veterinary College, Department of Pathobiology at the University of Guelph and is a long-time colleague of Dr. Bridle while at the University.

b) Her research interests focus on genetic regulation of the immune system and implications to disease resistance.

c) Dr. Mallard is the inventor of the High Immune Response Technology and the Immunity Technology that has been licensed to the Semex Alliance which is Canada's largest diary genetics company.

d) Due to her expertise over the past decade Dr. Mallard has been the highest funded medical researcher at the University

e) Dr MALLARD is the winner of the 2017 Governor Generals award for Innovation

f) MALLARD is Witness 11 on the North Shore Investigative report

g) MALLARD advises that it is commonplace for scientist to confront one another with differences of opinion in order to find common ground. "that is what science is about"

h) Its common place to drop off papers under the door of professors.

i) MALLARD believes that the issue between WEESE and BRIDLE began during a faculty meeting in April/May of 2021 and WEESE verbally redirected BRIDLE for speaking.

j) MALLARD further states that after the Alex PIERSON radio show wherein BRIDLE expressed caution with the vaccination process of youth and young females, WEESE was really was bothered.

k) The PFZIER document to which BRIDLE was in possession of and which he referenced on the Alex PIERSON radio show is proven accurate (pg 6 para. 1 sec.k) and against what WEESE has been promoting.

43) **On November 23rd 2021 Ontario Justice of the Peace CASSANO granted the authorization of emails for jsweese@uoguelph.ca**

44) On January 4th 2022 I reviewed an email of jsweese@uoguelph.ca located in his archived folder and learned the following:

a) On May 28th 2021, WEESE received an email from CDC (Centre of Disease Control) stating, "Since April 2021, increased cases of myocarditis and pericarditis have been reported in the United States after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna), particularly in adolescents and young adults.

b) "Onset was typically within several days after mRNA COVID-19 vaccination, and cases have occurred more often after the 2nd dose than the 1st dose".

c) "CDC continues to recommend COVID-19 vaccination for everyone 12 years of age and older given the risk of COVID-19 illness"

d) "Report all cases of myocarditis and pericarditis post COVID-19 vaccination to VAERS (Vaccine Adverse Event Reporting System)."

(It's the writer belief that the email document as dated May 28th 2021 exposes the fact that WEESE had prior verified knowledge from a appropriate reliable source, that being, the CDC Governing Scientific Body, stating in a scientific record the same concerns Dr. Bridle expressed on the Alex Pierson podcast as dated May 27th 2021. This information substantiates the premise

that WEESE was acting in a malicious manner in order to discredit Dr. Bridle and thus suppress academic discourse to better serve his own reputation)

45) On December 23rd 2021, I spoke with Alex PIERSON an employee of Global News and the host of the Radio show whom where Dr Byram BRIDLE expressed caution about the distribution of vaccines and youth. On the fictitious Byrambirdle.com webpage a section of it is dedicated to PIERSON and in attempt to make her sound as an anit-vaxxer it states the following:

a. Alex Pierson's ON Point is a member of the Global News Radio family. Bridle has been a regular guest of late, appearing on her show several times. For context, her other recent works include:

b. "Are the lockdown measures just as deadly as the virus itself?"

c. "Why are mental health experts telling all levels of government everything is Not Ok? Will China ever be held accountable for lies surrounding Covid?..."

d. "A secretive and conflicted federal vaccine task force..."

e. "Civil liberties are being sacrificed to help curb the spread of COVID-19, but to what end? And a new book by a former liberal MP that Trudeau might not want you to read"

f. "Why did Trudeau invite the Chinese military to see our military secrets? Why don't we have rapid testing in place yet? And a conversation with Trudeau's half brother"

g. "Environmentalist Michael Shellenberger apologizes for the 'climate scare'"

h. But it's not just her show that uncritically platforms those spreading misinformation. A concerned listener has documented misinformation on a wide range of topics presented on Global News Radio. They demonstrate the extent of Global News' abdication of responsibility with respect to their radio content."

46) PIERSON responded to the above exert via email:

a. All of this is nonsense. I had Byram on twice. I am an editorial show. I don't do news.

b. Those who don't agree with my politics don't like it.

c. We present both sides all day long. The day Bridle came on I had no idea he was going to say what he did.

d. You can hear it in my reaction because I said this is going to scare a lot of parents.

e. Global wouldn't put up with me if I went extreme. They just wouldn't. Someone clearly has an axe to grind.

47) In December, I learned of that a website AlexPIERSON.CA is linked and interconnected with Byrambridle.com.

48) On March 18th 2022, PIERSON contacted the writer advising the ongoing harassment she continues to receive from the interview and website.

49) On April 14th 2022 PIERSON emailed the writer regarding the website alexpierson.ca and I learned the following:

a. The website/domaine is no longer used by her but certainly is made to look like her

b. PIERSON had no idea it was in use and it was brought to her attention by their social media platforms where she received questions about it and the views

c. PERSION had used the website domain up to 2 years ago and let it expire and it was re-registered by someone else, an unknown suspect, using her name to push out attacks on Dr Byram BRIDLE.

d. PIERSON states that the website has changed a few times since being re-launched and has been using her likeness/image to discredit BRIDLE/herself and Global news.

e. PIERSON did not provide permission for her name and/or address to be used to launch any kind of attack on anyone and she is unaware who is responsible

f. PIERSON is concerned about the reputational damage and misinformation that the site spreads as it pushes the herself/BRIDLE are against vaccines and disseminates vaccine disinformation.

g. PIERSON states that the issues (Covid/vaccines) have become polarizing and for that reason she is careful with how the topic is discussed on the show.

h. PIERSON has made it clear numerous times that she is not anti-vaccine.

i. PIERSON states that the website is creating concern for the company (Global news) that has a responsibility to stop misinformation.

j. PIERSON personally has to defend herself against harassing and sometimes vicious attacks who are out to discredit and silence her views.

50) On April 20 2022, I spoke with Amanda CUPIDO who is a director of programing for Alex Pierson radio show since January 4 2022, in relation to PIERSON and the public harassment and learned the following:

a. PIERSON has advised that she has been receiving an unprecedented amount of hate emails, calls and tweets.

b. PIERSON has expressed concern for her safety, family safety since her employment commenced.

c. PIERSON is worried to talk about herself on the air in fear of the backlash/how people will use details against her.

d. PIERSON advised that alexpierson.ca was created by Adam OLDFIELD on behalf of Alex years ago, but they let it expire.

e. PIERSON is currently taking an extended leave of absence from Global.

51) On April 25th 2022, Alex Pierson radio show producer Glenn BRAGONIER submitted a statement on his experience working with PIERSON. I reviewed the statement and learned the following:

a. Since we did the segment with Dr. Byram BRIDLE we got an increase in aggressive or hostile people calling in whenever we tried to do call-in segments.

b. None were personally or physically threatening in nature, just increasingly hostile.

c. Many other shows were experiencing similar issues because of the divisive nature of the pandemic at the time (e.g. vaccines, masks, etc.).

d. we also reduced the amount of call-in segments we did in this time to avoid the issue.

e. I personally did not receive any hate or threatening mail, but I do know that Alex has.

f. PIERSON has sent BRAGONIER a few emails from one individual in particular who we believe was also one of the more persistent and volatile call-ins we would get before we blocked his number.

52) ON April 19th 2022 I contacted Cyber Unit officer D/C Allen to confirm the domain of the website Alexpierson.ca and learned the following:

a. The domain is held at Namecheap.com
b. The site originally appeared on June 23 2021

53) On July 8 2021 I contacted Cyber Unit officer D/C TURCZK to confirm the domain of the website Byrambridle.com and learned the following:

a. The domain is held by Namecheap.com
b. The site originally appeared on May 28th 2022

54) Review of the websites exhibit the same similarities in design but when on the Alexpierson.ca website a tab is present, that when opened will direct you to the Byrambridle.com

55) On July 9th 2021 via email to nameheap.com to confirm Byrambridle.com for the purpose of a production order I learned the following:

a. Namecheap.com stated that they wont confirm if they have information unless in receipt of a production order.

b. They may advise the subscriber of the website that an investigation has commenced.

c. A non-disclosure order must be present with the production order; however, namecheap.com can reserves the right to notify the subscriber.

d. Namecheap.com hold payments information and address IP'S of the subscriber.

56) On March 22nd 2022 I spoke with Homeland Security Investigator John WALKER who directed me to the website https://gogetcanada.ca/legal-information/ in regards to namecheap.com and websites ending in "ca". I reviewed the website and learned the following:

a. Namecheap.com will accept Canadian production order in relation to websites ending in ".ca"

b. Request must be directed to Go Get Canada Domain Registrar Ltd

c. Go Get Canada Domain Registrar Ltd. will respond to valid Canadian law enforcement requests and will be fulfilled by our back-end registry operator Namecheap, Inc

d. Please note that Namecheap, Inc. will not disclose any personal information about their customers unless required by law or pursuant to a U.S. court order or subpoena.

e. Canadian law enforcement officials may mail or email these requests directed to Go Get Canada Domain Registrar Ltd. to Namecheap, Inc. to info@gogetcanada.ca

f. Go Get Canada Domain Registrar Ltd. and/or Namecheap, Inc. **may notify the customer whose information is sought via email or mail**

g. Law enforcement officials who believe that notification would jeopardize an investigation should obtain an appropriate court order or other legal process establishing that notice is prohibited.

(information obtained from alexpierson.ca should assist in identifying who was her and byrambridle.com website)

57) On March 25th 2022, Ontario Justice of the Peace V FISHER GRANT granted a production order for files (transcripts, recordings, notes, appendices, statements) pertaining to the North Shore Consultant HR investigation file and held at (University of Guelph)

58)On March 29th 2022, I submitted the Production order to University of Guelph Legal represent, Hilary JARVIS.

59) On April 28th 2022 I spoke with Hilary JARVIS who advised that they are not in possession of the transcripts just the report and videos. JARVIS apologized for the misunderstanding and advised that she spoke with DULEY of North shore HR Consulting Inc. and confirmed he is receipt of the transcripts. JARVIS did provide school surveillance video, recordings and appendices (April 28th 2022).

60) On April 29th 2022, I spoke with Nick DULEY, North shore Consultants HR investigator and learned the following:

a. DULEY apologized for the misunderstanding that University of Guelph is in possession of transcripts etc.

b. DULEY stated that all interviews of the 11 witnesses were completed by zoom, recorded and transcribed.

c. After transcription, the recordings were destroyed as per their policy

d. DULEY will forward the transcripts upon receipt of a production order.

61) On April 29th 2022, DULEY was asked by the writer if a faculty member was to promote and/or possibly create a website defaming, discredit and smear another faculty member if it would be violation of a workplace harassment. DULEY advised the following:

a. Yes it would be and that he receives enquiries all the time especially in relation to twitter.

62) On April 29th 2022, the University of Guelph, who since January 1st have reduced BRIDLE's salary by 8% and assigned for him to work remotely, issued a letter stating that his office is to be moved in accordance of their findings from the investigation and for the safety of the other scientist (PYLE, PEREGRINE and BIENZLE) I spoke with BRIDLE upon review of the letter who advised the following:

a. Physically moving his research team to another building would be devastating.

b. His team members have close friends and colleagues in the department.

c. They need to be in proximity to a lot of shared equipment that we use on an almost daily basis.

d. This will have a devastatingly negative impact on my ability to conduct research.

63) On April 30th 2022, Dr Byram BRIDLE, Dr Paul ALEXANDER and Dr PONNESE held a Town Hall in Kitchener regarding "Shifting Perspectives, The Erosion of

Human Rights in Canada". On the same date, WEESE via twitter posted the following:

a.

b. PYLE later adds to the thread the following:

(Another example of PYLE like WEESE openly categorizing anyone who may be against the vaccine regardless of their reason, to be a racist. There appears to be conscious effort to associate BRIDLE et al, as racist in order to smear their reputations)

REASONABLE GROUNDS TO BELIEVE THAT THE OFFENCE HAS BEEN COMMITTED

The suspect WEESE, having intimate knowledge on how to ruin, BRIDLE's carrier and defame his character, specifically in the research field, which was intentionally initiated through a campaign to discredit BRIDLE for reasons yet to be fully determined but likely due to professional conflict of opinion. The manner in which this movement ensued was primarily through the introduction and promotion of the website Byrambridle.com. As professional reputations were at stake the purpose of this agenda appears to be means in which to suppress scientific knowledge rather than expand further discussion as should be the common practice with a University setting.

Reasonable and probable grounds that WEESE, PYLE and others has committed the offence of Identify Fraud and Criminal Harassment

- On Pg. 9 ***** via twitter PYLE states in reference to who was behind the website byrambridle.com said " **it was a scientist**"

- On Pg. 28 ****para 33 FISMAN writes in reference to who made the website byrambride.com that **it was a scientist**

- On Pg. 20 para 26 sec e MCKENNA replies back to PYLE in response to who was behind the website " **Figured it was someone in the dept but I'm not that great of a sleuth**

- On Pg. 21 para 27 ***sec a, Pyle writes that BRIDLE will call police for involvement with the website and WEESE in sec b writes "threatening to call the police **based on very benign, evidence-based conduct by you is completely unacceptable**"

- As per University of Guelph website, WEESE is a scientist

(What we do know now is that on the original website of byrambridle.com on the 29th a link to PYLES work is posted. The writer believes that WEESE is making reference to this as BRIDLE never threated to call police over the tweets post by PYLE. On June 1st 2021, the website is changed and the PYLES link is removed pg. 18 para 17 sec c, d & e)

- On pg. 22 par 28 sec c, WEESE writes the following to PYLE
"Not surprising, unfortunately. **I should ramp up what I'm saying so he can come after me at the same time.** If you need any support...moral, letter writing, sending the same statements...let me know. I'll be more than happy to do it

(The writer believes by WEESE saying "Ramp it up" means more misinformation associated to the website and lobby faculty staff against BRIDLE)

- On July 5th a letter is sent out by WEESE and PYLE signed by the faculty openly saying the views of BRIDLE are inappropriate and characterized as misinformation.

(WEESE utterances to PYLE come to fruition here as he stated)
"If you need any support...moral, letter writing, sending the same statements...let me know. I'll be more than happy to do it.)

- Between July 20th and July 22nd WEESE was included in an email advising campus police of criminal behavior by BRIDLE. WEESE was never interviewed as witness nor victim and therefore involvement from the preliminary remains suspect.

- From early May, WEESE has been tweeting many times, often slanderous and taunting tweets targeting BRIDLE. Pg. 23-25

- On September 30th 2021, WEESE was served with a cease and desist letter to stop harassing BRIDLE, to which he has willfully ignored and continue his social media campaign against BRIDLE. See appendix D,

- In early November 10 2021, WEESE retweeting FISMAN saying that Anti-Vaxxers are neo-Nazis and directly links the tweet with BRIDLE, thereby implying that BRIDLE is white supremacist pg. 26

- WEESE again associates BRIDLE to white supremacy and that he is a victim death threats with no proof.

(Such actions have become commonplace in today's society where if anyone believes or says something against the narrative they are defined as racist and anti-science)

- On November 15th 2021, WEESE wrongly characterized a website of Drbyrambridle.com as "Anti-vax".

- On pg. *** para. 25 sec a, and pg.**** 34 para sec. c, PYLE on two occasions advises GREER and HULEY that the website was made by a student/junior scientist

Its is of the writers opinion that WEESE had direct knowledge of the website (byrambridle.com), helped promote and continue his online attacks via twitter, slanderous letters and encouraging staff to attempt to file questionable police reports.

I believe the dates sought in Appendix A would capture WEESE colluding and organizing the website (May 27th to June 2nd 2021), soliciting information to add and identifying who may have created the website.

The emails between the dates of July 3rd to July 7th 2021, captured WEESE organizing with others to promote a letter amongst the faculty to purposely disparage BRIDLE

The emails sought between July 19th to July 24rd 2021, captured WEESE involvement with other faculty to file a police report.

The emails sought between November 9th to Nov 16th 2021 will capture WEESE ramping up the twitter post linking Bridle to white supremacy and associating a legitimate website with Anti-vaxxers,

Upon review of the first two websites, the 1st being on May 28th 2021, it alludes to "coming down the hall" with a link citing his work. Suspiciously, the website changes on June 1st 2021, as is noted on pg. 11 para 10 sec a,b BRIDLE accused PYLE of the website and advised University of Guelph Dean and Faculty of the incident. We do know that WEESE, PYLE and BRIDLE all work in the same department (Veterinary College)

An overview of the matter, WEESE is clearly invested into openly tarnishing the image of BRIDLE, with complete impunity

At the time of website BRIDLE had (5) Applications for funding present, unfortunately (3) have since been denied. Furthermore, due to the incident wherein PYLE and PERGRIENE/BEIDNZE filed complaints against BRIDLE, the school placed BRIDLE on "Administrative Leave" while an outside investigative firm reviewing allegations made by PYLE et al.

In speaking with BRIDLE, he has stated that he is stressed beyond reason and is concerned for his overall welfare due to these series of incidents. Moreover, he questions why no faculty/scientists are willing to conduct a scientific debate on this matter as would be the typical procedure for differences of scientific theory. Instead, the involved persons choose to turn this scientific matter into an unnecessary, unethical and potentially unlawful slander campaign.

To date, if one is to Google Byram Bridle and Alex PIERSON the fictitious website Byrambridle.com and Alex PIERSON.ca will appear. The promotion of the fictitious websites has caused both BRIDLE and PIERSON undue amount of public ridicule and stress.

As such, I believe the offence of Identity Fraud contrary to section 403 (1) C of the C.C., Criminal Harassment Contrary to section 264 of C.C. was committed.

GROUNDS TO BELIEVE THE THINGS TO BE SEIZED WILL AFFORD EVIDENCE OF THE OFFENCE

On the basis of the foregoing paragraphs;

1) I believe on reasonable grounds that the document's listed in Section II will afford evidence of the criminal offence of:

- **Identity Fraud section 403 (1) C of the CCC**
- **Criminal Harassment section 264 2 (b) of the C.C.C**

My grounds for belief may be summarized as follows:

I believe that the aforementioned suspect Scott WEESE is responsible for the above-mentioned charge in Appendix "B". The evidence that I am seeking will be used to compose a more substantial case against WEESE. Furthermore, the following information

has been documented by Peel Regional Police which will afford evidence of the offence, that being:

a. The items listed in Appendix "A" will afford evidence against WEESE, as listed in section "C" of this Production Order and may lead to additional witnesses, victims and person(s) of interest.

b. The items listed as evidence and associated transactions have been identified and located by the victim and via judicial authorization and submitted to Police Investigators being held pending further investigation. These items in addition to the outlined Production Order request will allow Peel Police investigators to fully access the incident increasing the probability of solving this incident. It will also assist in uncovering potential person(s) of interest, additional witnesses and in due course any others that may be involved that remain unidentified at this point.

c. North Shore Consultant HR transcripts will assisted in collaborating evidence already gathered that WEESE recruited and/or lobbied others (July 5th 2021, letter) to target BRIDLE just because he had a view that is different from himself.

d. Even though BRIDLE does not dispute the interaction with the named parties on July 21/22nd 2021, he believes their incentive to complain to the police were fueled by outside motives.

e. Capturing the investigative file (transcripts) will assist the writer on obtaining a version of the events of the parties involved and identify unknown persons who are involved in the incident either directly or indirectly.Specifically herein PYLE states it was a junior scientist

f. Over the several months since this email document WEESE employed a series deceitful events in order to malign Dr. Bridle both professionally and personally knowing full well (as per CDC document WEESE retrieved via email) Dr. Bridle

was simply asserting verified scientific information. As opposed to openly debating Dr. Bridle as would be the common practice at the university level, WEESE, attempted to prevent scientific dialogue through a sequence of criminal activity based upon WEESE's own conjecture, opinion and bias.

g. As per Officer BECKMANN who interviewed PEREGRINE and BIENZLE on July 22nd 2021 and noted that they were bothered that the Police were not pursuing a criminal matter against BRIDLE.(Pg *******c)

h. PEREGRINE, BIENZLE, PYLE and WEESE all were part of the letter of Guelph faculty released to the public on July 5th 2021, shaming BRIDLE.

i. WEESE advising PYLE upon hearing that BRIDLE will call police openly seeks confrontation from BRIDLE as noted on pg ***, para *** sec. WEESE proceeds to mislead North Shore Investigator, DULEY that he is a victim of death threats due to BRIDLE's association with "alt-right" and "white supremacy". No proff of this is ever provided as valid.

j. As acknowledged, this NAMECHEAP account was revealed as being utilized by the unknown suspect, in relation to this matter and thus potentially directly or indirectly involved in the offence. This account belonging to an unknown party will be evaluated for records pending authorization of this Production Order. It is believed that this information will assist investigators in bringing this matter to a successful outcome which will potentially prevent any further escalation of the criminal behavior. As such, investigators believe that the information contained in Appendix A will afford evidence of the alleged offences listed in Appendix B.

GROUNDS TO BELIEVE THE THINGS SOUGHT ARE PRESENTLY AT THE PLACE TO BE SEARCHED

On April 29th 2022 North Shore HR Consultants Inc. investigator Nick DULEY advised that he has transcripts of the interviews within his possession and can be provided upon receipt of a production order.

On March 22st 2022 viewed namecheap.co, website in relation to ".ca" and learned that, Go Get Canada Domain Registrar Ltd. will respond to valid Canadian law enforcement requests. The requests must be directed to Go Get Canada Domain Registrar Ltd. and will be fulfilled by their back-end registry operator Namecheap, Inc and email to info@gogetcanada.ca

CONCLUSION

I believe that WEESE as well as other unknown individuals are responsible for the above-mentioned charges in Appendix B. I am concerned that these individuals may have already attempted or are planning to utilize this pattern of behaviour to further victimize the complainant and/or other unwary professionals. I strongly believe that this behaviour will continue, as it appears that these exploits have become increasingly flagrant in nature over an extended period without any remorse or accountability. This activity is clearly noted in email communications as dated May 31st 2021, wherein WEESE writes "Ramp it up" – as well as a very recent Twitter submission attempting to link the victim with "Neo-Nazis/White-Supremacy" which is both unfounded and obviously highly offensive.

These series of incidents were carefully planned and utilized fictitious websites, online posting/documents, a concealed email address/domain as well as out of country locations in order to intentionally obscure the suspect(s) identity. From information obtained through the victim as well as numerous others it has been determined that WEESE carried out these unlawful acts throughout this incident while utilizing website byrambridle.com, twitter @weese_scott and email jsweese@uoguelph.ca. As a result, the suspect(s) have deliberately caused BRIDLE and PIERSON a great deal of personal and professional loss.

As such, the requested essential online information will afford Peel Regional Police with compelling evidence that will further link and/or identify the suspect(s) with this fraudulent activity.

Moreover, from detailed background analysis it has been revealed that this type of activity has become increasingly evident within certain social media enterprises thus placing a great strain on investigative resources as well as potentially victimizing scores of others in an anonymous and surreptitious manner. As is commonly noted within this criminal activity online communication is a paramount feature in keeping this pursuit in operation. These components would indicate that this was an intentional act which involved prior knowledge, planning and scheming by the suspect(s).

The evidence I am seeking is a crucial factor in order to maintain the integrity of the investigation as well as the quality and condition associated to any pending evidence that may be uncovered with additional investigative avenues that may ensue. Therefore, this material will be utilized to build a more compelling case against those involved and will help establish a convincing link in regards to the online activity as outlined within the criminal offence of Identity Fraud 403 (1) C of CC and Criminal Harassment 264 (2) (b) C.C.

In the interest of a full, frank and fair investigation, this information could also potentially exonerate any person(s) unwittingly involved in said incident.

_____ _____

A Commissioner of Oath
in and for
The Province of Ontario

Informant

PRODUCTION ORDER FOR DOCUMENTS
ORDONNANCE DE COMMUNICATION : DOCUMENTS

SUPERIOR/ONTARIO COURT OF JUSTICE
COUR SUPÉRIEURE DE JUSTICE/DE JUSTICE DE L'ONTARIO

CANADA
PROVINCE OF ONTARIO
PROVINCE DE L'ONTARIO

Form / *Formule* 5.005
Subsection / *paragraphe* 487.014(3)
of the *Criminal Code* / *du* Code criminel

Central West / Centre-Ouest
(Region / *Région*)

PR2102256170
Case/File No / *N° du cas/dossier*

To / *À* **Univeristy of Guelph -Computing and Commuincation Services** (name of person / *nom de la personne*), of / *de* **50 Stone Rd E, Guelph, ON N1G 2W1**:

Whereas I am satisfied by information on oath of / *Attendu que je suis convaincu, en me fondant sur une dénonciation sous serment par* **D/CST Bird #3115** (name of peace officer or public officer / *nom de l'agent de la paix ou du fonctionnaire public*), of / *de* **Peel Regional Police**,

that there are reasonable grounds to believe that an offence has been or will be committed under
qu'il existe des motifs raisonnables de soupçonner qu'une infraction prévue à

Identity Fraud Contrary to Sec. 403 (1) C of the Criminal Code
(specify the provision of the *Criminal Code* or other Act of Parliament / *préciser la disposition du* Code criminel *ou de l'autre loi fédérale*) *a été ou sera commise*

and that / *et que* (specify the document or data / *préciser le document ou les données*)
See Appendix 'A'

is in your possession or control and will afford evidence respecting the commission of the offence;
sont en votre possession ou à votre disposition et fourniront une preuve concernant la perpétration de l'infraction;

Therefore, you are ordered to produce a document that is a copy of / *En conséquence, vous êtes tenu(e) de communiquer un document qui est la copie de* **See Appendix 'A'** (specify the document / *préciser le document*)

that is in your possession or control when you receive this order
qui est en votre possession ou à votre disposition au moment où vous recevez la présente ordonnance,

AND/OR / *ET/OU*

prepare and produce a document containing / *d'établir et de communiquer un document comportant* (specify the data / *préciser les données*)
See Appendix 'A'

that is in your possession or control when you receive this order.
qui est en votre possession ou à votre disposition au moment où vous recevez la présente ordonnance.

The document must be produced to / *Le document doit être communiqué à* **D/CST Jeff Bird #3115** (name of peace officer or public officer / *nom de l'agent de la paix ou du fonctionnaire public*) within / *dans un délai de* **30 days** (time / *indiquer le délai*)

at / *à* **City of Mississauga** (place / *lieu*), in / *, et être présenté* **electronic form** (form / *indiquer la forme*)

This order is subject to the following conditions:
La présente ordonnance est assortie des conditions suivantes :

You have the right to apply to revoke or vary this order.
Vous avez le droit de demander la révocation ou la modification de la présente ordonnance.

If you contravene this order without lawful excuse, you may be subject to a fine, to imprisonment or to both.
Sachez que la contravention de la présente ordonnance, sans excuse légitime, peut entraîner une peine d'emprisonnement et une amende, ou l'une de ces peines.

Dated / *Fait le* 9 Sept 2021 (date)

at / *à (au)* **City of Brampton** (place / *lieu*)

(Signature of justice or judge / *Signature du juge de paix ou du juge*)
JAnand

CCO-487-5 005 (rev 03/15) CSD

"APPENDIX A"

THAT IT IS PROPOSED THAT University of Guelph Computing and Communication Services produce between the periods of May 27th to June 2nd 2021.

1. All subscriber Information and account registration information, unrestricted by date, associated to the email account, gpyle@uoguelph.ca including but not limited to: name(s), address (es), birthdate(s), phone number(s) and date of account creation.

2. I.P. logs for the I.P. addresses utilized by gpyle@uoguelph.ca between May 27 to June 2nd 2021

3. I.P. details associated to the date and time of account creation and/or deletion

Court File No./N° du dossier du greffe : CV-22-00691880-0000

ORDER TO COMMUNICATION : DOCUMENTS
SUPERIOR/ONTARIO COURT OF JUSTICE
COUR SUPÉRIEURE DE JUSTICE/DE JUSTICE DE L'ONTARIO

CANADA
PROVINCE OF ONTARIO
PROVINCE DE L'ONTARIO

Central West / Centre-Ouest
(Region / *Région*)

Form / *Formule* 5.005
Subsection / *paragraphe* 487.014(3)
of the *Criminal Code* / *du Code criminel*

PR2102256170
Case/File No / *N° du cas/dossier*

To **Computing and Communications Services** of **University of Guelph-50 Stone Rd East**
À (name of person / *nom de la personne*) *de*

Whereas I am satisfied by information on oath of **D/CST Bird #3115**, of **Peel Regional Police**
Attendu que je suis convaincu, en me fondant sur une dénonciation sous serment par (name of peace officer or public officer / *nom de l'agent de la paix ou du fonctionnaire public*) *de*

that there are reasonable grounds to believe that an offence has been or will be committed under
qu'il existe des motifs raisonnables de soupçonner qu'une infraction prévue à

Identity Fraud Contrary to Sec. 403(1) C of the Criminal Code
(specify the provision of the *Criminal Code* or other Act of Parliament / *préciser la disposition du Code criminel ou de l'autre loi fédérale*) *a été ou sera commise*

and that (specify the document or data)
et que (*préciser le document ou les données*)
See Appendix 'A'

is in your possession or control and will afford evidence respecting the commission of the offence;
sont en votre possession ou à votre disposition et fourniront une preuve concernant la perpétration de l'infraction;

Therefore, you are ordered to produce a document that is a copy of **See Appendix 'A'**
En conséquence, vous êtes tenu(e) de communiquer un document qui est la copie de (specify the document / *préciser le document*)

that is in your possession or control when you receive this order
qui est en votre possession ou à votre disposition au moment où vous recevez la présente ordonnance,

AND/OR / *ET/OU*

prepare and produce a document containing (specify the data)
d'établir et de communiquer un document comportant (*préciser les données*)
See Appendix 'A'

that is in your possession or control when you receive this order.
qui est en votre possession ou à votre disposition au moment où vous recevez la présente ordonnance.

The document must be produced to **D/CST Jeff Bird #3115** within **30 days**
Le document doit être communiqué à (name of peace officer or public officer / *nom de l'agent de la paix ou du fonctionnaire public*) *dans un délai de* (time / *indiquer le délai*)

at **City of Mississauga** in **electronic form**
à (place / *lieu*) *, et être présenté* (form / *indiquer la forme*)

This order is subject to the following conditions:
La présente ordonnance est assortie des conditions suivantes :

You have the right to apply to revoke or vary this order.
Vous avez le droit de demander la révocation ou la modification de la présente ordonnance

If you contravene this order without lawful excuse, you may be subject to a fine, to imprisonment or to both.
Sachez que la contravention de la présente ordonnance, sans excuse légitime, peut entraîner une peine d'emprisonnement et une amende, ou l'une de ces peines.

Dated 13 October 2021
Fait le (date)

at **City of Brampton**
à (au) (place / *lieu*)

Sapna Butany-Goyal
HW Butany-Goyal
(Signature of justice or judge / *Signature du juge de paix ou du juge*)

CCO-487-5 005 (rev 03/15) CSD

APPENDIX A

THAT IT IS PROPOSED THAT University of Guelph Computing and Communication Services produce between the periods of May 27th to June 2nd 2021.

1) incoming, outgoing, drafted and deleted emails associated to gpyle@uoguelph.ca
2) Including content for each email, recipient and sender email addresses.
3) Emails within those dates held in cloud services

Email Thread

June 2, 2021

between Dr. Weese, Dr. Pyle, Dr. Fisman, Dr. Greer and Daniel Funke, *USA Today* reporter

From: J. Scott Weese
To: Glen Pyle; David N. Fisman; Funke, Daniel
Cc: david.fisman@utoronto.ca; Amy Greer
Subject: Re: Media request from USA TODAY (Deadline: 5 p.m. ET)
Date: Wednesday, June 2, 2021 1:11:05 PM

Daniel

I don't have much to add unless you have other specific questions. The comments from Glen and David are great. I've never referred a fact checker to TikTok before but there's a great series of 11 videos debunking Byram's claims: https://www.tiktok.com/@laughterinlight?is_copy_url=1&is_from_webapp=v1 It's a careful fact check of his claims and it might be of use to you.

The efficacy and safety of mRNA vaccines is astounding, to me, particularly for a virus we've only known for a year and a half. mRNA vaccines have been used on millions of people, including extremely high rates of vaccination in high risk populations (elderly, patients with other diseases), with incredibly low adverse event rates. The reasons behind the misinformation about vaccine safety elude me but there are clearly some organized efforts that are creating fear and confusion during a critical time in this pandemic, something that is incredibly disappointing and frustrating.

Scott

J. Scott Weese DVM DVSc DACVIM FCAHS
Professor, Ontario Veterinary College
Director, Centre for Public Health and Zoonoses
University of Guelph
http://www.wormsandgermsblog.com
Twitter: @Weese_scott

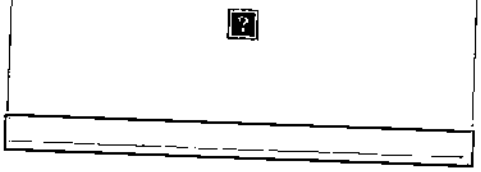
From: Glen Pyle <gpyle@uoguelph.ca>
Date: Wednesday, June 2, 2021 at 1:04 PM
To: David N. Fisman <david.fisman@gmail.com>, Funke, Daniel <DFunke@usatoday.com>
Cc: david.fisman@utoronto.ca <david.fisman@utoronto.ca>, J. Scott Weese <jsweese@uoguelph.ca>, Amy Greer <agreer@uoguelph.ca>
Subject: Re: Media request from USA TODAY (Deadline: 5 p.m. ET)

Hi Daniel.

I can comment on the general claims that the spike protein from the vaccine is dangerous:

The spike protein used in vaccines has been constructed to limit its ability to fully activate. This

Image removed by sender.



The tiny tweak behind COVID-19 vaccines - C&EN

Prepandemic coronavirus research by Jason McLellan and Barney Graham led to a trick for stabilizing the prefusion form of spike proteins

cen.acs.org

Glen,

W. Glen Pyle, PhD
Senior Career Investigator
Improving the Heart & Brain Health for Women in Canada, Heart & Stroke Foundation
Distinguished Professor, Innovation in Teaching
Co-Lead, COVID-19 Resources Canada Science Explained
Professor & Assistant Chair, Department of Biomedical Sciences
Ontario Veterinary College, University of Guelph
Associate Member, IMPART, Dalhousie University
LinkedIn: https://www.linkedin.com/in/glenpyle
Twitter: @glenpyle
"By a divine paradox, wherever there is one slave there are two. So in the wonderful reciprocities of being, we can never reach the higher levels until all our fellows ascend with us."
-- Edwin Markham

From: David N. Fisman <david.fisman@gmail.com>
Sent: 02 June 2021 12:46 PM
To: Funke, Daniel <DFunke@usatoday.com>
Cc: david.fisman@utoronto.ca <david.fisman@utoronto.ca>; J. Scott Weese <jsweese@uoguelph.ca>; Amy Greer <agreer@uoguelph.ca>; Glen Pyle <gpyle@uoguelph.ca>
Subject: Re: Media request from USA TODAY (Deadline: 5 p.m. ET)

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Hi Daniel

I am actually headed into a busy afternoon and will answer this briefly but I don't think I can really do justice to this topic. Bridle (who I don't know) appears to be distorting scientific evidence that's emerging on covid vaccines to suggest that they are unsafe. In fact, what we are seeing right now with the massive rollout of mRNA vaccines is that they seem remarkably safe. Bridle is suggesting

claims in general?

I expect to file this fact check today around 5 p.m. ET.

Thanks so much!

Daniel Funke
Fact Check Reporter
dfunke@usatoday.com
(813) 364-4369

Hi Scott,

I'm sorry it has taken so long to obtain an answer for you. The answer is not straight forward as liability coverage is dependent on our insurance policy and there is not yet a legal action filed against you for the insurer to evaluate.

There are several criteria that impact coverage under the University's insurance (CURIE):

1. There needs to be a claim for damages. These occur in civil actions, not with criminal charges.

   Defamation civil actions are generally covered as they usually involve a claim for damages. CURIE is currently covering some defamation claims made by Rocco Gelati at other institutions.

   If a criminal process was sought by Rocco/Byram and the police acted on the complaint to pursue charges, our liability insurance will not cover the situation.

2. The statements relate to your employment. Twitter is a challenging sphere as there can be a mix of personal and job-related statements. It's very new legal ground and isn't clearly delineated or defined. This took the bulk of the time. We sought a legal opinion on the tweets/posts we could find (outside of insurer general statement – to understand how we could push them if necessary) and think, though it isn't without risk of coverage denial, that they qualify as job related and would be covered. The closer they are to academic discussions, the better the chance of coverage.

3. If the matter is related to COVID, there is a $1M cap for all the university's claims. We've been fortunately not to have many, yet. But this is something of which we need to be cognizant. We spoke about whether this situation is actually COVID-related (e.g., it's not the university defending a class-action for tuition refund due to covid caused curriculum changes – like some other universities are facing). There's an argument that this is about research comments that happened to be about COVID vaccines so this cap may not apply.

The ultimate answer is one that I hate to give: it depends. It depends on what type of action is brought forward, what is said in the tweets that form the basis for the action, whether the action is considered covid-related and how many covid claims we have. If I had a crystal ball (so just a guess given what Rocco has pursued elsewhere), if action were pursued, I would imagine an unsuccessful attempt to have criminal charges laid and then an action for defamation, which I hope would be covered. But, that is just a gues, .

Scott, I welcome a chat with you about this and if you do receive an statement of claim please connect so that we can send it out.

Kind regards,
Laurie

Laurie Arnott | Assistant Vice-President, Faculty & Academic Staff Relations
Office of the Provost & Vice-President (Academic) | University of Guelph
50 Stone Rd E | Guelph, ON | N1G 2W1 | 519-824-4120 Ext. 53195 | l.arnott@exec.uoguelph.ca
Pronouns: she/her

I acknowledge with respect and gratitude that the University of Guelph resides on the ancestral lands of the Attawandaron people and the treaty lands and territory of the Mississaugas of the Credit. I recognize the significance of the Dish with One Spoon Covenant to this land and offer respect to our Anishinaabe, Haudenosaunee and Métis neighbours.

The information in this message is intended solely for the addressee(s). If you are not the designated recipient, please notify the sender immediately, and permanently delete the original and any copies. Any use of the message by those other than the intended recipients is prohibited.

From: "J. Scott Weese" <jsweese@uoguelph.ca>
Date: Monday, October 18, 2021 at 11:35 AM
To: Laurie Arnott <l.arnott@exec.uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>
Subject: Re: Letter

Thanks Laurie.

Scott

J. Scott Weese DVM DVSc DACVIM FCAHS
Professor, Ontario Veterinary College
Director, Centre for Public Health and Zoonoses
University of Guelph
http://www.wormsandgermsblog.com
Twitter: @Weese_scott

From: Laurie Arnott <l.arnott@exec.uoguelph.ca>
Date: Monday, October 18, 2021 at 11:34 AM
To: J. Scott Weese <jsweese@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>
Subject: Re: Letter

Hi Scott,

Sorry for the delay. I have prompted our counsel for response. They are reviewing the CURIE (Canadian Universities Reciprocal Insurance Exchange) insurance policy (as outlined in the collective agreement) to see if this fits within the policy. I hope to have an answer for you soon.

Laurie

From: "J. Scott Weese" <jsweese@uoguelph.ca>
Date: Wednesday, October 13, 2021 at 8:07 AM
To: Laurie Arnott <l.arnott@exec.uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>
Subject: Re: Letter

Laurie

I'm just following up on this email since I haven't heard back from anyone about possible support from the University.

Thanks

Scott

J. Scott Weese DVM DVSc DACVIM FCAHS
Professor, Ontario Veterinary College
Director, Centre for Public Health and Zoonoses
University of Guelph
http://www.wormsandgermsblog.com
Twitter: @Weese_scott

From: J. Scott Weese <jsweese@uoguelph.ca>
Date: Friday, October 1, 2021 at 4:24 PM
To: Laurie Arnott <l.arnott@exec.uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>
Subject: Re: Letter

Thanks Laurie. I appreciate your support and comments.

I'm not overly bothered by it. It's annoying and frustrating, but was largely expected as this is how they operate. (Admittedly, I probably lost some sleep last night but more out of being annoyed than really bothered). They threaten to intimidate people into silence. Galati seems to threaten to sue a lot and be quite adept at losing lawsuits, but causing hassles along the way. I'm pretty confident this is frivolous and vexatious and would go nowhere, but I guess my main concern (beyond impacts on my blood pressure) are financial, as I realize that even frivolous lawsuits can be expensive to defend against.

In terms of content, the letter's full of inaccuracies and I think statements of harassment (esp criminal harassment are laughable). The only place I think I've commented about Byram recently is one twitter and those are relatively benign (I've attached what I this is the extent of what I've said in Sept).

I've sent the email to UGFA but will send it to Nick Shore as well. I thought they might be realize it probably has to come from me directly.

I'm fine getting their emails for now. I might as well know what's being said. I can forward any as needed.

Thanks again. If you need more information from me at this time, let me know.

As a related FYI, CBC is doing an investigative report on the main misinformation people in Canada and Byram's on the list. I haven't spoken to them but they want a chat on background that I'll probably do in the next week or two. (I'm not sure I'll go on the record at the moment anyway.) I don't want to feed the fire but also think we need voices that are counteracting harmful misinformation. It's a tight line to walk, though, and I'm open to additional thoughts.

Scott

J. Scott Weese DVM DVSc DACVIM FCAHS
Professor, Ontario Veterinary College
Director, Centre for Public Health and Zoonoses
University of Guelph
http://www.wormsandgermsblog.com
Twitter: @Weese_scott

From: Laurie Arnott <l.arnott@exec.uoguelph.ca>
Date: Friday, October 1, 2021 at 4:04 PM
To: J. Scott Weese <jsweese@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>
Subject: FW: Letter

Hello Scott,

Dean Wichtel forwarded your message to me. I have a number of initial thoughts and responses.

1. Most importantly, I appreciate that letters like this are not easy to receive regardless of whether there is a legitimate foundation unpinning them or not. How are you doing? Of course, I want you to be aware of resources to help deal with the stress such as EFAP. But, I am also going to list some initial support or actions. In doing this, I want you to know that we can speak about other needs and actions - please reply to this message and we can arrange a time.
2. I recommend that you provide this email to Nick Shore, the investigator currently investigating the harassment complaint against Byram. It seems to me relevant to that process.

3. We think we can arrange to have emails from Mr. Gelati or Byram Bridle either blocked or redirected (to Jeff, for example) so that you do not receive any others. If redirected, we can arrange to let you know, if you choose, if something has come.
4. We have soought legal advice to sort through the issues raised in the letter. I'll be able to provide a better response on these next week.
5. You can reach out to UGFA for support too.

I'm available most of the weekend to respond to concerns so please reach out as needed and hope to have further information next week.

Kind regards,
Laurie

On 2021-09-30, 2:44 PM, "Jeffrey Wichtel" <jwichtel@uoguelph.ca> wrote:

Hi Laurie and Mary,

I know your file on Mr. Galati continues to grow!

Once you have reviewed, can you please either connect directly with Scott to let him know what action, if any he should take in response to this threat, or let me know, and I will make sure Scott gets the advice.

Thanks,

Jeff

On 2021-09-30, 1:59 PM, "rocco@idirect.com" <rocco@idirect.com> wrote:

CAUTION: This email originated from outside of the University of Guelph. Do not click links or open attachments unless you recognize the sender and know the content is safe. If in doubt, forward suspicious emails to IThelp@uoguelph.ca

Dear Mr. Weese,

I represent Professor Bryam Bridle, please find attached, a two-page letter that is self-explanatory.

Rocco Galati

ROCCO GALATI LAW FIRM
PROFESSIONAL CORPORATION
Rocco Galati, B.A., LL.B., LL.M.
1062 College Street, Lower Level
Toronto ON M6H 1A9

TEL: 416-530-9684
FAX: 416-530-8129

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"Oh why, oh why, does the wind never blow backwards?"---Woody Guthrie

This is Exhibit " K " to the Affidavit of

Byram Bridle, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

security@algolibre.io

Algo Libre

(705) 921-5035

The Impossible... Done Better

Cyber Security Report

Dr. Byram W. Bridle

Our goal in this report is to share our findings in the apparent defamation of Dr. Byram W. Bridle. We begin by detailing our findings, then suggest recommendations for next steps, and finally list our references including data dumps we produced for the report. We employed tools such as *Tor Browser*, nitter.net, *whois*, and *nslookup* in our open source analysis.

Findings

Substack

As described in Dr. Bridle's Substack post[1], this behaviour is primiliary through private messages. We have not analyzed any private messages, but we have not found any mentions of this behaviour in the public comments section. This may be due to the fact that Substack displays an "Author" badge next to the author of the post, which may deter their efforts of misleading people.

> "THANKS FOR YOUR COMMENTS, FOR YOUR LOVE AND SUPPORT YOU HAVE SHOWN ME, I'LL INTRODUCE YOU TO A LIFE CHANGING INVESTMENT THAT WILL HELP YOUR FINANCIAL LIFE, IF INTERESTED MESSAGE ME DIRECTLY ON TELEGRAM 👉@DR_BYRAM"

We want to bring your attention to the font of this private message. There may be a few reasons for this, at this time, we have no definitive explanation as to why it would be written in a such a manner. Further examples of messages would help to garner a more profound understanding of such curious patterns.

X (Twitter)

First registered: May 2021

There's an active user operating with the username @ByramBridle on X (with the name of the user written as Not Dr. Byram Bridle) with posts as recent as 6 days ago according to analysis through the Nitter platform interface to X. Of note, the bio has the website https://byrambridle.com and it seems to be promoting and referencing, which may be indicative of a close collaboration between individuals across the platforms or perhaps a singular person.

Upon further investigation on 2023-12-14, we concluded that @ByramBridle on X and https://byrambridle.com are highly likely to be intimately linked due to numerous posts that

1 https://viralimmunologist.substack.com/p/someone-is-impersonating-me-via-substack

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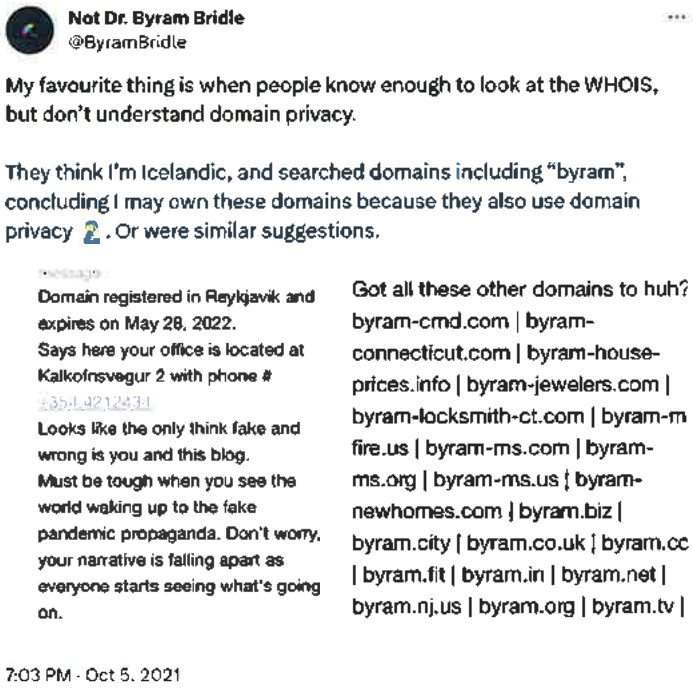
reference technical knowledge of the website, you can see these posts in our X @ByramBridle user select tweets (along with Tweet ID) section, an example is shown below. There is still a possibility that multiple people are involved but one of the contributor has undoubtedly intimate knowledge of privacy-focused internet practices and technology.



Not Dr. Byram Bridle
@ByramBridle

My favourite thing is when people know enough to look at the WHOIS, but don't understand domain privacy.

They think I'm Icelandic, and searched domains including "byram", concluding I may own these domains because they also use domain privacy 🤦. Or were similar suggestions.

Domain registered in Reykjavik and expires on May 28, 2022.
Says here your office is located at Kalkofnsvegur 2 with phone #
[redacted]
Looks like the only think fake and wrong is you and this blog.
Must be tough when you see the world waking up to the fake pandemic propaganda. Don't worry, your narrative is falling apart as everyone starts seeing what's going on.

Got all these other domains to huh?
byram-cmd.com | byram-connecticut.com | byram-house-prices.info | byram-jewelers.com | byram-locksmith-ct.com | byram-mfire.us | byram-ms.com | byram-ms.org | byram-ms.us | byram-newhomes.com | byram.biz | byram.city | byram.co.uk | byram.cc | byram.fit | byram.in | byram.net | byram.nj.us | byram.org | byram.tv |

7:03 PM · Oct 5, 2021

We also took the time to analyze the relationship between @DFisman, @glenpyle, @weese_scott, and the account @ByramBridle (and the website). Are findings are summarized below:

- @DFisman
  - byrambridle.com (https://nitter.net/DFisman/search?f=tweets&q=byrambridle.com&since=&until=&near=)
    - Referenced in 4 tweets (first one is under 36 hours of domain registration)
      - Websites are not instantly available on the internet after registering, there's a propagation delay for DNS records (think printing a phone book update). This time varies, but it can be up to a day depending on the provider
  - @ByramBridle (https://nitter.net/DFisman/search?f=tweets&q=@ByramBridle&since=&until=&near=)
    - Reference in 4 tweets

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- @glenpyle
  - byrambridle.com (https://nitter.net/glenpyle/search?f=tweets&q=byrambridle.com&since=&until=&near=)
    - Referenced in 0 tweets[2]
      - Websites are not instantly available on the internet after registering, there's a propagation delay for DNS records (think printing a phone book update). This time varies, but it can be up to a day depending on the provider
  - @ByramBridle (https://nitter.net/glenpyle/search?f=tweets&q=@ByramBridle&since=&until=&near=)
    - Reference in 5+ tweets
- @weese_scott
  - byrambridle.com (https://nitter.net/weese_scott/search?f=tweets&q=byrambridle.com&since=&until=&near=)
    - Referenced in 5+ tweets[3]
      - First one is within 4 days of domain registration
  - @ByramBridle (https://nitter.net/weese_scott/search?f=tweets&q=@ByramBridle&since=&until=&near=)
    - Referenced in 10+ tweets
- @ByramBridle
  - @Dfisman (https://nitter.net/ByramBridle/search?f=tweets&q=DFisman&since=&until=&near=)
    - Referenced in 10+ tweets
  - @weese_scott (https://nitter.net/ByramBridle/search?f=tweets&q=weese_scott&since=&until=&near=)
    - Referenced in 15+ tweets

---

2 Tweets that reference the website may have been removed and the search was actively looking for @glenpyle's promotion of the website link, so he may have participated in discourse involving the site along with @glenpyle's interactions. Furthermore, @glenpyle replied to a tweet citing the website by @Dfisman on May 30 2021, see https://nitter.net/glenpyle/status/1398842628817526786 and https://twitter.com/glenpyle/status/1398842628817526786

3 Tweets that reference the website may have been removed and the search was actively looking for @glenpyle's promotion of the website link, so he may have participated in discourse involving the site along with @glenpyle's interactions

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- @glenpyle (https://nitter.net/ByramBridle/search?f=tweets&q=glenpyle&since=&until=&near=)
  - Referenced in 10+ tweetsDue to the proximity of tweets to the domain registration through this simple open source search, it suggests to us that there are some relationships that exist between @ByramBridle and these accounts.

Telegram

It's unclear to us when this account was created and our analysis was brief as any interactions with the user could compromise details of our analysis at this stage.

We noticed that the message referenced in Dr. Bridle's Substack post[1] encourages users to contact a username through Telegram (seemlingly @DR_BYRAM[4]).

Domains

For our analysis of the domains, we looked at both the domain details (i.e. DNS and WHOIS records) and the webpage details as available. DNS is short for Domain Name System, that links a web address like google.com to an IP address to access the website. It may be helpful to think of it like a basic phone book where it links a name to a number. WHOIS is not an acronym as it is a porte-manteau of "who is", this augments a DNS record by linking a domain to an individual or company[5].

Every domain contains a WHOIS record identifying details about the domain owner. In recent years, much of this information tends to be redacted on the public facing record or masqued behind privacy-focused organizations. However, these are only barriers that slow down the processas these companies are required to have contact information should someone need to lodge a complaint or contact the domain owner. We included these publicly available records for each domain in our References section. Of note, these records could be falsefied, but that would be a breach of contract, giving you more leverage to have these pages removed. It was brought to our attention on 2023-12-13 that ongoing efforts are already in place by Peel Regional Police to request this information from the registrar. We augmented our report to consider this, but have preserved our original insights due to our employee's historical involvement[6] in investigating some of these domains as well as our detailed insights with respect to where these websites are hosted.

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4 It appears that the message was written with latin alphabet in manner, so we have not confirmed the spelling of this account.

5 It should be noted that it is typical of privacy-focused companies to redact the publicly available contents of these records or replace them with their own so as to limit the domain owner's exposure.

6 AlgoLibre was not founded at the time of this involvement and our employee was contacted on 2023-12-11 with a request to provide cyber security assistance for Dr. Bridle.

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byrambridle.com

Domain registration date (Namecheap, Inc.): *2021-05-28 at 20:54:18 UTC*

Source code initial upload date (GitLab): 2023-06-03 at 10:28:31 UTC

The domain is registered through Namecheap, Inc. One of our employees previously reported this to the company in Fall 2021 to no avail as they demanded legal action or law enforcement interactions before an intervention from their end. Of note, the domain was renewed this past April for another year, which implies that the company has recent transaction information. Due to the nature of the site now, it is unclear whether the user will try to host elsewhere or simply let the domain expire next year. We lean towards the theory that they are searching for another way to host because of the continued activity on X that seems entwinded with this page.

Site *was* hosted by GitLab Pages, there was a link to GitLab in the footer[7] and an archived page not found (404 error) leads to GitLab's page[8]. GitLab is a source code repository site that is very popular with people. The Pages features permits developers to publish a website based on a source code repository containing webpages. In AlgoLibre's experience in working with GitLab Pages, a credit card must be provided to the company to enable this feature. The reason we wrote the site *was* hosted by GitLab pages is that the company has since blocked the user (@concerned-scientist[9]) who created and ran the page. This seems to have hampered the efforts of this party because the DNS records look to be stale as well, still including domain verification tokens for GitLab in the records.

The records and IP addresses indicate that this domain is protected using the Cloudflare service. This company is typically used to protect a site from being spammed or attacked from the internet. That said, between GitLab Pages (a developer-focused tool) and Cloudflare (another technical tool), the configuration of the verification token in the DNS records, we believe may be indicative of a perpetrator with technical experience (or being assisted/guided by someone with this knowledge).

Additionally, performing a public search of other repositories containing "Byram Bridle", we discovered another user @Poltergiest made an exact public copy on November 24, 2022 (called a fork on GitLab) of the original[10]. Though we are unsure of when GitLab decided to block @concerned-scientist, we now this copy was done before the block as the original repository is no longer available to make a copy from with the message below. This means that the repository likely still exists on GitLab services.

Finally, AlgoLibre is in possession of copies in its archives of these publicly available repositories including from when the repository of @concerned-scientist available from the platform. Of note, this matches up with the @ByramBridle X account proclaiming to be a scientist .

7 https://web.archive.org/web/20210630130704/https://byrambridle.com/
8 https://web.archive.org/web/20210615033529/https://byrambridle.com/robots.txt
9 https://gitlab.com/concerned-scientist
10 https://gitlab.com/poltergiest/byrambridle

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drbyrambridle.com

Domain registration date (Internet.bs): *2021-05-28 at 20:54:18 UTC*

Site Creation (WordPress):

> *There's no exact date akin to the previous domain, due to the nature of Wordpress. That said, looking at the URL of the images indicates activity in January (main picture) and August (secondary photos) 2023*

This domain was brought to our attention on 2023-12-12, we examined it's records in the same manner as byrambridle.com (DNS and WHOIS records). We also examined the site through Tor Browser (in an effort to secure our tracks) to determine if there are any clues in its origin embed in the site content, sometimes details are accidentally left publicly visible. It is curious that this site uses entirely different architecture than the previous domain, including the domain registrar, hosting company, and hosting technology.

To start, the domain registrar is Internet Domain Service BS Corp. Site. Of note, the email used for the domain registration is publicly visible in this case, which seems to point a service at https://domain-contact.org/. While it is unclear whether the perpetrator is truly using the service provided by Key-Systems GmbH (visible after clicking Imprint button).

The hosting company is Cycorn Hong Kong Limited branded as TanzaniaHosting.com. Our evidence for this claim is that the DNS/WHOIS records of the domain point to their servers (i.e. their name servers), which is common practice for simplicity of web management. This company also clearly declares their payment options[11].

The webpage technology is WordPress. This is a popular solution for websites of all kinds, especially blogs. Such a technology would make it feasible to replicate a site to be used against other victims. The generic nature of the content apart from Dr. Bridle's name leads us to believe that it may be used elsewhere on the internet, but our efforts to search based on explicit portions of the content has not yielded any favorable results, so there may be efforts to mitigate the searchability of these sites. Of note, even a search of "drbyrambridle.com" (on Qwant for instance) does not in our experience guarantee it will be the first result or even show up.

11 https://tanzaniahosting.com/payment.php

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alexpierson.ca

We were made aware of a sister site to byrambridle.com on 2023-12-13. Due to the fact the site is now offline and the domain has been released, a more in-depth analysis would be required in a follow-up report. We do note however that both byrambridle.com and alexpierson.ca utilize a similar webpage design from the same template project (HTML5 UP[12]). Combined with the fact the websites reference each other, this is indicative of a coordinated effort because reusing a similar template simplifies the development of the sites. See the footer of both sites captured in Spring 2022[13][14]. Of note, both sites seem to converge to this template project following exploration of other technologies at first[15].

Recommendations

One common thing we noticed in these platforms selected is that many of them require credit cards and similar traceable payment options. There may be also identifiable information found in emails, domain records and similar. In our experience, these platforms will not reveal these insightful details without being compelled to do so through legal or law enforcement action. Please let us know of your questions or should you need additional insights from us on this case.

Substack

Ensure people who were sent messages have saved screenshots of the usernames of accounts that were sending these private messages, and report this information to Substack.

Similarly, keep an eye out for such messages in comments as well.

X (Twitter)

We have had negative experiences in getting Twitter to remove similar content using an employee's Twitter account, but without legal representation.

X has a few places to contact that may yield more successful results

- Abuse: https://help.twitter.com/en/forms/safety-and-sensitive-content/abuse/legal-rep
- Impersonation: https://help.twitter.com/en/forms/authenticity/impersonation/someone-i-represent

We are doubtful however of this platform's ability to identify a perpetrator considering they have not paid to receive a blue checkmark, so they likely have limited information on their identity.

12 https://html5up.net/
13 https://web.archive.org/web/20220613131416/https://byrambridle.com/
14 https://web.archive.org/web/20220516105118/http://alexpierson.ca/
15 https://web.archive.org/web/20210714145251/http://alexpierson.ca/

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Telegram

We have already contacted Telegram's Reporting Impersonation service at https://t.me/notoscam with one of our accounts on the service, as per their FAQ[16]. Having received no response (or acknowledgment of our message) from the company yet, we suggest that you contact them at abuse@telegram.org. Due to the privacy-first nature of this service, we believe other platforms will be more fruitful in an effort to identify perpetrators.

Domains

We learned that on 2023-12-13 that Peel Regional Police has already made efforts to contact Namecheap which have yet to be fulfilled due to the company's desire to protect their customer's information. We were also made aware of the potential for the domain registrar to alert their customer of the investigation unless a non-disclosure order is served along with the production order. With these new insights, our recommendation is to consider communicating to GitLab through a law enforcement request. AlgoLibre's experience with the organization indicates that the website's infrastructure, though hosted at no cost to the user, would require a valid credit card to verify the user's identity. We expect there to be less resistance from this organization in fulfilling this as their profile remains in a blocked state on their site, as shown in our References section of GitLab.

byrambridle.com

Domain registrar:

- Contact Namecheap by filling out the form: https://support.namecheap.com/index.php?/Tickets/Submit/RenderForm/219
- Law enforcement can contact directly at lea_abuse@namecheap.com
  - We were made aware that law enforcement has previously commenced this process
- Of note, the company will **not** disclose domain contact information without a legal demand such as a Court Order or Subpoena, as per their FAQ[17]

Cloudflare[18]:

- Note, the user may not be paying for this service, so billing information may not be available
- Complete this form: https://abuse.cloudflare.com/threat

16 https://telegram.org/faq#q-there-39s-illegal-content-on-telegram-how-
17 https://www.namecheap.com/support/knowledgebase/article.aspx/9196/5/how-and-where-can-i-file-abuse-

18 https://developers.cloudflare.com/fundamentals/reference/report-abuse

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- Law enforcement can contact directly at abuse+law@cloudflare.com
  - Note they ask you clearly identify yourself with "badge & case number, or other information such as your rank, agency, and unit"[19]

GitLab:

- Direct your communications to abuse@gitlab.com.
- They have a detailed process for law enforcement requests[20]
  - Note, in exigent circumstances, agents can email legal@gitlab.com with the subject "Emergency Disclosure Request" and complete this form [21]
- GitLab still has this account showing on their site with a note that it is blocked. Perhaps they still have some contact information including the credit card used to activate the Pages feature.

drbyrambridle.com

Domain registrar:

- Please contact abuse@internet.bs and provide the following information:
  - exact URL(s) where we can see the violation
  - for matters where URLs cannot be used (i.e. spam and/or phishing allegations), copies of files used as part of the violation and evidence as to their origins (i.e. emails including full headers).
  - any other supporting evidence such as screen shots and/or server log files. Upon request, the reporter should provide additional supporting information to help us investigate and assess the issue.
- Note: It is worthwhile collaborating with law enforcement for this process as to expedite the results
- As described in the Findings section, you can also contact Key-Systems GmbH abuse@key-systems.net to see if they have any insights

Hosting:

- It's not clear where to send the report
  - They have contact forms: https://my.tanzaniahosting.com/submitticket.php

19 https://www.cloudflare.com/trust-hub/law-enforcement/
20 https://handbook.gitlab.com/handbook/legal/privacy/law-enforcement-guidelines/
21 https://handbook.gitlab.com/handbook/legal/privacy/law-enforcement-guidelines/#emergency-requests

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- They also have support@tanzaniahosting.com according to their terms[22]

alexpierson.ca

Due to the timeline in which we were made aware of this website in combination with the status of the site being offline, we are unable to complete a similar analysis to the previous domains. As this domain has been returned to the pool of available web addreses, there are no current DNS and WHOIS records available for our analysis.

Uniform Domain-Name Dispute-Resolution Policy (UDRP)

The UDRP is a legal process typically used to ascertain the ownership of a domain[23]. It could be employed to forcibly take ownership or block the use of these domains in order to remove the defamation. While this could be used to compel the individual or some information about them, we feel in order to evade a confrontation, the current perpetrator may choose to simply move to another domain. A discussion with a legal firm capable of handling such a request would provide a more profound understanding of the process. Canadian International Internet Dispute Resolution Centre (CIIDRC) would be such a firm, they have on their site a flow chart explaining the process[24].

22 https://www.tanzaniahosting.com/terms.php
23 https://www.icann.org/resources/pages/help/dndr/udrp-en
24 https://ciidrc.org/how-it-works/

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Search Engines

Removing the results in search engines is possible but it is not always clear cut process. That said, it is important to also follow the above steps to address the problem at the source.

Google

You can contact Google through the forms available at https://support.google.com/websearch/troubleshooter/3111061 to file a request.

Bing

You can contact Google through the forms available at https://www.microsoft.com/en-us/concern/bing to file a request.

Qwant

Qwant is a privacy focused search engine based in France, we were pleased to see a contact email to reach for such situations: legal@qwant.net.

Other search engines (Yahoo, DuckDuckGo, etc.)

It is common industry practice for other search engines to feed their results from other search engines. Therefore, we feel the best approach is to address the ones above, then monitor other search engines and contact them if their page continues to show the older results.

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References

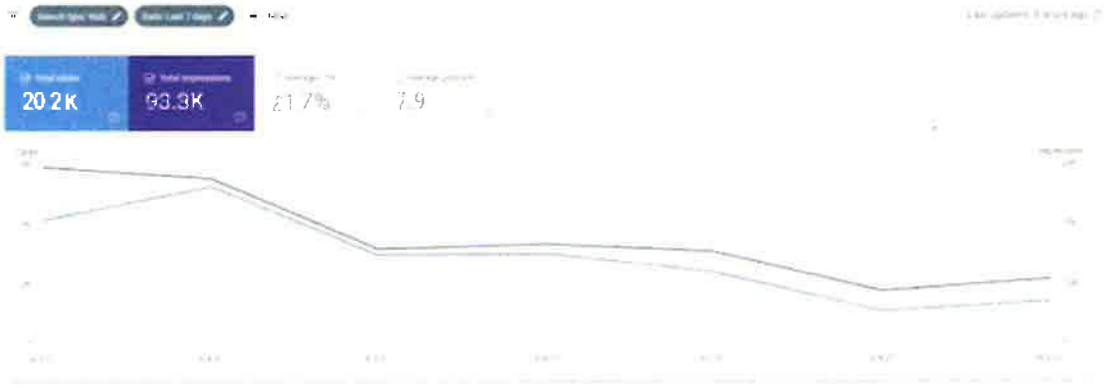
X @ByramBridle user select tweets (along with Tweet ID)

1403200193298894848

Not Dr. Byram Bridle
@ByramBridle

I don't collect stats on the site directly, but I did get 20k search click-throughs this week.

That's not half bad for a simple scientific site, especially since it doesn't include any of the times people have visited the URL directly. It's pretty easy to remember after all!



3:59 AM · Jun 11, 2021

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1406966983137058822

Not Dr. Byram Bridle
@ByramBridle

For all those in the back:

I've never claimed to work for, or be funded by @ScienceUpFirst.

There is a disclaimer at the bottom - which was there, and still is there right now - that none of the people linked to on ByramBridle.com fund or contribute.

💯% self-funded.

1:27 PM · Jun 21, 2021

1428132686514769927 (notice the reference to HTML code)

Not Dr. Byram Bridle
@ByramBridle

Both the disclaimer in the HTML code - and the disclaimer directly on the site - have been there for months.

You're not the first person to erroneously attribute the site to @ScienceUpFirst.

I'm also still not @DFisman, or @georgesoros as others have claimed.

11:12 PM · Aug 18, 2021

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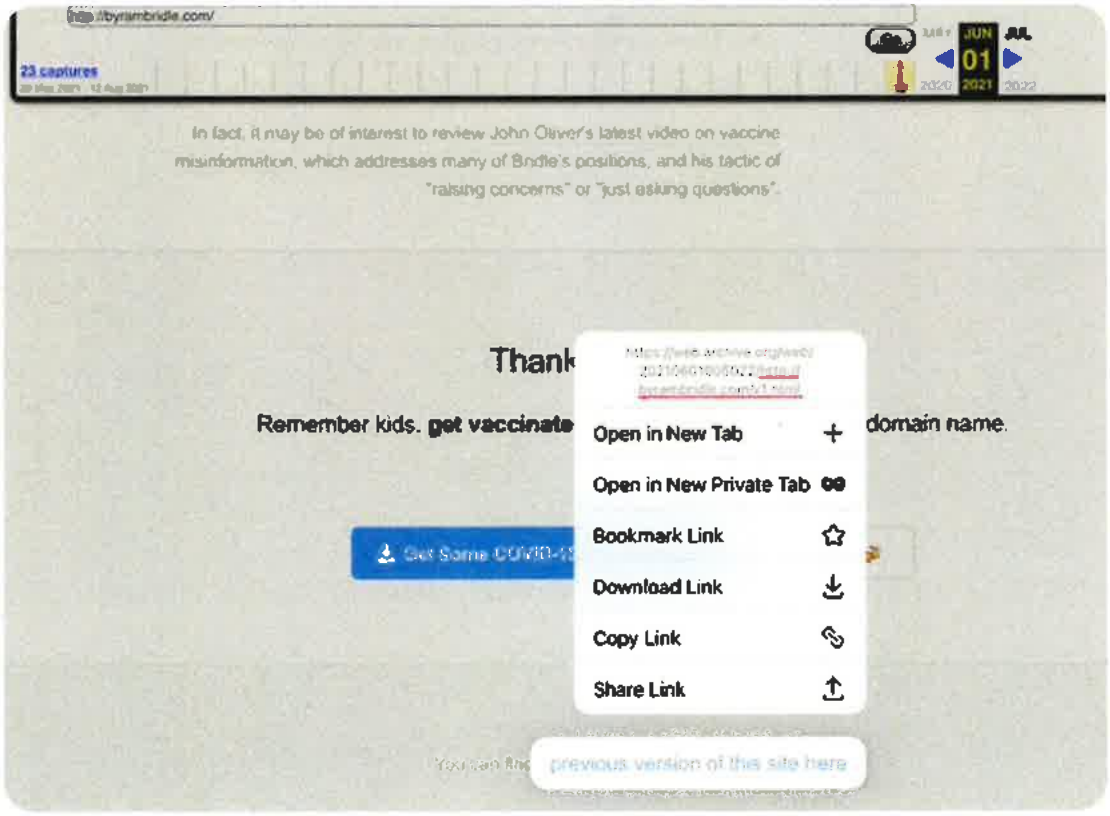
1428145824211607555 (shows that they are familiar with website archiving and that they use an Apple iPad, which supports the Peel Region Open Source Police investigation of the account)

Not Dr. Byram Bridle
@ByramBridle

I don't know what you're smoking.

It clearly goes to /v1. You're confusing it with the links above.



12:04 AM · Aug 19, 2021

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1445464589949304832

Not Dr. Byram Bridle
@ByramBridle

My favourite thing is when people know enough to look at the WHOIS, but don't understand domain privacy.

They think I'm Icelandic, and searched domains including "byram", concluding I may own these domains because they also use domain privacy 🤦. Or were similar suggestions.

[redacted]
Domain registered in Reykjavik and expires on May 28, 2022.
Says here your office is located at Kalkofnsvegur 2 with phone # +354.4212434
Looks like the only think fake and wrong is you and this blog.
Must be tough when you see the world waking up to the fake pandemic propaganda. Don't worry, your narrative is falling apart as everyone starts seeing what's going on.

Got all these other domains to huh?
byram-cmd.com | byram-connecticut.com | byram-house-prices.info | byram-jewelers.com | byram-locksmith-ct.com | byram-mfire.us | byram-ms.com | byram-ms.org | byram-ms.us | byram-newhomes.com | byram.biz | byram.city | byram.co.uk | byram.cc | byram.fit | byram.in | byram.net | byram.nj.us | byram.org | byram.tv |

7:03 PM · Oct 5, 2021

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1471150985087270913 (notice that they proclaim to be a scientist here)

Not Dr. Byram Bridle
@ByramBridle

I'm an actual scientist, trained in the field, who understands the limits of my knowledge and where to get high quality data and sound analyses.

Peterson is a religious grifter, who engages in motivated reasoning, and obfuscates with flowery language.

4:11 PM · Dec 15, 2021

1473720167519694854

Not Dr. Byram Bridle
@ByramBridle

Except everything at byrambridle.com.

I should update it over the holidays!

6:20 PM · Dec 22, 2021

1598732856846491649 (this plainly links the website to the X account)

Not Dr. Byram Bridle
@ByramBridle

Ahh, hence the influx of new followers.

My website got knocked offline - when it's back up, will have to feature a response!

5:36 PM · Dec 2, 2022

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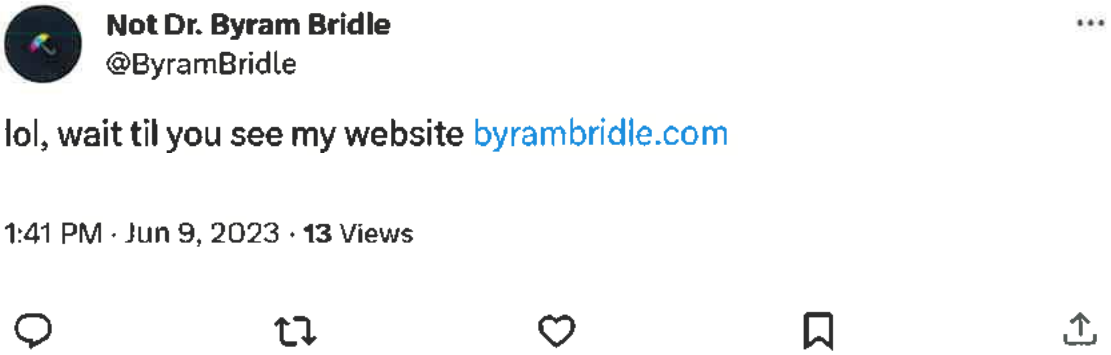
1667164995619045377

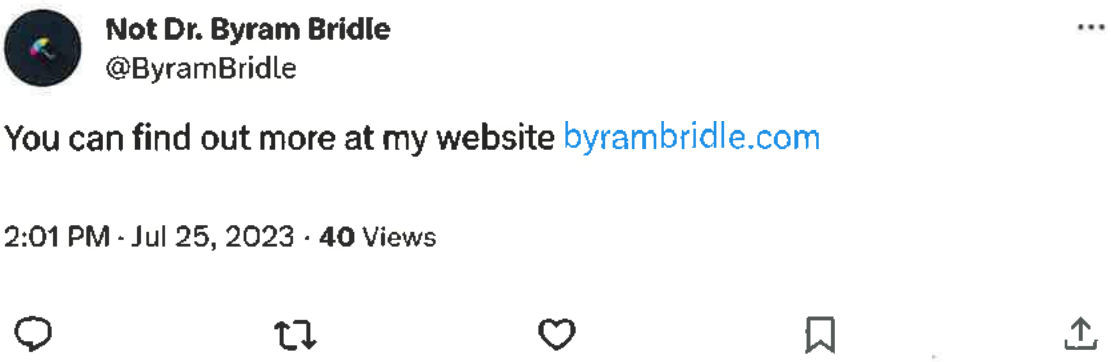


Not Dr. Byram Bridle
@ByramBridle

lol, wait til you see my website byrambridle.com

1:41 PM · Jun 9, 2023 · **13** Views

1683839795381022726



Not Dr. Byram Bridle
@ByramBridle

You can find out more at my website byrambridle.com

2:01 PM · Jul 25, 2023 · **40** Views

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Main profile bio and name

← **Not Dr. Byram Bridle**
2,044 posts

[102] Given the circumscribed nature and extent of Dr. Bridle's expertise, **the fact that he expresses opinions well outside the parameters of his expertise and apparently at odds with the prevailing state of medical and scientific knowledge**, I prefer the opinio[illegible] Drs. Leis and Vaisman, and cannot accept Dr. Bridle's op[illegible]pinning the applicants' arguments described a[illegible] that I cannot and do not accept the applicants'

Follow

Not Dr. Byram Bridle
@ByramBridle

I'm Not Dr. Byram Bridle, a parody account highlighting COVID-19 related misinformation.

I do my homework, and I bring receipts. Do you?

byrambridle.com Joined May 2021

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WHOIS Record byrambridle.com (obtained using the software WHOIS version 5.5.17 by Marco d'Itri)

```
 Domain Name: BYRAMBRIDLE.COM
   Registry Domain ID: 2615732698_DOMAIN_COM-VRSN
   Registrar WHOIS Server: whois.namecheap.com
   Registrar URL: http://www.namecheap.com
   Updated Date: 2023-04-28T06:00:05Z
   Creation Date: 2021-05-28T20:54:18Z
   Registry Expiry Date: 2024-05-28T20:54:18Z
   Registrar: NameCheap, Inc.
   Registrar IANA ID: 1068
   Registrar Abuse Contact Email: abuse@namecheap.com
   Registrar Abuse Contact Phone: +1.6613102107
   Domain Status: clientTransferProhibited https://icann.org/epp#clientTransferProhibited
   Name Server: DUKE.NS.CLOUDFLARE.COM
   Name Server: WREN.NS.CLOUDFLARE.COM
   DNSSEC: unsigned
   URL of the ICANN Whois Inaccuracy Complaint Form: https://www.icann.org/wicf/
>>> Last update of whois database: 2023-12-12T20:36:50Z <<<

For more information on Whois status codes, please visit https://icann.org/epp

NOTICE: The expiration date displayed in this record is the date the
registrar's sponsorship of the domain name registration in the registry is
currently set to expire. This date does not necessarily reflect the expiration
date of the domain name registrant's agreement with the sponsoring
registrar.  Users may consult the sponsoring registrar's Whois database to
view the registrar's reported date of expiration for this registration.

TERMS OF USE: You are not authorized to access or query our Whois
database through the use of electronic processes that are high-volume and
automated except as reasonably necessary to register domain names or
modify existing registrations; the Data in VeriSign Global Registry
Services' ("VeriSign") Whois database is provided by VeriSign for
information purposes only, and to assist persons in obtaining information
about or related to a domain name registration record. VeriSign does not
guarantee its accuracy. By submitting a Whois query, you agree to abide
by the following terms of use: You agree that you may use this Data only
for lawful purposes and that under no circumstances will you use this Data
to: (1) allow, enable, or otherwise support the transmission of mass
unsolicited, commercial advertising or solicitations via e-mail, telephone,
or facsimile; or (2) enable high volume, automated, electronic processes
that apply to VeriSign (or its computer systems). The compilation,
repackaging, dissemination or other use of this Data is expressly
prohibited without the prior written consent of VeriSign. You agree not to
use electronic processes that are automated and high-volume to access or
query the Whois database except as reasonably necessary to register
domain names or modify existing registrations. VeriSign reserves the right
to restrict your access to the Whois database in its sole discretion to ensure
operational stability.  VeriSign may restrict or terminate your access to the
Whois database for failure to abide by these terms of use. VeriSign
reserves the right to modify these terms at any time.

The Registry database contains ONLY .COM, .NET, .EDU domains and
```

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```
Registrars.
Domain name: byrambridle.com
Registry Domain ID: 2615732698_DOMAIN_COM-VRSN
Registrar WHOIS Server: whois.namecheap.com
Registrar URL: http://www.namecheap.com
Updated Date: 2023-04-28T06:00:05.41Z
Creation Date: 2021-05-28T20:54:18.00Z
Registrar Registration Expiration Date: 2024-05-28T20:54:18.00Z
Registrar: NAMECHEAP INC
Registrar IANA ID: 1068
Registrar Abuse Contact Email: abuse@namecheap.com
Registrar Abuse Contact Phone: +1.9854014545
Reseller: NAMECHEAP INC
Domain Status: clientTransferProhibited https://icann.org/epp#clientTransferProhibited
Registry Registrant ID:
Registrant Name: Redacted for Privacy
Registrant Organization: Privacy service provided by Withheld for Privacy ehf
Registrant Street: Kalkofnsvegur 2
Registrant City: Reykjavik
Registrant State/Province: Capital Region
Registrant Postal Code: 101
Registrant Country: IS
Registrant Phone: +354.4212434
Registrant Phone Ext:
Registrant Fax:
Registrant Fax Ext:
Registrant Email: 4de50ec07fbe4f78a659965896a2ab47.protect@withheldforprivacy.com
Registry Admin ID:
Admin Name: Redacted for Privacy
Admin Organization: Privacy service provided by Withheld for Privacy ehf
Admin Street: Kalkofnsvegur 2
Admin City: Reykjavik
Admin State/Province: Capital Region
Admin Postal Code: 101
Admin Country: IS
Admin Phone: +354.4212434
Admin Phone Ext:
Admin Fax:
Admin Fax Ext:
Admin Email: 4de50ec07fbe4f78a659965896a2ab47.protect@withheldforprivacy.com
Registry Tech ID:
Tech Name: Redacted for Privacy
Tech Organization: Privacy service provided by Withheld for Privacy ehf
Tech Street: Kalkofnsvegur 2
Tech City: Reykjavik
Tech State/Province: Capital Region
Tech Postal Code: 101
Tech Country: IS
Tech Phone: +354.4212434
Tech Phone Ext:
Tech Fax:
Tech Fax Ext:
Tech Email: 4de50ec07fbe4f78a659965896a2ab47.protect@withheldforprivacy.com
Name Server: duke.ns.cloudflare.com
Name Server: wren.ns.cloudflare.com
DNSSEC: unsigned
```

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```
URL of the ICANN WHOIS Data Problem Reporting System: http://wdprs.internic.net/
>>> Last update of WHOIS database: 2023-12-11T21:37:11.01Z <<<
```

Select DNS records for byrambridle.com

- *A record, for IP addresses of the web server*

  Points to 172.64.80.1, which is an IP known to be used by CloudFlare[25][26]

  This is curious to us because it's an unnecessary extra protection when GitLab Pages is hosted as the hosting service already has a similar protection system in-place

- *MX records, for email systems*

  No records found, so no email is currently set up

- *TXT records, notice this GitLab domain verification token*[27]

  ```
  byrambridle.com text = "_gitlab-pages-verification-code.byrambridle.com TXT gitlab-pages-v
  erification-code=d660cd2c363fa12c1ecf528f0c05eac9"
  ```

WHOIS Record drbyrambridle.com (obtained using the software WHOIS version 5.5.17 by Marco d'Itri)

```
 Domain Name: DRBYRAMBRIDLE.COM
   Registry Domain ID: 2806531868_DOMAIN_COM-VRSN
   Registrar WHOIS Server: whois.internet.bs
   Registrar URL: http://www.internet.bs
   Updated Date: 2023-08-26T14:22:39Z
   Creation Date: 2023-08-17T13:35:36Z
   Registry Expiry Date: 2024-08-17T13:35:36Z
   Registrar: Internet Domain Service BS Corp
   Registrar IANA ID: 2487
   Registrar Abuse Contact Email: abuse@internet.bs
   Registrar Abuse Contact Phone: +1.5163015301
   Domain Status: ok https://icann.org/epp#ok
   Name Server: NS1.TANZANIAHOSTING.COM
   Name Server: NS2.TANZANIAHOSTING.COM
   DNSSEC: unsigned
   URL of the ICANN Whois Inaccuracy Complaint Form: https://www.icann.org/wicf/
>>> Last update of whois database: 2023-12-13T01:43:41Z <<<

For more information on Whois status codes, please visit https://icann.org/epp

NOTICE: The expiration date displayed in this record is the date the
registrar's sponsorship of the domain name registration in the registry is
currently set to expire. This date does not necessarily reflect the expiration
date of the domain name registrant's agreement with the sponsoring
registrar.  Users may consult the sponsoring registrar's Whois database to
view the registrar's reported date of expiration for this registration.
```

25 https://ipinfo.io/172.64.80.1
26 https://www.whois.com/whois/172.64.80.1
27 https://docs.gitlab.com/ee/user/project/pages/custom_domains_ssl_tls_certification/index.html

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```
TERMS OF USE: You are not authorized to access or query our Whois
database through the use of electronic processes that are high-volume and
automated except as reasonably necessary to register domain names or
modify existing registrations; the Data in VeriSign Global Registry
Services' ("VeriSign") Whois database is provided by VeriSign for
information purposes only, and to assist persons in obtaining information
about or related to a domain name registration record. VeriSign does not
guarantee its accuracy. By submitting a Whois query, you agree to abide
by the following terms of use: You agree that you may use this Data only
for lawful purposes and that under no circumstances will you use this Data
to: (1) allow, enable, or otherwise support the transmission of mass
unsolicited, commercial advertising or solicitations via e-mail, telephone,
or facsimile; or (2) enable high volume, automated, electronic processes
that apply to VeriSign (or its computer systems). The compilation,
repackaging, dissemination or other use of this Data is expressly
prohibited without the prior written consent of VeriSign. You agree not to
use electronic processes that are automated and high-volume to access or
query the Whois database except as reasonably necessary to register
domain names or modify existing registrations. VeriSign reserves the right
to restrict your access to the Whois database in its sole discretion to ensure
operational stability.  VeriSign may restrict or terminate your access to the
Whois database for failure to abide by these terms of use. VeriSign
reserves the right to modify these terms at any time.

The Registry database contains ONLY .COM, .NET, .EDU domains and
Registrars.
Domain Name: drbyrambridle.com
Registry Domain ID: 2806531868_DOMAIN_COM-VRSN
Registrar WHOIS Server: whois.internet.bs
Registrar URL:
Updated Date: 2023-08-26T14:22:39Z
Creation Date: 2023-08-17T13:35:36Z
Registrar Registration Expiration Date: 2024-08-17T13:35:36Z
Registrar: Internet Domain Service BS Corp.
Registrar IANA ID: 2487
Registrar Abuse Contact Email: abuse[at]internet.bs
Registrar Abuse Contact Phone: +1.5163015301
Domain Status: ok https://icann.org/epp#ok
Registry Registrant ID: REDACTED FOR PRIVACY
Registrant Name: REDACTED FOR PRIVACY
Registrant Organization: REDACTED FOR PRIVACY
Registrant Street: REDACTED FOR PRIVACY
Registrant Street: REDACTED FOR PRIVACY
Registrant Street: REDACTED FOR PRIVACY
Registrant City: REDACTED FOR PRIVACY
Registrant State/Province:
Registrant Postal Code: REDACTED FOR PRIVACY
Registrant Country: MT
Registrant Phone: REDACTED FOR PRIVACY
Registrant Phone Ext: REDACTED FOR PRIVACY
Registrant Fax: REDACTED FOR PRIVACY
Registrant Fax Ext: REDACTED FOR PRIVACY
Registrant Email: info@domain-contact.org
Registry Admin ID: REDACTED FOR PRIVACY
Admin Name: REDACTED FOR PRIVACY
Admin Organization: REDACTED FOR PRIVACY
Admin Street: REDACTED FOR PRIVACY
```

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```
Admin Street: REDACTED FOR PRIVACY
Admin Street: REDACTED FOR PRIVACY
Admin City: REDACTED FOR PRIVACY
Admin State/Province: REDACTED FOR PRIVACY
Admin Postal Code: REDACTED FOR PRIVACY
Admin Country: REDACTED FOR PRIVACY
Admin Phone: REDACTED FOR PRIVACY
Admin Phone Ext: REDACTED FOR PRIVACY
Admin Fax: REDACTED FOR PRIVACY
Admin Fax Ext: REDACTED FOR PRIVACY
Admin Email: info@domain-contact.org
Registry Tech ID: REDACTED FOR PRIVACY
Tech Name: REDACTED FOR PRIVACY
Tech Organization: REDACTED FOR PRIVACY
Tech Street: REDACTED FOR PRIVACY
Tech Street: REDACTED FOR PRIVACY
Tech Street: REDACTED FOR PRIVACY
Tech City: REDACTED FOR PRIVACY
Tech State/Province: REDACTED FOR PRIVACY
Tech Postal Code: REDACTED FOR PRIVACY
Tech Country: REDACTED FOR PRIVACY
Tech Phone: REDACTED FOR PRIVACY
Tech Phone Ext: REDACTED FOR PRIVACY
Tech Fax: REDACTED FOR PRIVACY
Tech Fax Ext: REDACTED FOR PRIVACY
Tech Email: info@domain-contact.org
Registry Billing ID: REDACTED FOR PRIVACY
Billing Name: REDACTED FOR PRIVACY
Billing Organization: REDACTED FOR PRIVACY
Billing Street: REDACTED FOR PRIVACY
Billing Street: REDACTED FOR PRIVACY
Billing Street: REDACTED FOR PRIVACY
Billing City: REDACTED FOR PRIVACY
Billing State/Province: REDACTED FOR PRIVACY
Billing Postal Code: REDACTED FOR PRIVACY
Billing Country: REDACTED FOR PRIVACY
Billing Phone: REDACTED FOR PRIVACY
Billing Phone Ext: REDACTED FOR PRIVACY
Billing Fax: REDACTED FOR PRIVACY
Billing Fax Ext: REDACTED FOR PRIVACY
Billing Email: info@domain-contact.org
Name Server: ns1.tanzaniahosting.com
Name Server: ns2.tanzaniahosting.com
DNSSEC: unsigned
URL of the ICANN WHOIS Data Problem Reporting System: https://wdprs.internic.net/
>>> Last update of WHOIS database: 2023-12-13T01:43:49Z <<<

For more information on Whois status codes, please visit https://www.icann.org/epp

To contact the registered registrant please proceed to:
https://www.domain-contact.org


This data is provided by
for information purposes, and to assist persons obtaining information
about or related to domain name registration records.
does not guarantee its accuracy.
By submitting a WHOIS query, you agree that you will use this data
```

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```
only for lawful purposes and that, under no circumstances, you will
use this data to
1) allow, enable, or otherwise support the transmission of mass
  unsolicited, commercial advertising or solicitations via E-mail
  (spam) or
2) enable high volume, automated, electronic processes that apply
  to this WHOIS server.
These terms may be changed without prior notice.
By submitting this query, you agree to abide by this policy.
```

Select DNS records for drbyrambridle.com

- *A record, for IP addresses of the web server*

  There is no A record for this domain, which means another DNS record type is used to link the domain to the website

- *MX records, for email systems, unclear whether this is being used (could be just a bonus offering of the service)*

  ```
  drbyrambridle.com        mail exchanger = 0 drbyrambridle.com.
  ```

- *TXT records, this record is used in verifying email domains in an effort to combat spam*

  ```
  drbyrambridle.com        text = "v=spf1 ip4:83.149.126.239 +a
  +mx ~all"
  ```

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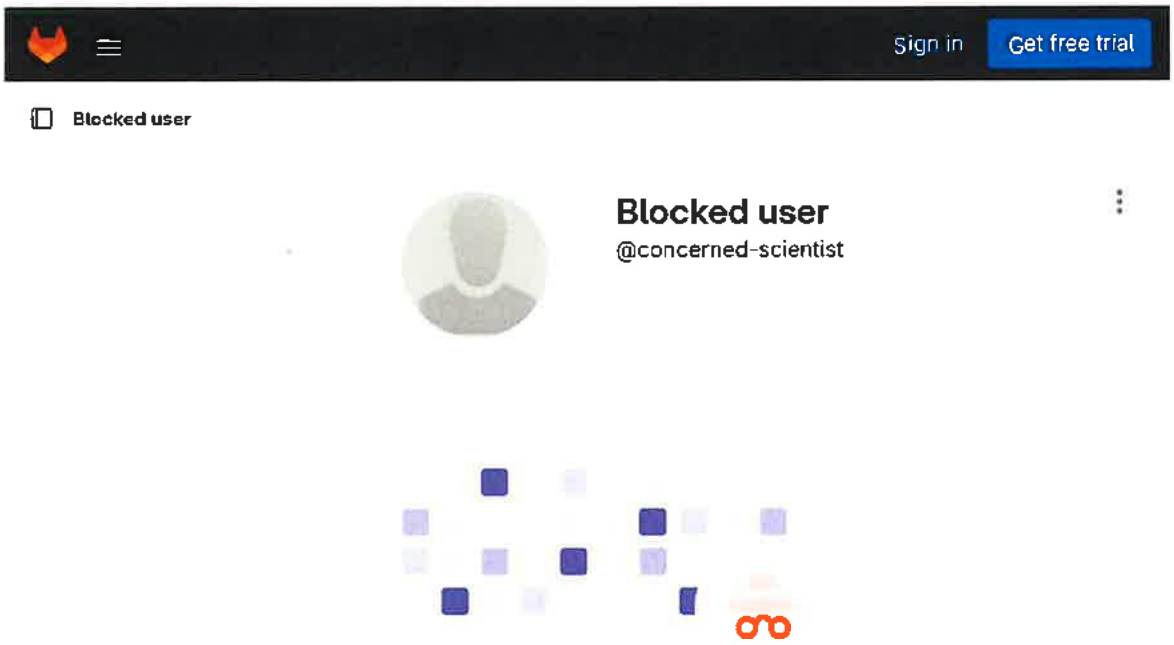
GitLab

The page of the blocked user @concerned-scientist



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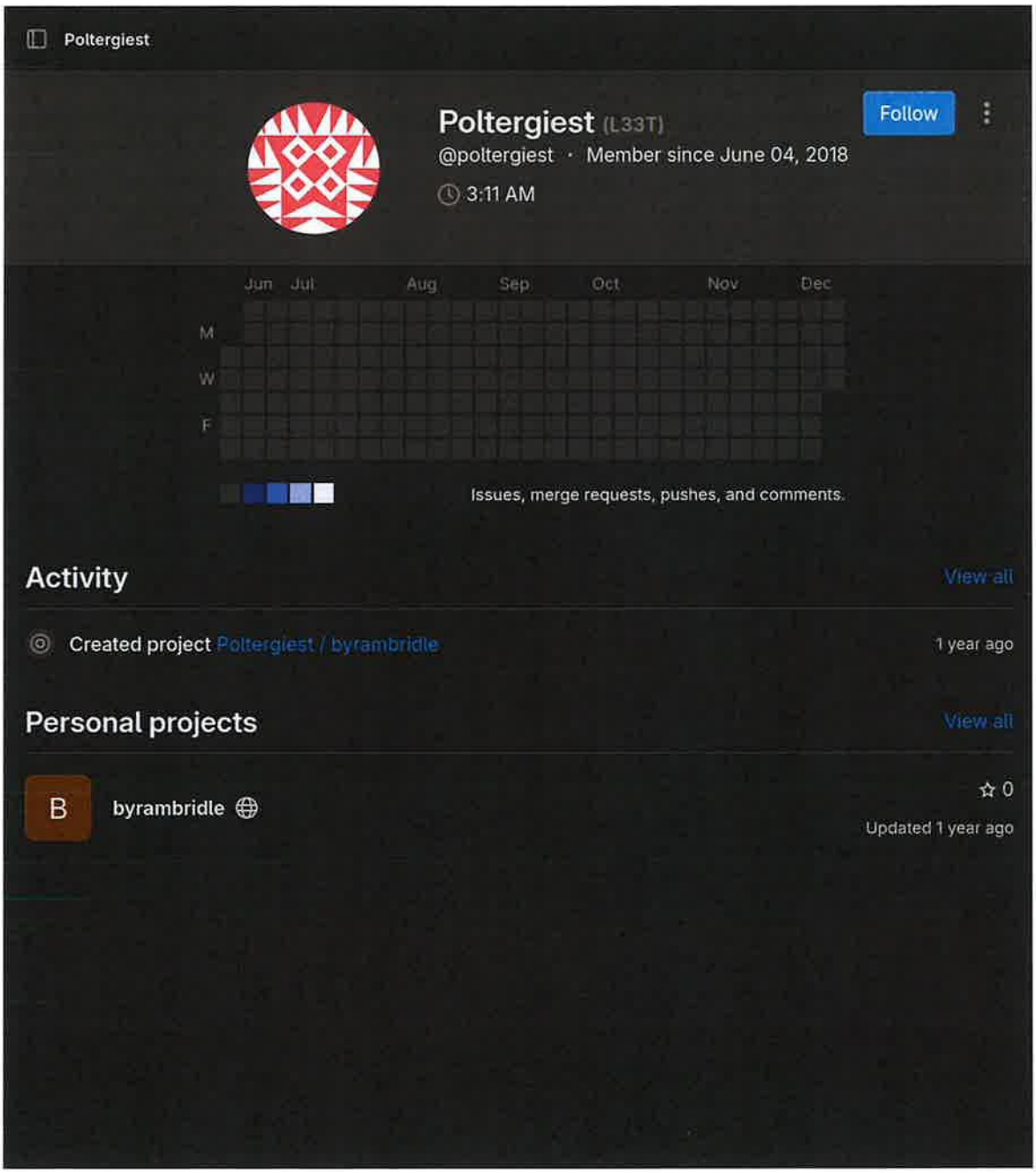
The page of the @Poltergiest user, notice the account creation date (https://gitlab.com/poltergiest):



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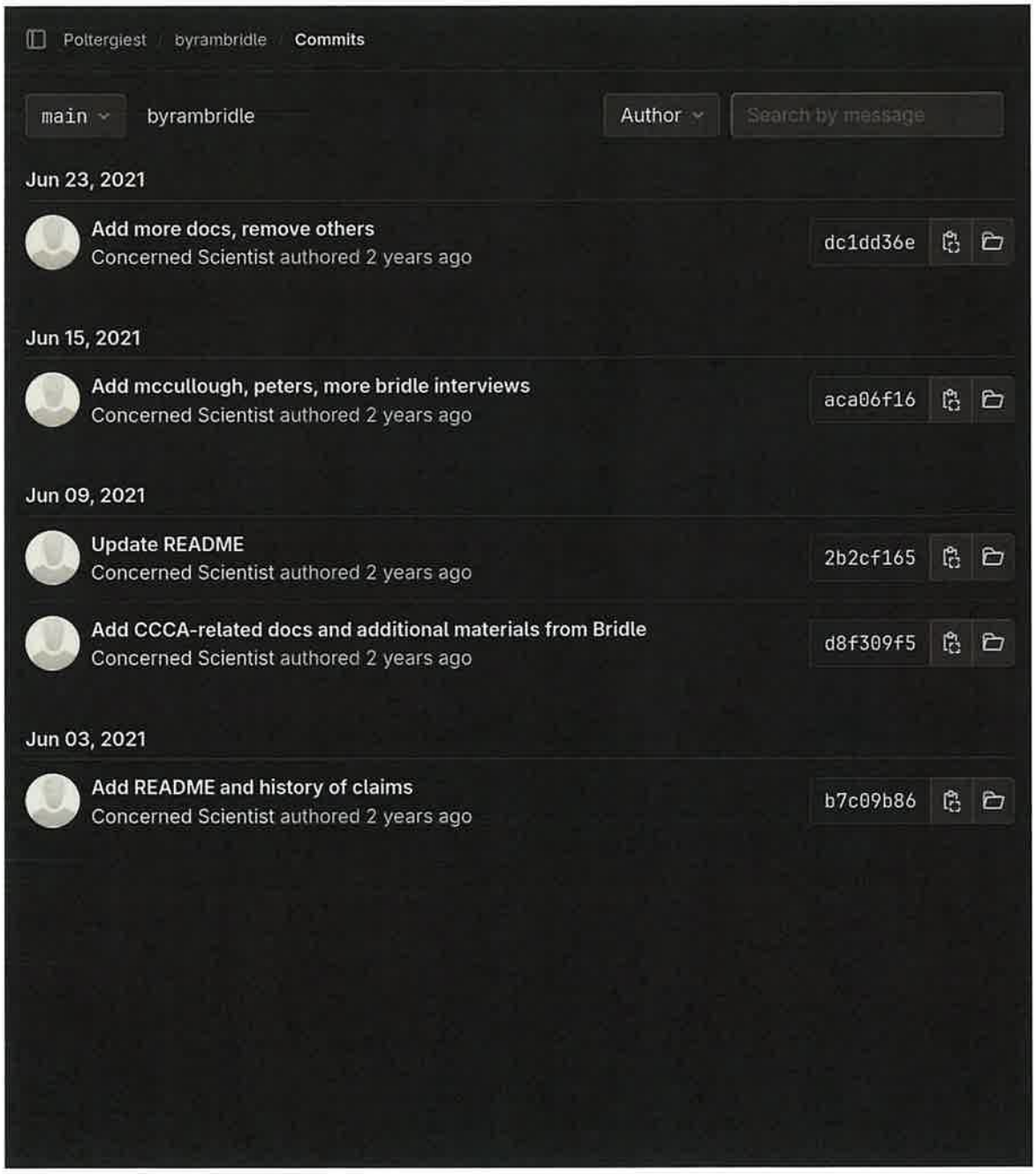
The commit log messages history from the @Poltergiest copy (https://gitlab.com/poltergiest/byrambridle/-/commits/main)



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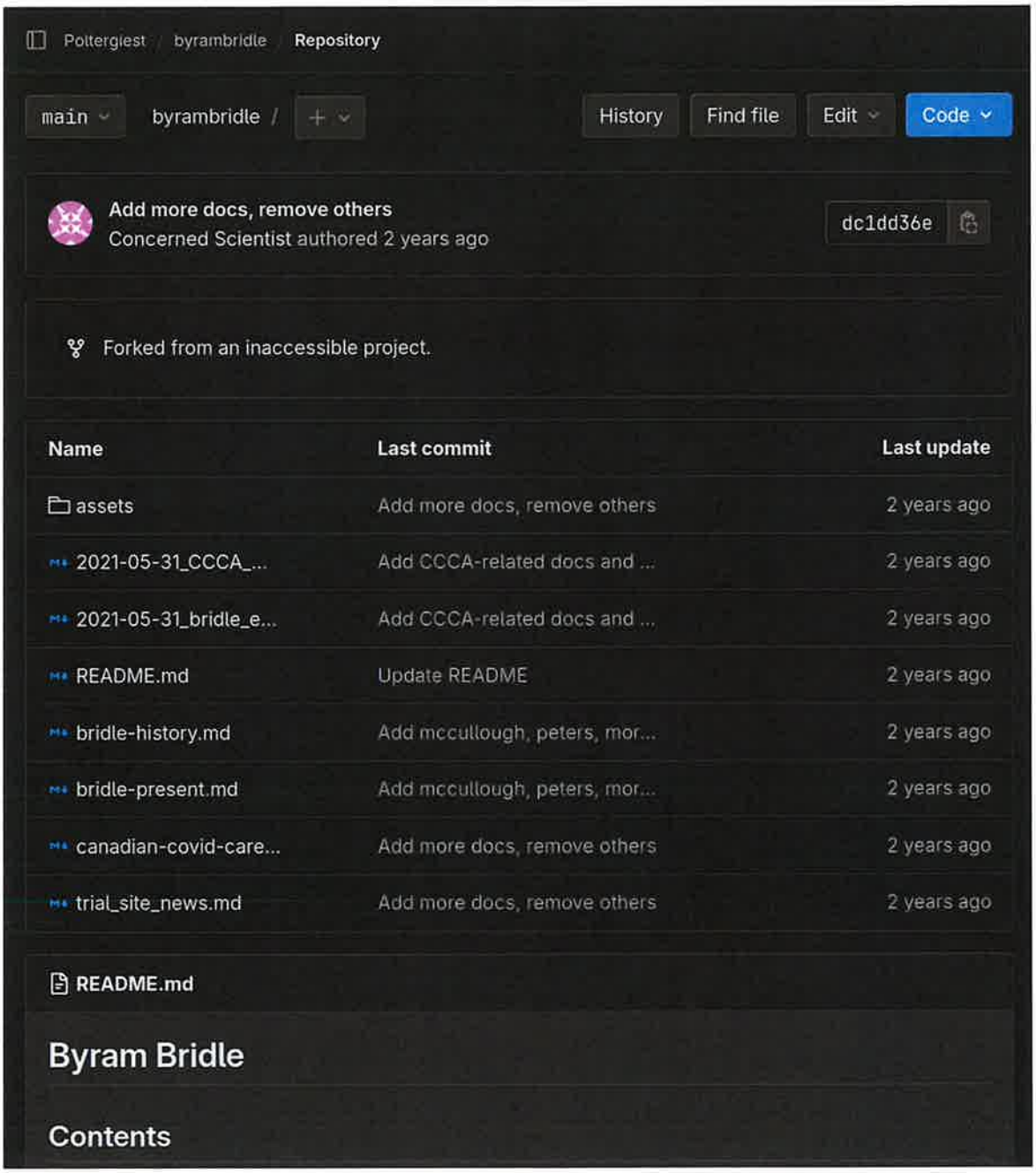
The main code repository page (https://gitlab.com/poltergiest/byrambridle/-/tree/main)



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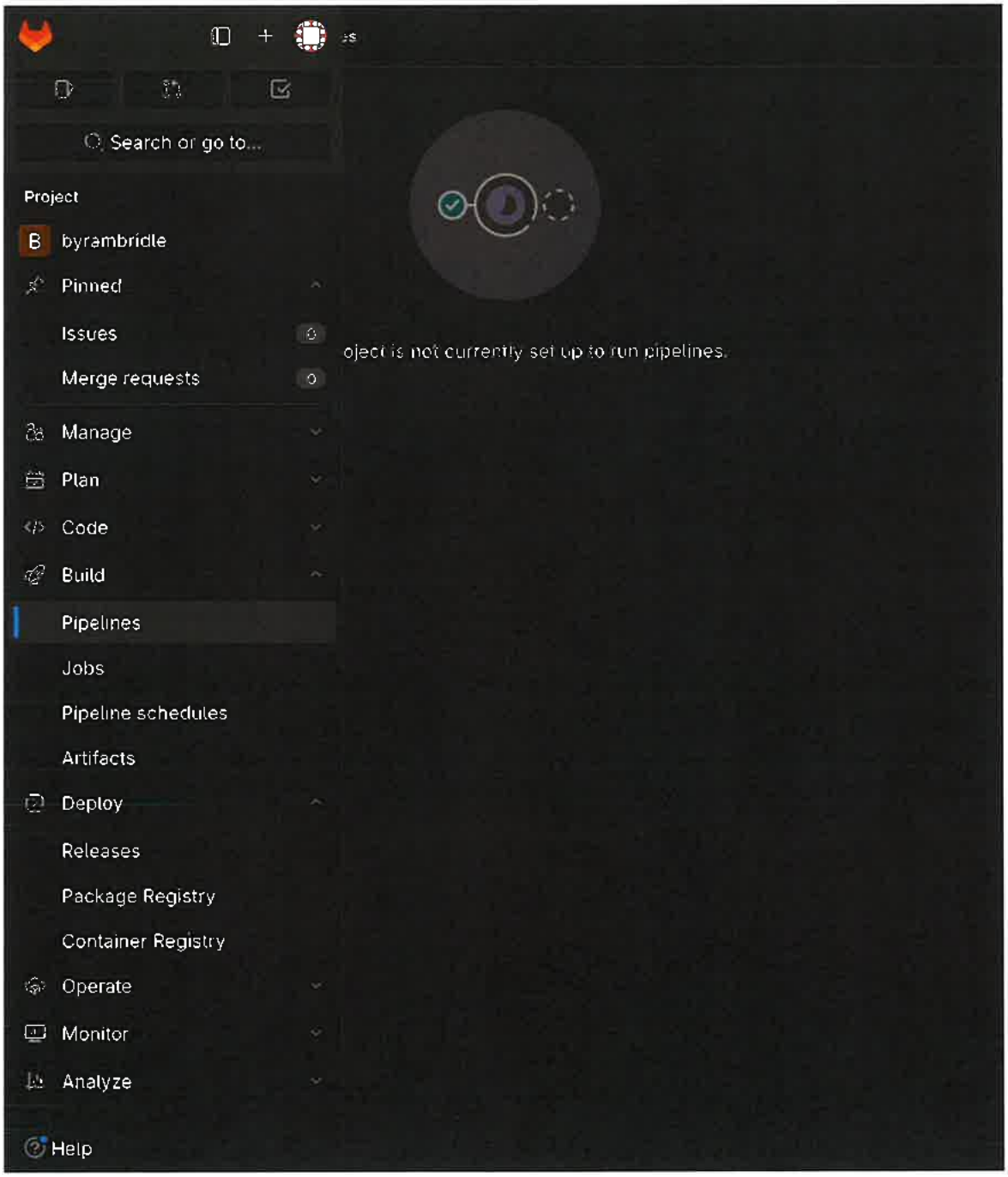
The Build > Pipelines and Deploy > Pages sections are blank, which indicate that this user has not used the GitLab Pages features with this particular repository address (https://gitlab.com/poltergiest/byrambridle/-/pipelines)



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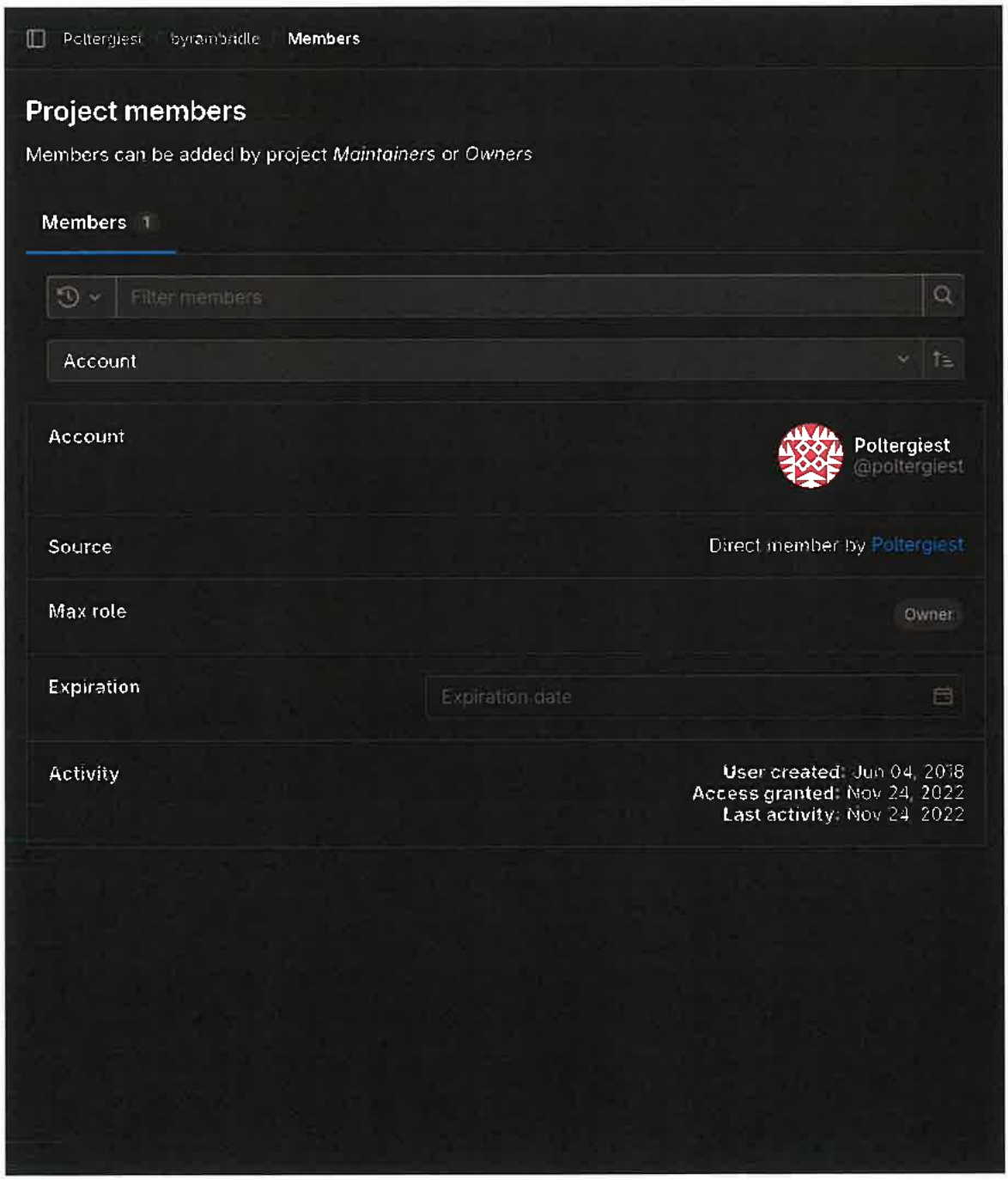
The project members page (https://gitlab.com/poltergiest/byrambridle/-/project_members) shows that @Poltergiest has simply copied the site from @concerned-scientist.



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X (Twitter)

Notice this user doesn't have a verified account.

Not Dr. Byram Bridle
2,044 posts

[102] Given the circumscribed nature and extent of Dr. Bridle's expertise, the fact that he expresses opinions well outside the parameters of his expertise and apparently at odds with the prevailing state of medical and scientific knowledge, I prefer the opinio[illegible] Drs. Leis and Vaisman, and cannot accept Dr. Bridle's op[illegible]pinning the applicants' arguments described a[illegible] that I cannot and do not accept the applicants'

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Not Dr. Byram Bridle
@ByramBridle

I'm Not Dr. Byram Bridle, a parody account highlighting COVID-19 related misinformation.

I do my homework, and I bring receipts. Do you?

byrambridle.com Joined May 2021

53 Following **1,623** Followers

Posts Replies Media Likes

Pinned

Not Dr. Byram Bridle @ByramBridle · Apr 22

You can find information about Byram Bridle's misinformation at byrambridle.com.

Wondering about his spike protein claims? The Alex Pierson interview? byrambridle.com/spike

6 1 5 2.4K

Don't miss what's happening
People on X are the first to know.

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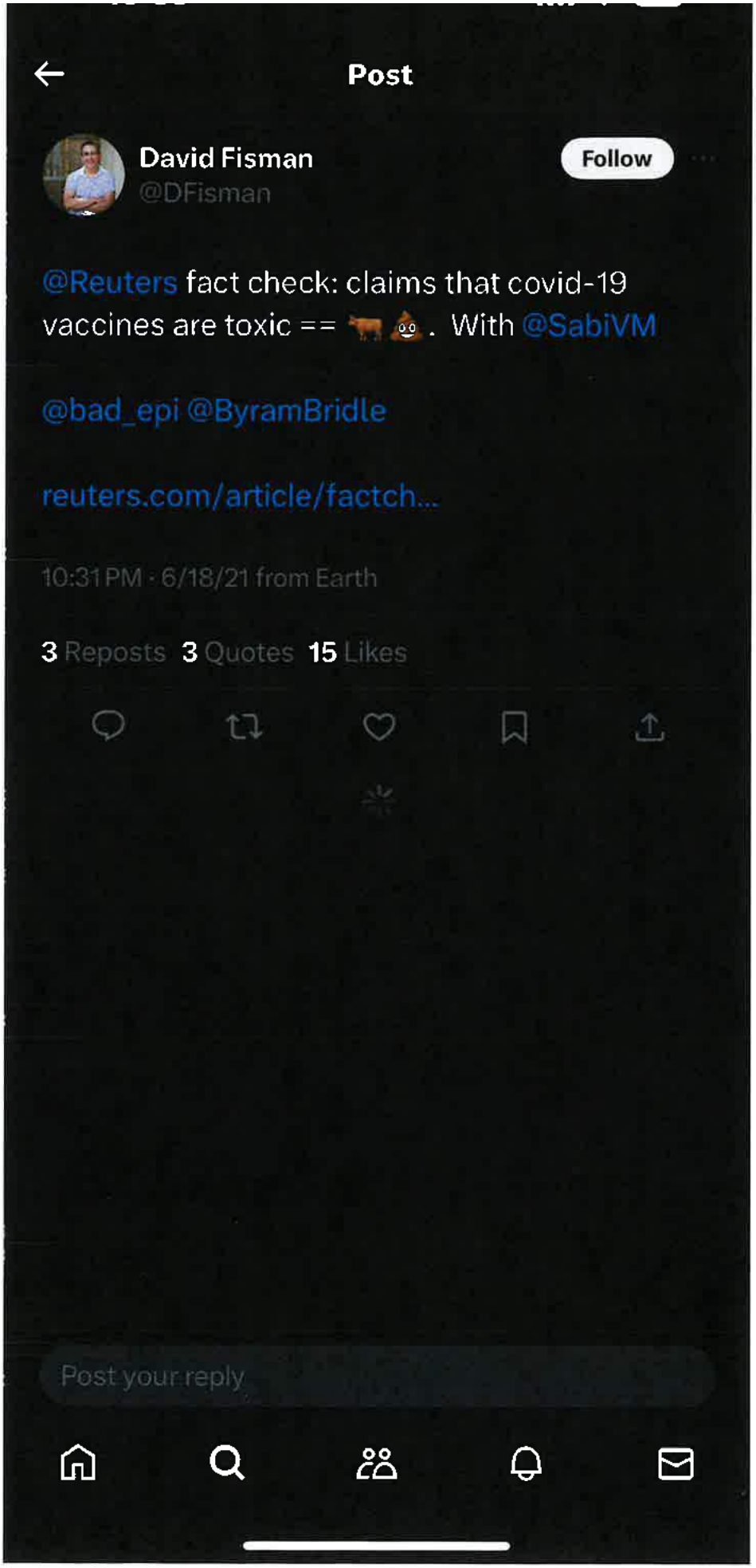
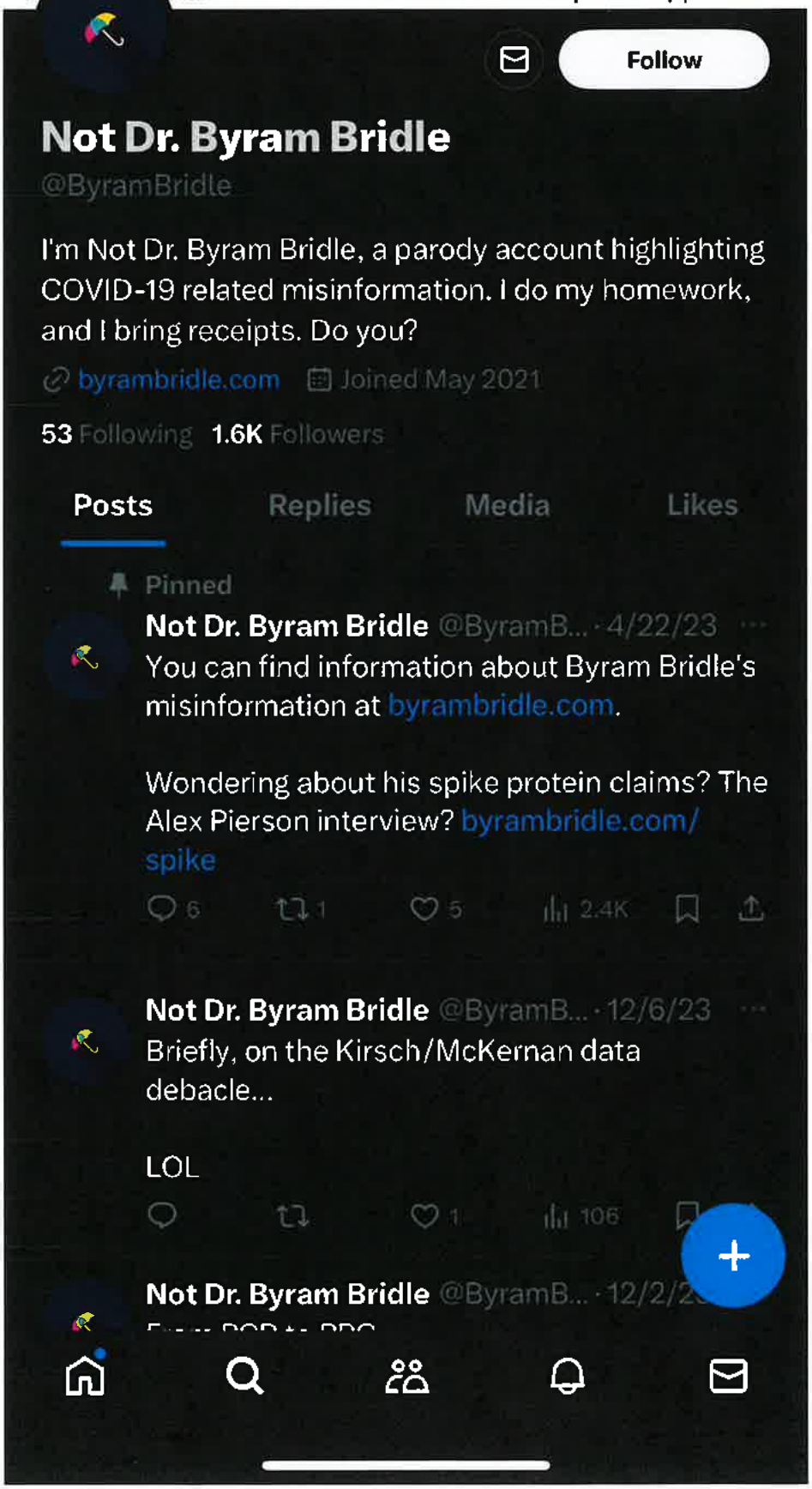
This is Exhibit " L " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.


Post
David Fisman
@DFisman
Follow
@Reuters fact check: claims that covid-19 vaccines are toxic == 🐂💩. With @SabiVM
@bad_epi @ByramBridle
reuters.com/article/factch...
10:31 PM · 6/18/21 from Earth
3 Reposts 3 Quotes 15 Likes
Post your reply

parameters of his expertise and apparently at odds with the prevailing state of medical and scientific knowledge, I prefer the opinions of Drs. Leis and Vaisman, and cannot accept Dr. Bridle's opinions underpinning the applicants' arguments described ab lows that I cannot and do not accept the applicants'



This is Exhibit " M " to the Affidavit of

Byram Bridle, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

Faculty and staff at the University of Guelph support SARS-[illegible]

July 6, 2021

We are a science-based faculty and staff at the University of Guelph who support evidence-based decisions and disagree with misinformation being circulated by a member of the faculty at the Ontario Veterinary College.

COVID-19 is an unprecedented pandemic due to a novel coronavirus. Nearly four million people globally have died as a result, and nearly two hundred million have been reported as infected.[1] Many millions more have suffered and continue to suffer from physical and mental illness associated with the pandemic, isolation, poverty, and the long-term effects of the infection.[2]

Vaccines for SARS-CoV-2 were designed, tested and produced at an unprecedented speed and on an extraordinary scale. The ability to quickly develop safe and effective vaccines was made possible through remarkable global co-operation and by concurrently running clinical trials, not by cutting corners. Many countries rapidly authorized vaccines for emergency use. Various types of vaccines are available, including those based on mRNA coding for the viral spike (S) protein, vector-based DNA vaccines coding for the S protein, and recombinant S protein particles. Two doses of the vaccines (type-dependent) have dramatically reduced illness and infections in many parts of the world.[3] The vaccines are highly effective and have very few adverse effects.[4] The coordinated effort of scientists, pharmaceutical companies, public health and regulatory agencies to produce effective vaccines against COVID-19 for billions of people in less than a year is an achievement previously unimaginable.

Dr. Byram Bridle has stated on multiple platforms and numerous outlets that COVID-19 vaccines are unsafe. These statements are contrary to overwhelming scientific evidence. The S protein generated by or incorporated into vaccines is an effective immunogen but does not alter DNA, does not induce infertility or pass through breast milk, and is not a toxin.[5, 6] Adverse vaccine effects do occur but at a similar or lower frequency than for routine vaccines.[4] In the face of this terrible pandemic, widespread vaccination is the best way out of the devastation we currently face. Many people have limited understanding of the complexities of immunization against infectious agents, and rely on scientists in epidemiology and immunology to share their knowledge and experience, especially at times such as these when fear is high. Misinformation spread by individuals such as Dr. Bridle targets uncertainty.

The University of Guelph, including us, supports freedom of expression. However, as scientists and academics we also have a responsibility to counter misinformation, particularly when the misinformation causes harm. A high rate of vaccine acceptance is essential for prevention of SARS-CoV-2 disease and deaths, and for a return to normalcy. In particular, given the high transmissibility of recent variants, very high vaccination rates among people eligible for vaccination are critical. We are very concerned that people who are not seeking vaccination because of misinformation will suffer ill effects from SARS-CoV-2 infection, will infect others, and will slow the return to a more normal life. Academic freedom is important but should not be a license to spread misinformation that has been clearly refuted, including by authors of publications that Dr. Bridle cites in support of his statements.[7] Some may even consider the University of Guelph complicit by failing to provide a clear and effective response to this misinformation

campaign, which is impacting the reputation of the institution and its faculty. Considering the harmful effects of COVID-19 on individuals and communities, the continued spread of misinformation undermines Canadian public health measures, including our vaccine program, and threatens global health security more broadly.

Therefore, we wish to state publicly that as scientists, faculty, and/or staff of the University of Guelph we stand firmly against the continued spread of factually incorrect and misleading information that is being disseminated by Dr. Bridle. We have confidence that the SARS-CoV-2 vaccines approved for use in Canada are safe and effective, and we wish to reassure the public that as members of the University of Guelph community we fully support evidence-based public health, which includes vaccination against COVID-19.

References

1. https://www.worldometers.info/coronavirus/; accessed June 24, 2021
2. https://www.un.org/development/desa/dspd/everyone-included-covid-19.html, accessed June 24, 2021
3. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html; accessed June 24, 2021
4. https://health-infobase.canada.ca/covid-19/vaccine-safety/; accessed June 24, 2021
5. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. COVID-19 vaccines. [Updated 2021 Jun 21]
6. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html; accessed June 24, 2021
7. https://www.reuters.com/article/factcheck-vaccine-safe-idUSL2N2NX1J6; accessed June 24, 2021

Supporting signatures from University of Guelph faculty and staff

Name, Credentials	Title	University of Guelph College
Amy Greer, MSc, PhD	Canada Research Chair in Population Disease Modelling and Associate Professor	Ontario Veterinary College
Dorothee Bienzle, DVM, PhD	Professor of Veterinary Pathology	Ontario Veterinary College
Scott Weese DVM DVSc DACVIM FCAHS	Director, Centre for Public Health and Zoonoses	Ontario Veterinary College
Glen Pyle, PhD	Professor of Biomedical Sciences	Ontario Veterinary College
Sarah Adamowicz, PhD	Associate Professor & Director of Bioinformatics Graduate Program, Integrative Biology	College of Biological Science
Emma Allen-Vercoe, PhD	Professor; Canada Research Chair in Human Gut Microbiome Function and Host Interactions	College of Biological Science

Luis G. Arroyo, Lic. Vet Med. DVSc, PhD, DACVIM	Associate Professor, Clinical Studies	Ontario Veterinary College
Daniel Ashlock, PhD	Professor and Chair, Mathematics and Statistics	College of Physical and Engineering Sciences
France-Isabelle Auzanneau, PhD	Professor, Chemistry	College of Engineering and Physical Sciences
John Baird, BVSc, PhD	Professor Emeritus, Clinical Studies	Ontario Veterinary College
Ian K. Barker DVM PhD	Professor Emeritus, Pathobiology	Ontario Veterinary College
Cathy Bauman, DVM, MPH, PhD	Assistant Professor, Population Medicine	Ontario Veterinary College
Janet Beeler-Marfisi, BA, DVM, DVSc, DACVP	Assistant Professor, Pathobiology	Ontario Veterinary College
Olaf Berke, PhD	Associate Professor, Statistical Epidemiology, Population Medicine	Ontario Veterinary College
Shauna Blois, DVM, DVSc, DACVIM	Associate Professor, Clinical Studies	Ontario Veterinary College
P. Suzanne Carman DVM, Dip SAMed, PhD	Diagnostic Virologist, Retired	Animal Health Laboratory
Catherine Carstairs, PhD	Professor, History	College of Arts
Christina Caruso, PhD	Associate Professor, Integrative Biology	College of Biological Science
Katie M. Clow, DVM, PhD	Assistant Professor, Population Medicine	Ontario Veterinary College
Joseph Colasanti, PhD	Associate Professor; Molecular and Cellular Biology	College of Biological Sciences
Marc Coppolino, PhD	Associate Professor, Molecular and Cellular Biology	College of Biological Science
Georgina Cox, PhD	Assistant Professor, Molecular and Cellular Biology	College of Biological Science
Teresa Crease, PhD	Professor, Integrative Biology	College of Biological Science
Nicola Cribb, MA VetMB DVSc DACVS	Assistant Professor, Clinical Studies	Ontario Veterinary College
John Dawson, PhD	Professor, Molecular and Cellular Biology	College of Biological

		Science
Giannina Descalzi, PhD	Assistant Professor, Biomedical Sciences	Ontario Veterinary College
Todd Duffield, DVM, DVSc	Professor and Chair, Population Medicine	Ontario Veterinary College
John Fryxell, PhD	Professore, Integrative Biology	College of Biological Science
Dan Gillis, PhD	Associate Professor & Statistician, School of Computer Science	College of Engineering & Physical Sciences
Lawrence Goodridge, PhD	Professor and Director, Canadian Research Institute for Food Safety	Ontario Agricultural College
T. Ryan Gregory, PhD	Professor and Chair, Integrative Biology	College of Biological Science
Steffen Graether, PhD	Professor, Molecular and Cellular Biology	College of Biological Science
Carlton Gyles, DVM, PhD, FCAHS	Professor emeritus, Pathobiology	Ontario Veterinary College
Jutta Hammermueller PhD	Staff, Pathobiology	Ontario Veterinary College
Brad Hanna, BSc, DVM, MSc, PhD	Associate Professor, Biomedical Sciences	Ontario Veterinary College
George Harauz, PhD	Professor Emeritus, Molecular and Cellular Biology	College of Biological Science
Tony Hayes BVSc PhD	Professor Emeritus, Pathobiology	Ontario Veterinary College
Paul Hebert PhD, FRSC	Professor & Canada Research Chair in Molecular Biodiversity	College of Biological Science
Stephen Henighan, PhD	Professor, School of Languages and Literature	College of Arts
Shoshanah Jacobs, PhD	Associate Professor, Integrative Biology	College of Biological Science
Fiona James, DVM, DVSc, Dipl ACVIM	Associate Professor, Clinical Studies	OVC
Claire Jardine, DVM, PhD	Associate Professor, Pathobiology	Ontario Veterinary College
Andria Jones-Bitton, DVM, PhD	Associate Professor, Epidemiology Director of Well-Being Programming, Ontario Veterinary College	Ontario Veterinary College

David Kelton, DVM, PhD	Professor of Epidemiology and Dairy Farmers of Ontario Research Chair in Dairy Cattle Health	Ontario Veterinary College
Cezar Khursigara, PhD	Associate Professor, Molecular and Cellular Biology	College of Biological Science
Judith Koenig, DVM DVSc, DAVCS	Associate Professor, Clinical Studies	Ontario Veterinary College
Jasmin Lalonde, PhD	Assistant Professor, Molecular and Cellular Biology	College of Biological Science
Mark Lipton, PhD	School of English and Theatre Studies	College of Arts
Ray Lu, PhD	Associate Professor, Molecular and Cellular Biology	College of Biological Science
Karol Mathews DVM, DVSc, DACVECC	Professor Emerita, Clinical Studies	Ontario Veterinary College
Judi McCuaig, PhD	Associate Professor, School of Computer Science	College of Engineering and Physical Sciences
Rob McLaughlin, PhD	Associate Professor and Partnership for Ecosystem Research and Management Scientist, Integrative Biology	College of Biological Science
Jennifer Murray, PhD	Associate Professor, Psychology	College of Arts
Lucy Mutharia, PhD	Adjunct Associate Professor, Molecular and Cellular Biology	College of Biological Sciences
Eva Nagy DVM, PhD, DSc	Professor Emerita, Pathobiology	Ontario Veterinary College
Annette Nassuth, PhD	Associate Professor, Molecular and Cellular Biology	College of Biological Sciences
Lee Niel, PhD	Associate Professor, Population Medicine	Ontario Veterinary College
Ryan Norris, PhD	Associate Professor, Integrative Biology	College of Biological Sciences
Anthony Ogg, DVM, DVSc, DACVIM	Professor, Clinical Studies	Ontario Veterinary College
Andrew Papadopoulos, PhD	Professor, Population Medicine	Ontario Veterinary College
Jane Parmley, DVM, PhD	Associate Professor, Population Medicine	Ontario Veterinary College
Andrew Peregrine, BVMS,	Associate Professor, Pathobiology	Ontario Veterinary College

PhD, DVM, DEVPC, DACVM		
Melissa Perreault, PhD	Associate Professor, Biomedical Sciences	Ontario Veterinary College
Zvonimir Poljak, DVM, PhD	Associate Professor, Population Medicine	Ontario Veterinary College
John Prescott VetMB PhD FCAHS	Professor Emeritus, Pathobiology	Ontario Veterinary College
Katherine Preuss, PhD	Professor, Research Leadership Chair, and Chair of Chemistry	College of Engineering and Physical Science
David Renaud, DVM, PhD	Assistant Professor, Population Medicine	Ontario Veterinary College
Beren Robinson, PhD	Professor, Integrative Biology	College of Biological Science
Michael A. Rogers PhD	Associate Professor and Canada Research Chair in Food Nanotechnology	Ontario Agricultural College
Tarek Saleh, PhD	Professor and Chair, Biomedical Sciences	Ontario Veterinary College
Shaun Sanders, PhD	Assistant Professor, Molecular and Cellular Biology	College of Biological Science
Jan M. Sargeant, PhD	Professor of Epidemiology, Population Medicine	Ontario Veterinary College
Stephen Seah, PhD	Associate Professor; Molecular and Cellular Biology	College of Biological Science
Rebecca Shapiro, PhD	Assistant Professor, Molecular and Cellular Biology	College of Biological Sciences
Patricia Shewen DVM PhD	Professor Emerita, Pathobiology	Ontario Veterinary College
Paul Sibley, PhD	Interim Director, School of Environmental Sciences	Ontario Agricultural College
Jeremy Simpson, PhD	Associate Professor, Human Health and Nutrition	College of Biological Sciences
Ameet Singh, DVM, DVSc, DACVS	Professor, Clinical Studies	Ontario Veterinary College
Kelsey Spence, PhD	Assistant Professor, Population Medicine	Ontario Veterinary College
Patricia V Turner MS, DVM, DVSc, DACLAM, DABT, DECAWBM	Professor Emerita, Pathobiology	Ontario Veterinary College

Siavash Vahidi, PhD	Assistant Professor, Molecular and Cellular Biology	College of Biological Science
Alexander Valverde, DVM, DVSc	Professor, Clinical Studies	Ontario Veterinary College
George van der Merwe, PhD	Associate Professor; Molecular and Cellular Biology	College of Biological Science
Matthew Vickaryous, PhD	Associate Professor, Biomedical Sciences	Ontario Veterinary College
Laurent Viel, DVM, PhD	Professor Emeritus, Clinical Studies	Ontario Veterinary College
Chris Whitfield PhD FRSC	Professor and Canada Research in Microbial Cell Biology, Molecular and Cellular Biology	College of Biological Sciences
Charlotte Winder, DVM, DVSc	Assistant Professor, Population Medicine	Ontario Veterinary College
Alex zur Linden, DVM, DACVR	Associate Professor, Clinical Studies	Ontario Veterinary College

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

From: Byram Bridle <bbridle@uoguelph.ca>
Sent: 06 October 2021 14:21
To: reutersfactcheck@thomsonreuters.com <reutersfactcheckthomsonreuters.com@thomsonreuters.com>
Subject: Re: Reuters request for comment

Bcc: lawyers and members of the media

Dear Reuters 'Fact Checkers',

My statements are always founded on scientific data. Please note that your e-mail demonstrates an inappropriate journalistic practice. Two of your statements misrepresent what I said. I would urge you to review the video that you sent me to confirm this. My responses are bolded and embedded in your text below.

I trust that your published 'fact check' will: (a) include my responses verbatim with all my references that I provided, (b) be written by a highly qualified scientist(s) who will describe their credentials and explain how the information that I provided is or is not valid, and (c) be written to much higher professional and objective standards than were applied to the text you provided below.

Please forward a copy of the official fact check.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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From: reutersfactcheck@thomsonreuters.com <reutersfactcheckthomsonreuters.com@thomsonreuters.com>
Sent: Wednesday, October 6, 2021 12:27 PM
To: Byram Bridle <bbridle@uoguelph.ca>; reutersfactcheck@thomsonreuters.com <reutersfactcheckthomsonreuters.com@thomsonreuters.com>
Subject: Reuters request for comment

CAUTION: This email originated from outside of the University of Guelph. Do not click links or open attachments unless you recognize the sender and know the content is safe. If in doubt, forward suspicious emails to IThelp@uoguelph.ca

Dear Dr Bridle,
We are fact checking the claims you made in a video address in Toronto on 18/9/21: https://www.facebook.com/watch/?v=263920672309632
Do you have any additional evidence to support these claims?

1. Males aged 12-15 are 6 times more likely to get heart inflammation following the vaccine than to get severe Covid-19
   Please see the attached pre-print article of a study run out of the University of California. You may also be keen to know that many countries just recently suspended the use of Moderna's vaccine in young males, including in Canada (eg, https://o.canada.com/news/provincial/ontario-now-recommending-against-moderna-vaccine-for-men-18-24-years-old), due to an excessively high incidence of heat inflammation. I have also attached a recent peer-reviewed scientific publication (first author is Dr. Jessica Rose) that shows the myocarditis signal is 19-fold higher than background in the VAERS database.

2. There is a confirmed link between abnormal menstrual bleeding and vaccination
   I did not state that there is a confirmed link. I stated that this has finally been acknowledged as problem in many women that have been vaccinated as evidenced by the initiation of several studies to evaluate this potential link (see the announcement here: https://www.nichd.nih.gov/newsroom/news/083021-COVID-19-vaccination-menstruation). I stated that this is practicing science in reverse. The potential for problems should have been thoroughly investigated prior to a mass rollout into the public; not after observing too many problems accumulate post-rollout.

3. The vaccine is not safe for pregnant women

   I did not make the statement that the vaccine was unsafe. I said that a key study underpinning the declaration of safety was debunked. I have stated on numerous occasions that the onus is not on the general scientific and medical community to prove these vaccines are dangerous. The onus is on those pushing the vaccines to prove they are safe. This is standard

practice. A debunked safety study fails to provide evidence of safety. Specifically, the authors made a simple mathematical error that precluded them from drawing any conclusions Re: risks during pregnancy. I have attached a copy of the original paper that was published in the NEJM, as well as the correction.

Thanks,

Reuters Fact Check team

This e-mail is for the sole use of the intended recipient and contains information that may be privileged and/or confidential. If you are not an intended recipient, please notify the sender by return e-mail and delete this e-mail and any attachments. Certain required legal entity disclosures can be accessed on our website: https://www.thomsonreuters.com/en/resources/disclosures.html

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You received this message because you are subscribed to the Google Groups "Scientific & Medical Advisory Committee" group.
To unsubscribe from this group and stop receiving emails from it, send an email to SMAC+unsubscribe@ iance.org.

By Tom Kertscher June 7, 2021

No proof for researcher claim that COVID-19 vaccines' spike protein is a 'toxin'

If Your Time is short

- Experts say there is no evidence that the vaccines produce a toxin that could cause heart problems and neurological damage, as Canadian viral immunologist Byram Bridle maintained.
- Bridle has not produced evidence to prove his claim, which has been widely shared on social media.

See the sources for this fact-check

A university expert claimed on talk radio that he has new evidence that COVID-19 vaccines produce a "toxin."

The credentials of Byram Bridle, a viral immunologist at the University of Guelph in Ontario, Canada, include research funding from the Canadian government and the Canadian Cancer Society, as well as dozens of publications in research journals.

But experts told PolitiFact that, despite a document Bridle cites, there is no evidence to back his claim that what is known as the vaccines' spike protein produces a toxin that could cause heart problems and neurological damage.

"There is no data that the spike is a toxin," said Dr. Drew Weissman, a vaccine expert and professor of medicine at the University of Pennsylvania. "The document he cites is an anti-vaxxer product with no real scientific data supporting its claims."

Bridle's interview sparks social media burst

Bridle began a Canadian talk show interview with a dramatic warning: "I'll forewarn you and your listeners that the story I'm about to tell is a bit of a scary one."

Describing himself as "very much pro-vaccine," Bridle said he had assembled scientific information that he intends to make public, but "your listeners are going to be the first to hear the public release of this conclusion."

He claimed the information shows that the spike protein produced by the vaccines, which is intended to prevent the coronavirus from infecting the body, does not remain in the shoulder muscle but gets into the blood — and can lead to clotting, bleeding, heart problems and neurological damage.

"In short, the conclusion is, we made a big mistake," Bridle said. "We didn't realize it until now. We thought the spike protein was a great target antigen. We never knew the spike protein itself was a toxin, and was a pathogenic protein. So, by vaccinating people, we are inadvertently inoculating them with a toxin. Some people, this gets into circulation, and when that happens in some people, they can cause damage, especially in the cardiovascular system. And I have many other legitimate questions about the long-term safety, therefore, of this vaccine."

The interview led to claims widely shared on websites and social media, including posts that linked to an article from the website of the Hal Turner Radio Show, which uses internet and radio broadcasts to float conspiracy theories and hate speech. The article carried this headline:

"Doctor on COVID Vax: 'We Screwed-Up. We didn't realize the Spike Protein is a TOXIN' Does this mean everyone vaccinated is manufacturing their own Spike Protein Toxins in their own bodies?"

The post was flagged as part of Facebook's efforts to combat false news and misinformation on its News Feed. (Read more about our partnership with Facebook.)

Explaining "spike proteins"

COVID-19 mRNA (messenger RNA) vaccines use the human body's natural immune response to its advantage. The shot contains the recipe for making the molecule known as the spike protein, which the COVID-19 virus uses to bind to cells. Once the cell receives these instructions, it creates the protein and displays it on its surface. The immune system then spots the unknown protein and makes antibodies to fight it.

The technology in the vaccines made by Pfizer-BioNTech and Moderna stems from research that began in the early 1990s, said Weissman. He and his colleague Katalin Karikó, a senior vice president of BioNTech, are credited with the breakthrough discovery that enabled these vaccines to be safe and highly effective.

Featured Fact-check

This is Exhibit " O " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

Workplace Harassment Reporting Form

CONFIDENTIAL

Submission Date: (yy/mm/dd): 2021/06/02

The University of Guelph takes all reasonable steps to ensure that an employee's right to freedom from harassment and discrimination is upheld. For more information concerning the definition of harassment, refer to the University's Policy and Program on *Workplace Harassment Prevention, 851.01.18.*

The purpose of this report is to obtain sufficient information about the incident to trigger action by appropriate individuals. Submit the completed form to Occupational Health & Wellness (OHW).

Fax or Send to (519) 780-1796 / ohw@uoguelph.ca

This form is not to be used to report incidents of workplace violence. For violence-related cares, refer to the Policy and Program on *Workplace Violence Prevention*.

Complainant:

Full Name: Dr. Byram W. Bridle Initial: _____

Status:

☒ Employee ☐ Student ☐ Visitor ☐ Volunteer ☐ Contractor

☐ Other: _____

Department: Pathobiology Building: #89 (PAHL)

Phone/Extension: (Work) x54657 (Cell) 519-362-5637

Employee Group (if applicable):

☐ UGFA Unit 1 ☐ CUPE 3913 ☐ OSSTF/TARA ☐ PSA

X UGFA (not sure which unit)

☐ UGFA Unit 2 ☐ Exempt ☐ UNIFOR ☐ OPSEU

☐ CUPE 1334 ☐ ONA ☐ UGFSEA ☐ USW

☐ Other (specify): _____

Incident(s)

Date of Incident(s): Started May 29, 2021

Where did the Incident Occur?

☐ Guelph Campus ☐ Research Station: _____

☐ Ridgetown Campus ☒ Other: online

Name of Supervisor: Dr. Brandon Lillie, Dept. Chair
Dr. Jeffrey Wichtel, Dean of OVC

Have you notified your Supervisor?

☒ Yes ☐ No

Respondent(s):

Last Name	First Name	Work Location
Pyle	Glen	Faculty member in the Dept. of Biomedical Sciences
Weese	Scott	Faculty member in the Dept. of Pathobioloy

Relationship to you:

☒ Co-worker ☐ Visitor ☐ Volunteer

☐ Employee ☐ Student ☐ Other (specify): _____

☐ Supervisor ☐ Client

Witness Information, if any:

Name	Department	Phone number/Extension
Tweets from both faculty members have been viewed by innumerable people around the world.		

Description of events

Provide a thorough description of the events, including who, what, where and when. Note witness names and dates and times of incident(s). If necessary, you may use additional pages:

Please see the appended description of events.

Have you notified anyone else of the events? If so, who and when?

I have not had a chance yet, but intend to contact the Guelph Police to see if they will perform an investigation.

A complaint has been filed about Dr. David Fisman to the College of Physicians and Surgeons of Ontario; Drs. Pyle and Weese were listed as possible witnesses. This complaint is appended at the end of this document.

Recommendations (if any)/Remedy Sought:

Please see the appended recommendations.

Signatures

Reported by: Dr. Byram W. Bridle

Signature: Dr. Byram W. Bridle Digitally signed by Dr. Byram W. Bridle DN: cn=Dr. Byram W. Bridle, o=University of Guelph, ou=Department of Pathobiology, email=bbridle@uoguelph.ca, c=CA Date: 2021.06.02 18:25:28 -04'00'

Date: (yy/mm/dd) 2021/06/02

The University of Guelph takes every complaint of harassment in the workplace very seriously. You can assist in the investigation of the incident(s) by providing as much information and as many details as possible. Information provided about a complaint or incident will not be disclosed except to the extent necessary to protect workers, to investigate the complaint or incident, to take corrective action or as otherwise required by law. By signing this report, you certify that the information herein is factual and accurate to the best of your knowledge.

Report received by: _____

Date received: (yy/mm/dd) _____

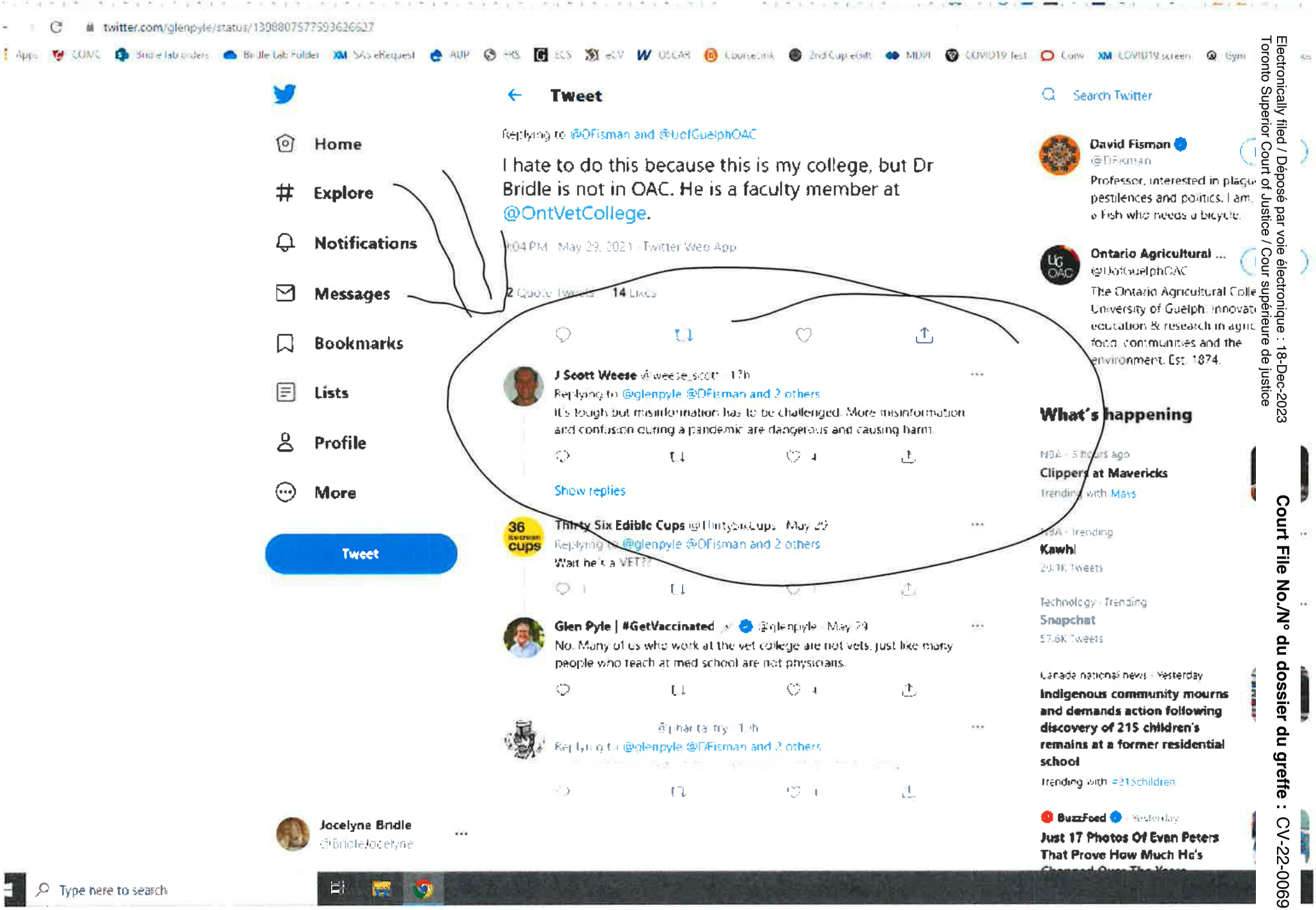
Description of Events

In the fulfillment of my responsibility as a public servant at a publicly funded academic institution I gave an interview, when invited. I answered a question posed by a radio show host to the best of my ability. It was an honest, unbiased answer that I could back-up with multiple peer-reviewed scientific papers. Following this interview, a Dr. David Fisman from the University of Toronto (and a member of Ontario's COVID-19 Science Advisory Table) began a series of Tweets that appear to have been part of or initiated a very public smear campaign against me. This has included the creation of a libelous website that was created using my domain name "byrambridle.com". The host of the radio show was also slandered on this website. Also, a slanderous Twitter account was made ("Not Byram Bridle" @ByramBridle). Both Drs. Pyle and Weese have made and/or promoted slanderous comments about me. I have appended some screenshots to provide examples. For example, many of the negative conversations in his Twitter feed revolve around attacking the 'scientific references' for the statements I made on the radio show. However, I never had a chance to state what my references were. I obviously could not show people the science via the air waves. No attempt was made by Drs. Pyle and Weese to engage me in respectful scientific discussion; they did not ask me what my evidence was prior to posting comments. The appended comments may only represent a partial list of commentary on Twitter (to the best of my knowledge, Dr. Weese was responsible for only one slanderous Tweet; Dr. Pyle was responsible for multiple). For maintenance of my mental health, I have stopped following and documenting the Twitter feeds, so additional investigation into what has transpired would be required. This is the account in question: https://twitter.com/DFisman/status/1398756044004802565. The harmful Twitter feeds began at 5:40 P.M. on May 29, 2021. As a result of the smear campaign that Drs. Pyle and Weese have actively participated in I have had to cancel major academic commitments, including service this and next week on a grant review panel for the Canadian Institutes of Health Research. I have also had to contact three journal editors to request extensions to deadlines for three invited manuscripts. I am receiving some malicious e-mails and phone messages from members of the public. The roles of Drs. Pyle and Weese seems contradictory to the tent of appropriate academic conduct. Their harmful messaging has had a negative influence on my mental and physical health. Notably, since the Tweets were initiated, I averaged only ~2 hours of sleep for three consecutive nights. I cannot currently fulfill all my work responsibilities. I have had to remove names of my trainees from my website to try to protect them from defamation. I felt compelled to right a report to circulate on social media to show that my comments on radio were backed up by science.

Of grave concern, Dr. Pyle openly shared on Twitter that he knows the person who made the libelous website using my domain name. In an e-mail chain that included members of the senior administration in my college Dr. Pyle denied stating this. I was appalled at the lie and went to Twitter to take a screenshot of the comment. To my dismay he has removed that post. However, a colleague of mine had taken a screenshot to show others. I have appended the two screen shots that prove he attempted to cover up a deliberate lie. It also confirms that he knows the identify of the person who created the website.

Recommendations

1. If it hasn't stopped already, that the slandering being done by Drs. Pyle and Weese be stopped as soon as possible.
2. That Drs. Pyle and Weese be disciplined in a manner befitting of someone that is actively harming a fellow academic and attempting to suppress open respectful scientific discussions.
3. That Dr. Pyle's role in setting up the libelous website be disclosed.
4. That Dr. Pyle reveal the name of the scientist who set-up the website to facilitate efforts to take it down.
5. That Drs. Pyle and Weese be questioned to determine if they played any role in setting up a false Twitter account in my name that is slandering me.
6. That I can return to conducting my academic work without being harassed by Drs. Pyle and Weese and others that they are inciting.
7. That Drs. Pyle and Weese will issue a public apology to me. At a minimum, this should be done via the U of G campus community and via Twitter.
8. That Drs. Pyle and Weese will undertake sensitivity training to promote respectful academic conduct.



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twitter.com/DFisman/status/1398756044004802565

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David Fisman ✓
@DFisman

I've had questions over the past 48 h about vaccine safety concerns aired Dr Byram Bridle at @UofGuelphOAC in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here: byrambridle.com

5:40 PM · May 29, 2021 · Twitter Web App

34 Retweets 6 Quote Tweets 166 Likes

Peggy Blair @peggy_blair · 23h
Replying to @DFisman and @UofGuelphOAC
Question for you. I am one of those people who had a delayed adverse reaction to Moderna (small fibre neuropathy) and probably an immune reaction to one of the ingredients. Since I can't take Moderna or Pfizer which has the same ingredients, how will I get a second dose?

4 · 8

David @DavidjacobMBA · 23h
Replying to @DFisman and @UofGuelphOAC
Yup, the study he quoted actually demonstrates mRNA vaccines work as designed.

Ultrasensitive blood test detects viral protein, confi...
In series of samples collected from individuals vaccinated against COVID-19, an ultrasensitive test ...
sciencedaily.com

Jocelyne Bridle
@BridleJocelyne

1 · 1 · 17

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Relevant people

David Fisman ✓
@DFisman
Professor, interested in plagu pestilences and politics. I am, a Fish who needs a bicycle.

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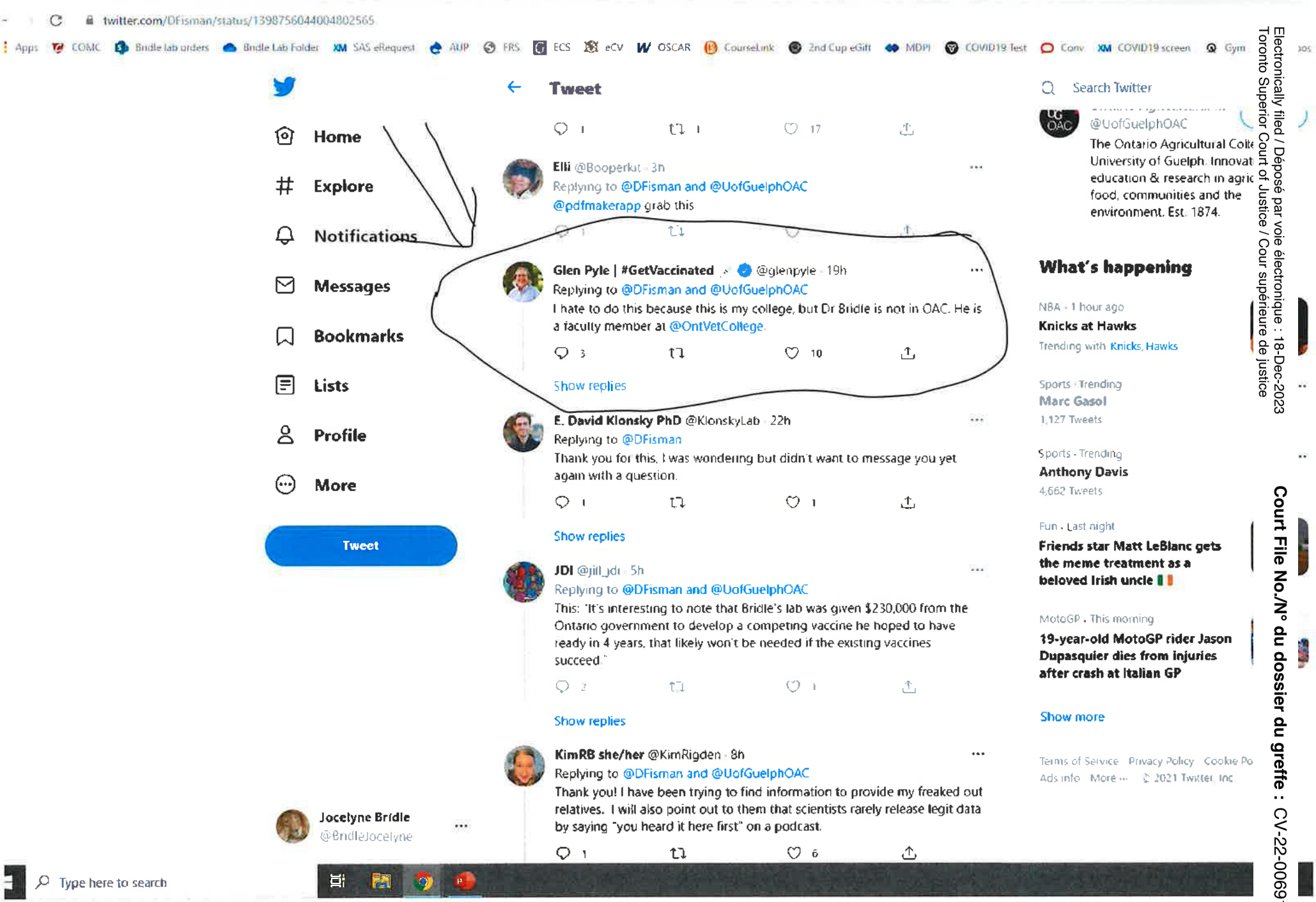

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relatives. I will also point out to them that scientists rarely release legit data by saying "you heard it here first" on a podcast.

1 · 6

Show replies

LC23 @LC2342803053 · 22h
Replying to @DFisman and @UofGuelphOAC
I thought this was a peer-reviewed study that clearly demonstrated the organ distribution of the spike protein. Why is this considered misinformation?

2

Glen Pyle | #GetVaccinated @glenpyle · 19h
You'll notice he never mentions the levels. By my calculations the spike protein peaks at ~300-350 fM. The Kd for the ACE2 receptor it binds to ~1.5 nM. This means it is 10,000 times below the amount needed.

Show replies

1 @DFisman and @UofGuelphOAC

1

David Fisman @DFisman · 9h
An excellent follow for good immune science from @UofGuelphOAC is Dr @glenpyle, who has addressed some of the misinformation in these interviews in his own tweets

> **Glen Pyle | #GetVaccinated** @glenpyle · 19h
> Replying to @kimmymend @DFisman and @UofGuelphOAC
> The paper Byram cited doesn't support his claim. That's pretty telling that a study cited to support his claims actually goes against those claims.

He had no idea what paper I 'cited'; I gave a 5-min. radio interview.

Jocelyne Bridle @BridleJocelyne

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@BridleJocelyne

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that a study cited to support his claims actually goes against those claims.

5 · 7 · 29

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TraumaaaNurse @TraumaaaNurse · 4h
Replying to @DFisman and @UofGuelphOAC
Curious as we vaccinate in a frenzy like hamsters on a hamster wheel, why EARLY prophylactic treatment with promising antivirals for positive COVID patients is not part of the Combat Covid Plan? Obviously the "wait and see if they get sicker and require ICU" is NOT WORKING!

1

J Scott Weese @weese_scott · 2h
Prevention is better than treatment.

Vaccines are much more effective than antivirals or other treatments (early tx isn't prophylaxis).

Even if treatments were highly effective, you have to get sick first, transmission and healthcare burden.

Focus has to be on prevention.

1 · 2

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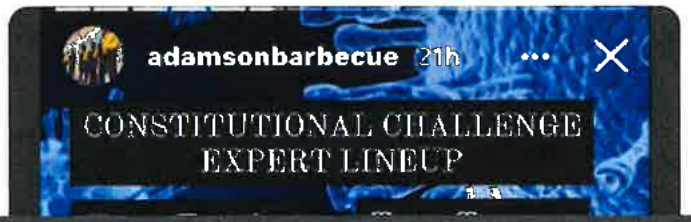
Renny Ronson @RennyRonson · 21h
Replying to
Look into it I started to about a month ago when I noticed he is going to be an expert for Adam Skelly of Adamsons BBQ.



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1 · 2 · 8

Renny Ronson @RennyRonson · 21h
It concerns me that he is associating with these folks.

> **Police on Guard for Thee**
>
> **Police on Guard for Thee**
> Watch the Canadian Professionals Unite Panel, recorded on April 15th, 2021. Dr. Dolores Cahill, Dr. Byram Bridle, Rocco Galati, Dr. Stephen Malthouse and Len Foul, answered the questions sent in by you!

2 · 1 · 1

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ScienceGuru @ScienceGuruMam · 7h
Replying to @DFisman and @UofGuelphOAC
There are no pharmacokinetic studies of the spike protein. Byram may be referring to a preprint by Ogata wherein spike protein was detected in the plasma of 3 of 13 subjects after Moderna vaccination...for up to 29 days in one of them.

Jocelyne Bridle
@BridleJocelyne

Circulating SARS-CoV-2 Vaccine Antigen Detected i...
Abstract. SARS-CoV-2 proteins were measured in

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@BridleJocelyne

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Circulating SARS-CoV-2 Vaccine Antigen Detected ...
Abstract. SARS-CoV-2 proteins were measured in longitudinal plasma samples collected from 13 ...
academic.oup.com

ScienceGuru @ScienceGuruMam · 7h
Replying to @DFisman and @UofGuelphOAC
I appreciate that the spike protein isn't supposed to be getting into circulation...but this was never investigated and pk studies of the spuke protein were not required by any of the regulators. Which is completely insane to me.

ScienceGuru @ScienceGuruMam · 7h
Replying to @DFisman and @UofGuelphOAC
Correction, David, Ogata study showing detectable plasma levels of spike protein in 3 of 13 subjects and the S1 subunit which contains the ACE2 receptor binding domain, in 11 of 13 subjects is now ACCEPTED in Clinical Infectious Diseases. No longer a preprint.

Control_Group @ControlGroup9 · 7h
Will only take the MSM 2 months to report it...how many young adults will have been vaccinated ? How many "rare" side affects?

NCameron @CamNichelle · 3h
Replying to @DFisman and @UofGuelphOAC
Do your posts usually fill up with conspiracy type information? Seems like a red flag here and concerning given that Dr Bridle is a "legit immunologist". Why are professionals not held to a higher standard when making claims to the public without facts?

Adventureover40 @cwwhitehead · 5h
Replying to @DFisman and @UofGuelphOAC

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MotoGP · This morning
19-year-old MotoGP rider Jason Dupasquier dies from injuries after crash at Italian GP

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Jocelyne Bridle
@BridleJocelyne

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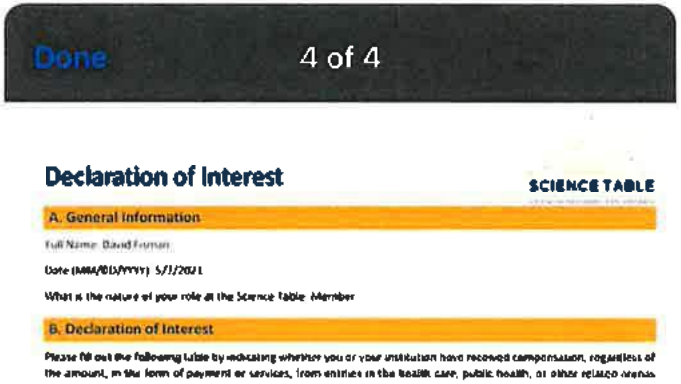
Adventureover40 @cwwhitehead · 5h
Replying to @DFisman and @UofGuelphOAC
I wonder if @DFisman would like to discuss his own conflicts of interest?



4

Jennifer Drogell @JenDrogell · 3h
Replying to @DFisman and @UofGuelphOAC
I am pro science and pro vaccine. But I don t understand why you'd direct us to an attack style website created to discredit Dr. Bridle instead of providing scientific data to reassure? Who is this website even authored by?

2

BC Think Tank : Covid Chapter @COVIDUpdate2020 · 22h
Replying to @DFisman and @UofGuelphOAC
There seems to be a not insignificant number of qualified people in public health, ID, immunology, and virology who are magical thinkers. It's certainly interesting. And hella dangerous.

2 · 1 · 9

Eve Examines @EveCritical · 21h
Yes, they have a big clot of them at Stanford.

1 · 1

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Canada national news · 2 hours ago
Indigenous community mourns and demands action following discovery of 215 children's remains at a former residential school
Trending with Indigenous, #215children

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Matt Unruh @matthewunruh · 3h
Replying to @DFisman and @UofGuelphOAC
@BogochIsaac would be interested for you to weigh in on this one too...

> In short, the conclusion is, we made a big mistake. We didn't realize it until now. We thought the spike protein was a great targeted antigen. We never knew the spike protein itself was a toxin and was a pathogenic protein. So by vaccinating people we are inadvertently inoculating them with a toxin. [For] some people this gets into circulation and when that happens, in some people that can cause damage especially in the cardiovascular system and I have many other, I don't have time, but many other legitimate questions about the long-term safety there.

Dave @justice_4_yall · 23h
Replying to @DFisman and @UofGuelphOAC
It is absolutely right for the vulnerable to be vaccinated, but I worry that the message coming from someone who has just advocated masks for 3 year olds and ventilation in schools as a mental wellness measure might be somewhat ... counter-productive.

TraumaaaNurse @TraumaaaNurse · 4h
Replying to @DFisman and @UofGuelphOAC
Odd that this appears to have only happened in Norway???? According to the hijacker of the domain name :The Seniors who have been vaccinated are "perfectly healthy" post vaccination??? Where is the study to support this claim?

Jocelyne Bridle @BridleJocelyne

Covid-19: Pfizer-BioNTech vaccine is "likely" respon...

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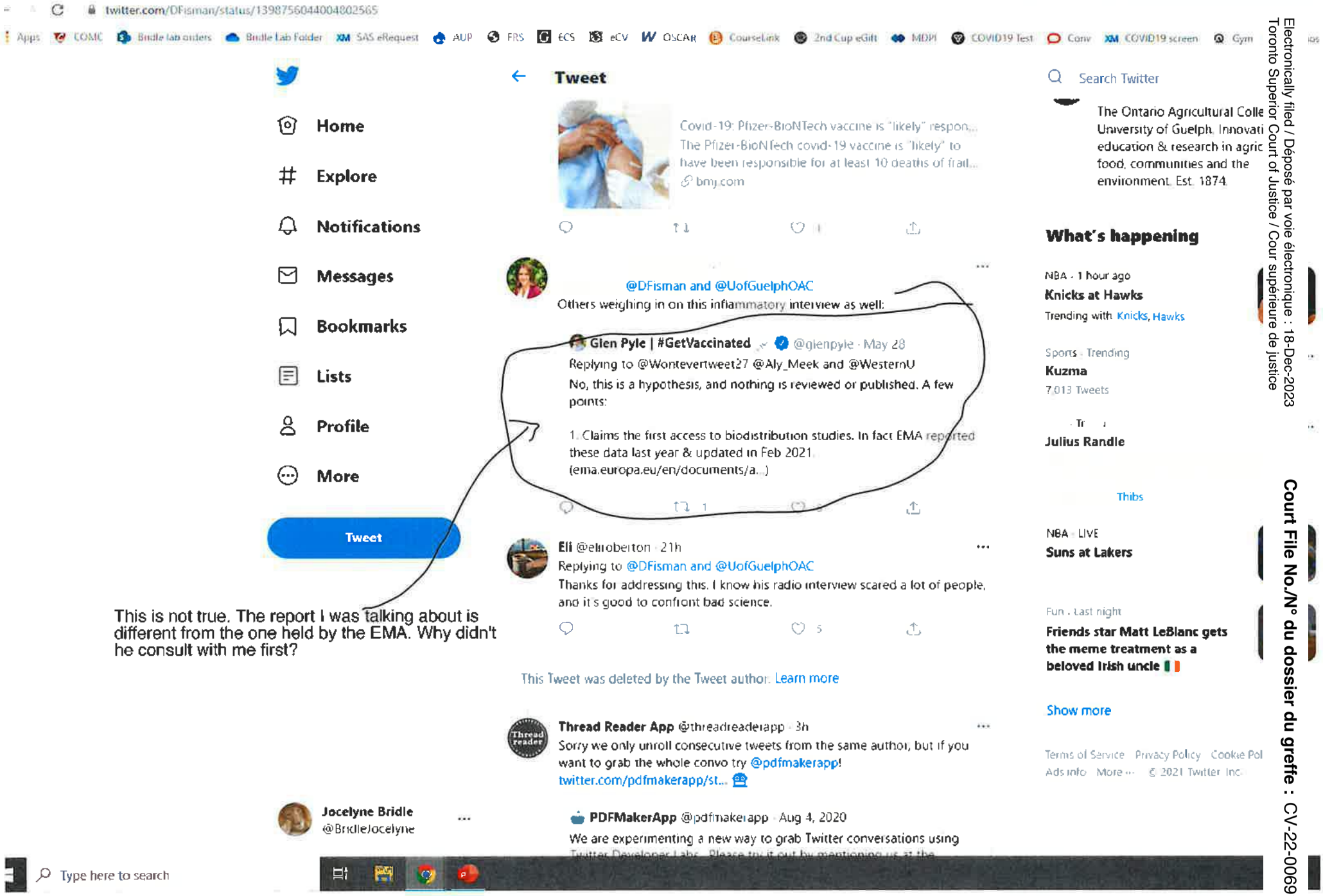

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PDFMakerApp @pdfmakerapp · Aug 4, 2020
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twitter.com/haruno07/statu...
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gforbes @gforbes · 19h
Replying to @DFisman and @UofGuelphOAC
LOL great website

DaniNigro @dani_nigro · 21h
Replying to @DFisman and @UofGuelphOAC
I was hoping you were going to address this...thank you!

Caroline Sugarman @CarolineSugarm1 · 7h
Replying to @DFisman and @UofGuelphOAC
I'm so relieved! Thank you.

More replies

Adventureover40 @cwwhitehead · 5h
Replying to @DFisman and @UofGuelphOAC
Now your in my world. Internet domains. I have successfully sued many with settlements in the millions. I would invite Dr. Bridle to contact me and I'll help him with his statement of claim.

Jocelyne Bridle @BridleJocelyne · 22m
Dear Adventureover40, I do not usually use social media, hence my use of

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Jocelyne Bridle
@BridleJocelyne

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Jocelyne Bridle @BridleJocelyne · 23m
Dear Adventureover40, I do not usually use social media, hence my use of my wife's account. Could you please contact me at "bbridle@uoguelph.ca"? Thank-you. Byram (Bridle)

Thebodylibrary @thebodylibrary · 23h
Replying to @DFisman and @UofGuelphOAC
You mention the spike does not accumulate in the spleen, liver, etc. Any data on this please?
2 · 5

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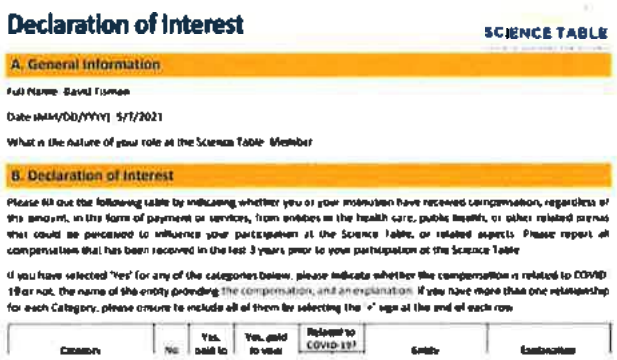
Wolf @Wolf_3141_59 · 7h
Replying to @DFisman and @UofGuelphOAC



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SCIENCE TABLE

A. General Information

Full Name: David Fisman

Date (MM/DD/YYYY): 5/7/2021

What is the nature of your role at the Science Table: Member

B. Declaration of Interest

Please fill out the following table by indicating whether you or your institution have received compensation, regardless of the amount, in the form of payment or services, from entities in the health care, public health, or other related arenas that could be perceived to influence your participation at the Science Table, or related aspects. Please report all compensation that has been received in the last 3 years prior to your participation at the Science Table.

If you have selected 'Yes' for any of the categories below, please indicate whether the compensation is related to COVID 19 or not, the name of the entity providing the compensation, and an explanation. If you have more than one relationship for each category, please ensure to include all of them by selecting the '+' sign at the end of each row.

Category	No	Yes, paid to me	Yes, paid to my institution	Related to COVID-19?	Entity	Explanation

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Evita Siu @EvaSiu21 · 17m
Replying to @DFisman and @UofGuelphOAC

Jocelyne Bridle
@BridleJocelyne

Spike Protein Behavior
I've been getting a lot of questions in the last few

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Spike Protein Behavior
I've been getting a lot of questions in the last few days about several Spike-protein-related (and ...
blogs.sciencemag.org

Evita Siu @EvaSiu21 · 15m
Consider what happens when you're infected by actual coronavirus. We know that huge majority of infections R spread by inhalation of virus-laden droplets from other infected people,so route of admin is via nose &/or lungs & cells lining ur airway R thus 1st ones 2 get infected.

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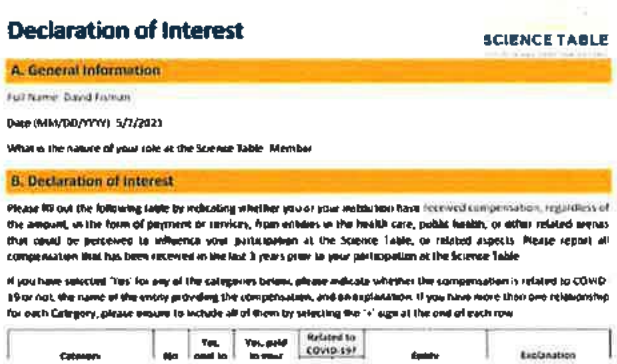
Jordan @method_4747 · 6h
Replying to @DFisman and @UofGuelphOAC
Wait, so you or someone under you set up a website, under Dr Bridle's name to discredit him? Wow.

Can people not see through this?

Just take a quick glance at this image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A. General Information
Full Name: David Fisman
Date (MM/DD/YYYY): 5/7/2021
What is the nature of your role at the Science Table: Member
B. Declaration of Interest
Please fill out the following table by indicating whether you or your institution have received compensation, regardless of the amount, in the form of payment or services, from entities in the health care, public health, or other related arenas that could be perceived to influence your participation at the Science Table, or related aspects. Please report all compensation that has been received in the last 3 years prior to your participation at the Science Table.
If you have selected 'Yes' for any of the categories below, please indicate whether the compensation is related to COVID-19 or not, the name of the entity providing the compensation, and an explanation. If you have more than one relationship for each category, please ensure to include all of them by selecting the '+' sign at the end of each row.
Category | Yes, cash in hand | Yes, paid in kind | Related to COVID-19? | Details | Explanation

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@BridleJocelyne

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7,246 Tweets

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twitter.com/DFisman/status/1398756044004802565

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Evita Siu @EvaSiu21 · 6h
Replying to @DFisman and @UofGuelphOAC
David, could you Comment on this study and if this phenomena is limited to adenovirus delivery and why it would not be present in mRNA vaccines? #covide #cdnpoli

Research Square
"Vaccine-Induced Covid-19 Mimicry" Syndrome:Spl...
During the last months many countries have started the immunization of millions of people by ...
researchsquare.com

Evita Siu @EvaSiu21 · 6h
These soluble Spike variants initiate severe side effects when binding 2 ACE2-expressing endothelial cells in blood vessels. In analogy 2 thromboembolic events caused by Spike protein encoded by SARS-CoV-2,we termed underlying mechanism "Vaccine-Induced Covid-19 Mimicry" syndrome

Show replies

Kimmymend @kimmymend · 19h
Replying to @DFisman and @UofGuelphOAC
Not surprising that you are trying to discredit him. He doesn't support vaccines are best narrative.

Glen Pyle | #GetVaccinated @glenpyle · 19h
The paper Byram cited doesn't support his claim. That's pretty telling that a study cited to support his claims actually goes against those claims.

Show replies

Again, I have a brief interview and could not show the papers over the radio waves. He has no idea what I was referring to. My primary data source is a report that he hadn't seen. Why not talk to me to get the fact first?

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@BridleJocelyne

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Sports · Trending
Marc Gasol
1,249 Tweets

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Julius Randle
Knicks fans are reacting to Julius Rand performance in Game 4 against the Ha
Trending with Derrick Rose, Thibs

Canada national news · 2 hours ago
Indigenous community mourns and demands action following discovery of 215 children's remains at a former residential school
Trending with Indigenous

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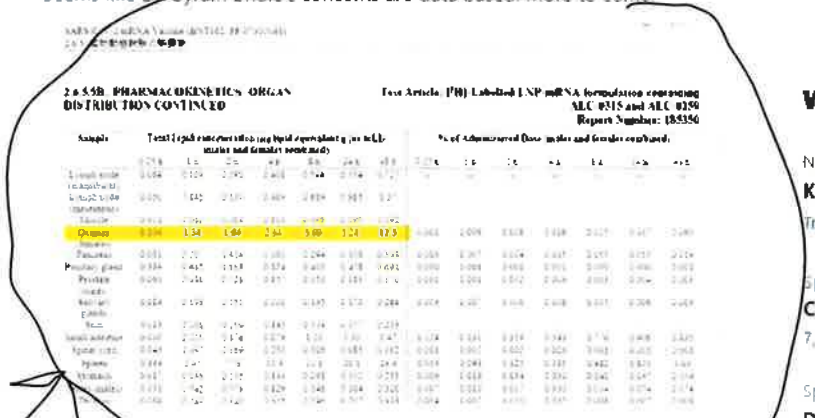
Sam W. @datavibe_io · 6h
Replying to @DFisman and @UofGuelphOAC
Seems like Dr. Byram Bridle's concerns are data based. More to come.



Pat @Pat_nebraska · 47m
Replying to @DFisman and @UofGuelphOAC
Did you read his latest research/data from the study in Japan yet? It's not really refuting when all you say is "it doesn't". You both should be showing your data. Otherwise it's just 1 person's opinion and people are gonna pick between the two.

Liam McKinnon @liam_p_mckinnon · 16h
Replying to @DFisman and @UofGuelphOAC
Strange to link to a website that uses Dr. Bridle's name only to discredit each of his data-backed claims, and yet offer no data in return. Where are the footnotes, sources?

Evita Siu @EvaSiu21 · 23m
Replying to @DFisman and @UofGuelphOAC

This is partial data from the report that I was talking about. Remarkably, all the detractors suddenly went silent. Not a single reply to this Tweet!

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Sports · Trending
Chris Paul
7,614 Tweets

Sports · Trending
Drummond
5,812 Tweets

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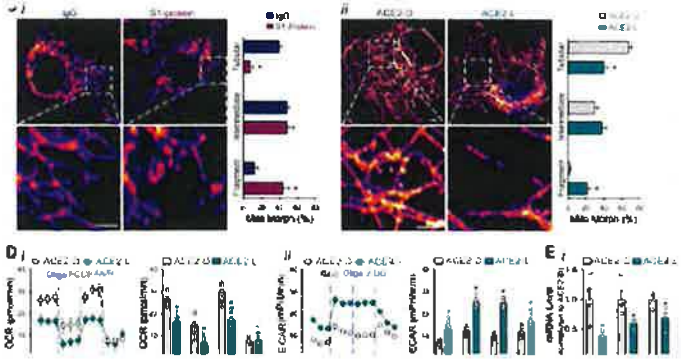
Evita Siu @EvaSiu21 · 24m
Replying to @DFisman and @UofGuelphOAC



SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2
ahajournals.org

cm @cm93967811 · 23h
Replying to @DFisman and @UofGuelphOAC
Isn't Dr. Bridle an animal doctor?
If he was given research money to find a different kind of vax, is that not automatically SUS?

Glen Pyle | #GetVaccinated @glenpyle · 20h
No. He works at @OntVetCollege but we are not all veterinarians. Many of us do research focused on human health.

Evita Siu @EvaSiu21 · 23m
Replying to @DFisman and @UofGuelphOAC

Spike Protein of SARS-CoV-2 Virus Alone Can Caus...
Exposure to a segment of the viral spike protein

Jocelyne Bridle
@BridleJocelyne

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NBA · Trending
Gasol
6,822 Tweets

Sports · Trending
Chris Paul
7,651 Tweets

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Jocelyne Bridle
@BridleJocelyne

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nolan pine @nthnbtnt · 23h
Replying to @DFisman and @UofGuelphOAC
RE:
'He says the spike protein from the vaccine leaves the deltoid (your arm muscle), and...
accumulates in the blood, spleen, and liver (it doesn't)
accumulates in the bone marrow, and the adrenal glands (it doesn't)
accumulates in the ovaries (it really doesn't)'

nolan pine @nthnbtnt · 23h
From what I understand, it's too early to say 'it doesn't' about any of these things...

Lesley - I do not consent! @CountryMom_07 · 21h
Replying to @DFisman and @UofGuelphOAC
Okay you took the time to secure his name as a URL and then explain why he's wrong. Maybe he is. But please explain the deaths, strokes, heart attacks, seizures, paralysis, sepsis and blood clots etc that tens of thousands (that we know of) are experiencing. Details please.

Lesley - I do not consent! @CountryMom_07 · 8h
And crickets...

If only you took as much time to answer these questions for the vaccine injured. The people that have died are voiceless and WE are speaking for them. We will remember those who were complicit in this crime against humanity.

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Kuzma
8,398 Tweets

NBA · Trending
Gasol
7,076 Tweets

Fun · Last night
Friends star Matt LeBlanc gets the meme treatment as a beloved Irish uncle

Canada national news · 3 hours ago
Indigenous community mourns and demands action following discovery of 215 children's remains at a former residential school
Trending with Indigenous, #215children

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humanity.

@DFisman and @UofGuelphOAC

Denmark have a policy of aspirating vax injections to avoid the risk of injecting into a vein.

Why isn t this policy elsewhere?

I asked my vaccinator to aspirate the injection and they had no clue.

V. Oden @Pathskr · 7h
Replying to @DFisman and @UofGuelphOAC
Who is the author of the article you cited please? The author of byrambridle.com? There is no attribution. Thanks.

Interstellar Angel ✨🇨🇦 @Tickety05965929 · 12h
Replying to @DFisman and @UofGuelphOAC
How do we know Dr. Byram Bridle is over the target? David Fisman discredits him.

The irreversible biomedical experimental gene editing injection is dangerous, as is David Fisman.

It is what it is @Linda59836531 · 23h
Replying to @DFisman and @UofGuelphOAC
I heard it and I fully agree with him. He has our backs. If this vax is gonna harm down the road it needs to be banned

Jocelyne Bridle
@BridleJocelyne

Maggie 🇨🇦 @maggieoutabout · 23h
Replying to @DFisman and @UofGuelphOAC
wait 48 hours and you'll see the evidence to back his claims.

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Trending with Knicks, Hawks

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Knicks fans are reacting to Julius Randl performance in Game 4 against the Ha
Trending with Thibs

Sports · Trending
Chris Paul
7,771 Tweets

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Friends star Matt LeBlanc gets the meme treatment as a beloved Irish uncle 🇮🇪

Canada national news · 3 hours ago
Indigenous community mourns and demands action following discovery of 215 children's remains at a former residential school
Trending with Indigenous, #215children

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Jocelyne Bridle
@BridleJocelyne

Tweet

Maggie 🇨🇦 @maggieoutabout · 23h
Replying to @DFisman and @UofGuelphOAC
wait 48 hours and you'll see the evidence to back his claims.

If you can't wait, then go ahead and ask Pfizer about the data they submitted to Japan.

Kirstin Adam @roxxishaker · 9h
I'll be interested to see this. No one here seems to be mentioning the FOI request from Japan that he cited. That's where he said the info re: spleen, bone marrow etc came from.

Gnosys @GnosysAwakening · 6h
Replying to @DFisman and @UofGuelphOAC
Science is actually on Dr. Bridle's side.

PMC
SARS-CoV-2 Spike Protein Elicits Cell Signaling in ...
The world is suffering from the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute...
ncbi.nlm.nih.gov

Lawrence Gold @LawrenceGold12 · 19h
Replying to @DFisman and @UofGuelphOAC
This is not evidence based and a bit odd. He says "there have been reports of infant bleeding". This is unsubstantiated info. @UofGuelphOAC @UofGuelphNews @am640

It is what it is @Linda59836531 · 23h
Replying to @DFisman and @UofGuelphOAC
And Toronto is planning a youth vax blitz?!? This is a disgusting reality

Maggie 🇨🇦 @maggieoutabout · 23h

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NBA · Trending
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Knicks fans are reacting to Julius Rand
performance in Game 4 against the Ha
Trending with Bullock, Derrick Rose

NBA · Trending
Gasol
7,126 Tweets

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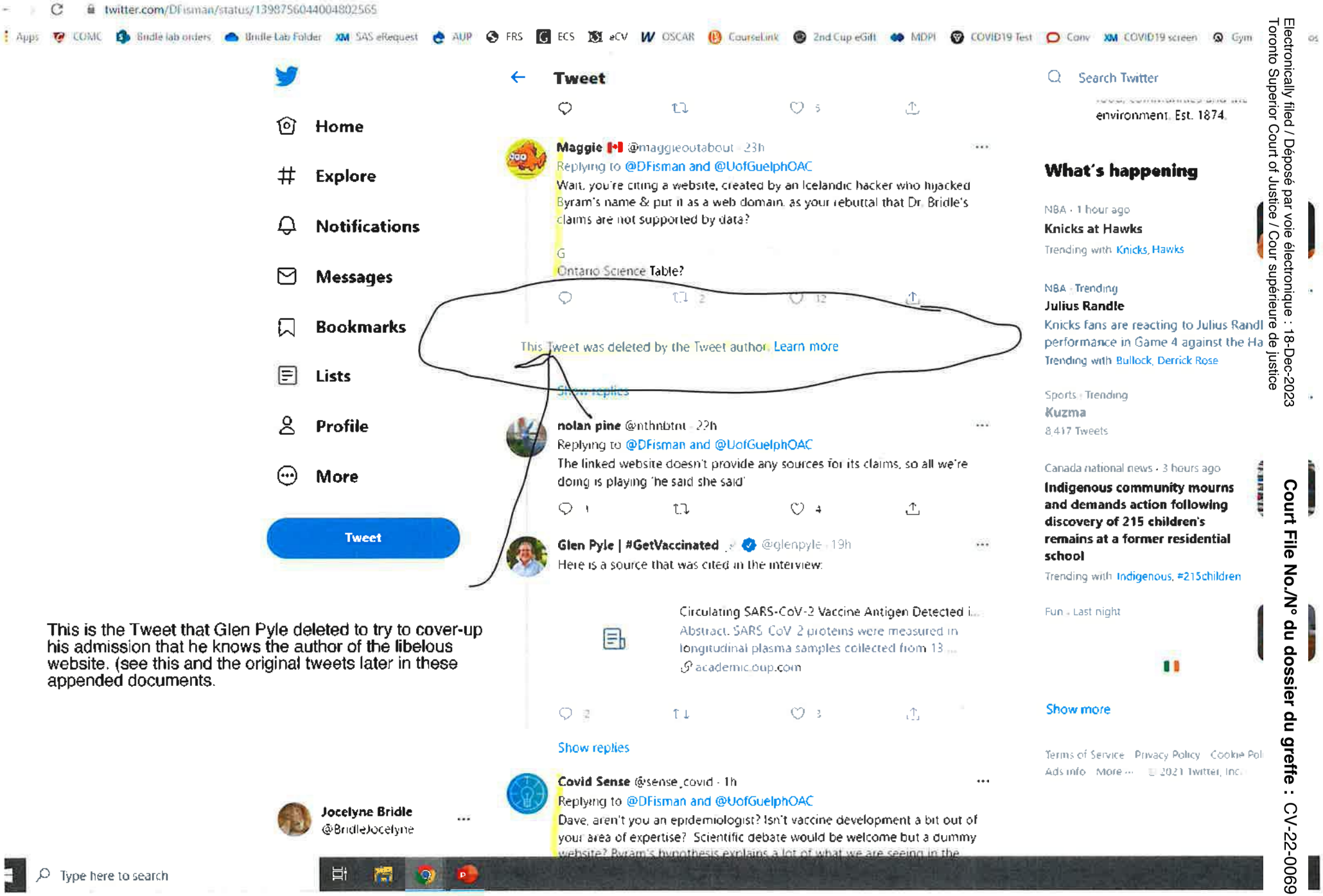

This is the Tweet that Glen Pyle deleted to try to cover-up his admission that he knows the author of the libelous website. (see this and the original tweets later in these appended documents.

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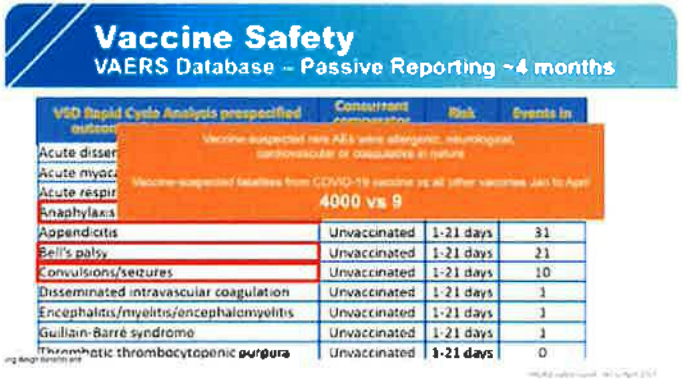
Jocelyne Bridle
@BridleJocelyne

Tweet

Dave, aren't you an epidemiologist? Isn't vaccine development a bit out of your area of expertise? Scientific debate would be welcome but a dummy website? Byram's hypothesis explains a lot of what we are seeing in the database #SafetyFirst



Seraphina @seraphina416 · 22h
Replying to @DFisman and @UofGuelphOAC

How kind of you to purchase Dr. Bridle's .com domain name for that greasy "takedown."

Is this your come back after deleting your @RufusValhalla account?

> **Amy** @skepticalzebra · May 27
> So, I was gonna do this thread later. But so many people have picked up on this- I think it's time to have a look:
>
> THREAD: @RufusValhalla What is this account?
>
> To start, as many ppl have gathered, the profile is a stock photo. But that's only the beginning of the weirdness
>
> 1/

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Anthony Davis
9,192 Tweets

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Eva Migdal @WellSchool · 17h
Please tell more..

SovietRepublicofOntario @PravdaDC · 23h
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Gasol
7,212 Tweets

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Jocelyne Bridle
@BridleJocelyne

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Tweet

David Fisman @DFisman · 7h
I've had questions over the past 48 h about vaccine safety concerns aired Dr Byram Bridle at @UofGuelphOAC in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here: byrambridle.com

Gosh, maybe too much Harðfiskur & Brennivín being passed around the Ontario Science Table?

Glen Pyle | #GetVaccinated
@glenpyle

Replying to @maggieoutabout @DFisman and @UofGuelphOAC

It's not a hacker. The person who made it has contacted me. They are a scientist.

Tweet your reply

Reply

Maggie @maggieoutabout · 3h
Replying to @glenpyle @DFisman and @UofGuelphOAC
hmmm...I'm a scientist too (and a Uof G grad, at that). As a fellow scientist, I am embarrassed for this "scientist" to have crafted such an unprofessional way to engage a colleague. Make a website with the guy's name? Really? Sarcastic punchlines at the bottom? wow, no class.

Glen Pyle | #GetVaccinated @glenpyle · 3h
They are not a colleague. I don't say that to be dismissive, just to clarify that this is not someone who is at the same level & has legitimate reason to fear retribution.

You are certainly entitled to your opinion on the website & I'm not here to change anyone's mind on that.

Original Tweet from Glen Pyle.

This was later deleted!

The next page shows his e-mail where he lied about knowing the scientist who made the website...

Tweet

David Fisman @DFisman · 21h
I've had questions over the past 48
Byram Bridle at @UofGuelphOAC
Bridle but he's a legit immunologi
based, and are answered here: byr

Maggie @maggieoutabout · 2
Wait, you're citing a website, creat
Byram's name & put it as a web d
claims are not supported by data?

Gosh, maybe too much Harðfiskur
Ontario Science Table?

This Tweet was deleted by the Tweet auth

You are certainly entitled to your o
change anyone's mind on that.

Maggie @maggieoutabout · 1
Thank you for clarifying. If you are

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Here is the lie!

RE: smear campaign

Glen Pyle <gpyle@uoguelph.ca>
Sun 5/30/2021 1:00 PM

To: Byram Bridle <bbridle@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>

Hi Byram.

I'm removing some of the cc on this in the hope that a more focused discussion will help. Jeff conveyed to h more focused approach and I understand he did the same for you. Hopefully this helps

First, I appreciate the clarification about the article. Stress or not, I can see how a small language error (ina er misunderstanding. Happy to move past that.

Second, I don't know who made the website. You've mentioned you are not on social media so you may n a chose to remain anonymous. The website was flagged to me and that was the info I was given. Others trie a someone mentioned a hacker. I simply clarified that my understanding was this was not the case. I think y n **someone been mistakenly linked to material they didn't create, that could create stress for them.**

Finally, I would like to point out that anything I posted was based on publically available information and t h I have not attacked you as a person and have no intention of doing so. I think we can have profound disag ıe stay away from character attacks. If others have made it personal I don't condone that. In all honesty, I hav : s that, but these things do happen on social media and I don't think they help any side of the debate. I mys ve end, including threats of violence, so I can speak from experience.

We have deep disagreements over the science. I have no issue with you presenting your arguments based tu never called for your academic freedom to be curtailed. You don't need my permission, so hopefully that l at across like that. I hope that you will afford me the same opportunity to discuss the scientific literature, and a swayed by each other's arguments).

I am sorry you feel you have been personally attacked and that this has created stress. If I have inadverten ıs appears to be personal, I apologize without reservation. I can't be responsible for the words of others, but ıe who attacks you as a person is not supported by me.

Glen.

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Meeting Request

Jeffrey Wichtel <jwichtel@uoguelph.ca>
Sun 6/20/2021 2:44 PM

To: Byram Bridle <bbridle@uoguelph.ca>
Cc: Laurie Arnott <l.arnott@exec.uoguelph.ca>

Dear Byram,

I am in receipt of the workplace harassment complaint you submitted.

I have had an opportunity to review the complaint and the attached evidence submitted in support of it. As I understand it, the complaint involves comments attributed to the Drs. Scott Weese and Glen Pyle, faculty members at the University, that occurred on a third-party social media platform (Twitter). There is also reference to a website with your name as the domain name, the creator of which is unknown but is not alleged to be one of the Respondents, though you indicate that Dr. Pyle knows its creator.

I have also had an opportunity to consult with Faculty and Academic Staff Relations regarding the workplace harassment process and its definition, I have also had an opportunity to consult with Faculty and Academic Staff Relations regarding the workplace harassment process, its definition and the behaviour that constitutes harassment thereunder.

Can we schedule a meeting to discuss your complaint? I'm available between 2 and 4pm tomorrow (Monday) – so feel free to get back to me and choose a 30-minute timeslot between 2 and 4. Laurie Arnott will join me on the meeting. If that time does not work, please get back to me and we will find another. If it works, I'll send a Teams invitation for the elected time.

You mention impact on your mental and physical health as a result of the issue you bring forward in your complaint. We've spoken about EAP, but I want to remind you about this service as it can be very helpful. At our meeting we can also discuss the challenges that you indicate you are experiencing completing work.

Sincerely,

Jeff

Jeffrey J. Wichtel | Professor and Dean
Ontario Veterinary College | University of Guelph
OVC Main Building | 50 Stone Road East | Guelph, ON | N1G 2W1
jwichtel@uoguelph.ca
Website, Facebook, Twitter, and Instagram ***@OntVetCollege***

UNIVERSITY of GUELPH

IMPROVE LIFE.

CONFIDENTIALITY NOTICE:
Please use discretion when sending sensitive information. The contents of this email message and any attachments are intended solely for the addressee(s) and may contain confidential information that may be legally protected. If you are not the intended recipient of this message, please immediately alert the sender then delete this message. If received in error, any use, dissemination, copying, or storage of this message or its attachments is strictly prohibited.

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Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

This is Exhibit " P " to the Affidavit of

Byram Bridle, sworn before me on

this 15th day of December 2023

_____

From: Byram Bridle <bbridle@uoguelph.ca>
Date: Thursday, June 24, 2021 at 6:39 AM
To: "J. Scott Weese" <jsweese@uoguelph.ca>, Glen Pyle <gpyle@uoguelph.ca>
Cc: "OVC-PATHOBIO-FACULTY (ovc-pathobio-faculty@listserv.uoguelph.ca)" <ovc-pathobio-faculty@listserv.uoguelph.ca>, Tarek Saleh <tsaleh@uoguelph.ca>, JJW <jwichtel@uoguelph.ca>, Laurie Arnott <l.arnott@exec.uoguelph.ca>
Subject: Invitation to publicly discuss COVID-19 vaccines for children

Hi Scott and Glen,

I am sick and tired of your immature behaviours in social media. The continual fanning of the flames of the smear campaign against me is hurtful, harmful, and childish. Graduate students of other faculty members have taken notice and are appalled by the ongoing behaviour. Glen, you were caught in an outright lie (see below). You know who set-up the libelous website and lied to our college administration about knowing this. Will you reveal the name of the person who set-up the site to facilitate its removal or do you continue to feel it is appropriate to cause major ongoing harm to the career of a colleague? It is notable that neither one of you has been willing to engage me in any discussions about the science. Talking to someone who can respond in real-time is very different than slamming them in one-sided Tweets. I do not have a social media presence and you provide great examples of why this was a wise decision. It is time to start acting your age. I invite you to discuss the science underpinning the use of COVID-19 vaccines in children in an on-line public forum. You are the local experts on COVID-19 vaccines and now have an opportunity to demonstrate to our colleagues, and the public at large that I do not know what I am talking about in a respectful discussion. We can find a moderator and we can either do this one-on-one, the two of you and then I will choose one colleague to attend with me, or you can even select one additional colleague and we will have teams of three. You have one week to respond to this invitation. The public discussion will take place within a week of me receiving a response. A negative response or non-response will be taken as a public acknowledgement that you have been wrong and will be implied as a public apology. To help you prepare, please see the attached open letter that was written by the inventor of the mRNA vaccine technology, read my guide for parents (the full version, not the two-pager), which can be found at this website: https://www.canadiancovidcarealliance.org/, and view this video in which I rebut every argument made against me that I was aware of... https://rumble.com/vilrsj-doctor-talks-10-dr-byram-bridle-returns-fire-to-critics.html

The time starts now.

A few examples of the many Tweets sent to me by horrified graduate students and some colleagues from around the world can be found below (Scott and Glen, do you really want the public and our trainees to believe that this is how we conduct our business at the U of G?; Are you willing to work towards re-building a respectful work environment at OVC?)...

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

---

Tweet
Tweet
Original Tweet from Glen Pyle.
This was later deleted!
The next page shows his e-mail where he lied about knowing the scientist who made the website...
It's not a hacker. The person who made it has contacted me. They are a scientist.
This tweet was deleted by the Tweet author. Learn more

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

Here is the lie!

RE: smear campaign

Glen Pyle <gpyle@uoguelph.ca>
Sun 5/30/2021 1:00 PM
To: Byram Bridle <bbridle@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>; Brandon Lilly <blilly@uoguelph.ca>

Hi Byram,

I'm removing some of the cc on this in the hope that a more focused discussion will help. Jeff conveyed to me the suggestion that we try a more focused approach and I understand he did the same for you. Hopefully this helps

First, I appreciate the clarification about the article. Stress or not, I can see how a small language error (inadvertent) can cause a misunderstanding. Happy to move past that.

Second, I don't know who made the website. You've mentioned you are not on social media so you may not be aware that some people chose to remain anonymous. The website was flagged to me and that was the info I was given. Others tried to tag it to Dr Fisman and someone mentioned a hacker. I simply clarified that my understanding was this was not the case. I think you can appreciate that had someone been mistakenly linked to material they didn't create, that could create stress for them.

Finally, I would like to point out that anything I posted was based on publically available information and that I have stuck to the evidence. I have not attacked you as a person and have no intention of doing so. I think we can have profound disagreements about the science and stay away from character attacks. If others have made it personal I don't condone that. In all honesty, I have not seen personal attacks like that, but these things do happen on social media and I don't think they help any side of the debate. I myself have been on the receiving end, including threats of violence, so I can speak from experience.

We have deep disagreements over the science. I have no issue with you presenting your arguments based on studies and data, and have never called for your academic freedom to be curtailed. You don't need my permission, so hopefully that last statement doesn't come across like that. I hope that you will afford me the same opportunity to discuss the scientific literature, and we can disagree (or perhaps be swayed by each other's arguments).

I am sorry you feel you have been personally attacked and that this has created stress. If I have inadvertently posted something that appears to be personal, I apologize without reservation. I can't be responsible for the words of others, but let me clearly state that anyone who attacks you as a person is not supported by me.

Glen.

fly @dankdly111 · Jun 15

Breaking: Dr Byram Bridle's massive new 202 page report detailing all relevant research about vaccine safety concerns.

Spread it, post research here.

COVID-19 Vaccines and Children: A Scientist's Guide for Parents

smallpdf.com/result#r=b6a6f...
files.catbox.moe/mhg7u6.pdf

Smallpdf.com
smallpdf.com

12 128 168

J Scott Weese @weese_scott · Jun 17

Spreading it.....

Glen

W. Glen Pyle, PhD
Senior Career Investigator
Improving the Heart & Brain Health for Women in Canada, Heart & Stroke Foundation
Distinguished Professor, Innovation in Teaching
Co-Lead, COVID-19 Resources Canada Science Explained
Professor & Assistant Chair, Department of Biomedical Sciences
Ontario Veterinary College, University of Guelph
Associate Member, IMPART, Dalhousie University
LinkedIn: www.linkedin.com/in/glenpyle
Twitter: @glenpyle
"By a divine paradox, wherever there is one slave there are two. So in the wonderful reciprocities of being, we can never reach the higher levels until all our fellows ascend with us."
-- Edwin Markham

-------- Original message --------
From: Byram Bridle <bbridle@uoguelph.ca>
Date: 2021-06-22 6:55 PM (GMT-05:00)
To:
Subject: COVID-19 vaccines for children; the tide is changing

Some people on this e-mail have been steadfast supporters, others have remained neutral (which I also respect), others have tried to brutalize me via a cowardly smear campaign. Particularly for the latter, before you judge me further, I would ask that you first do four things: 1. Read my attached report if you have not done so already (to get a full understanding of why I have concerns about children receiving experimental COVID-19 vaccines). 2. Listen to this podcast, in which Dr. Robert Malone, the inventor of the mRNA vaccine technology clearly states that my interpretation of the science is 100% correct: https://podcasts.apple.com/ng/podcast/mrna-inventor-robert-malone-backs-up-byram-bridle-on/id1513237951?i=1000526212312. 3. See the latest posting on the website of the World Health Organization (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice), which has just added the following in bolded letters: "**Children should not be vaccinated for the moment.**" ...because "Children and adolescents tend to have milder disease compared to adults, so unless they are part of a group at higher risk of severe COVID-19, it is less urgent to vaccinate them than older people, those with chronic health conditions and health workers. More evidence is needed on the use of the different COVID-19 vaccines in children to be able to make general recommendations on vaccinating children against COVID-19." 4. View this interview in which I provide rebuttals to all opposing statements that I was aware of, including addressing the libelous website that was made in my domain name: https://www.facebook.com/WhatsUpCanadians/videos/206400258023039

The need for this e-mail came to my attention when a local article in the Guelph MercuryTribune was released yesterday (https://www.thestar.com/local-guelph/news/2021/06/21/immunologists-raise-concerns-on-u-of-guelph-prof-s-views-on-covid-19-vaccine-safety.html). It is a very poorly researched, imbalanced, and highly biased article that seems to do nothing other than contribute to the smear campaign against me. Among many things, the reporter failed to mention the reason why I did not

agree to go on record after a ~1 hr discussion (that was ignored); which was because the reporter refused to allow me to see a draft to ensure they would not misquote me (the end-product justifies why I made this request). They also failed to interview anyone representing the side opposite the narrow public health narrative. Of those they interviewed, all but one remained cowardly and refused to be named, making the statements of the reporter no more than hearsay. Of note, a federal MP invested time to write a lengthy e-mail to this local reporter to give them a slap on the wrist for such poor reporting and to highlight their numerous omissions that would have made the story somewhat balanced. The fact that this disrespectful behaviour is ongoing indicates to me that people still have not placed my views into an appropriate context. The above four sources of information should help to do this.

Note that I previously contributed to an open letter expressing concerns about the safety of the AstraZeneca vaccine just after Health Canada authorized its use. That vaccination program has now largely ended after being declared too dangerous for Canadians. This, and the fact that the WHO and the inventor of mRNA vaccine technology agree with me about concerns regarding vaccinating youth, should alleviate concerns raised by so-called 'fact-checkers' and others that I have no clue what I am talking about.

If anyone remains intent upon trying to defame me and harm my career, I kindly ask, out of respect, that you try to do so in a public forum where you and I can openly discuss the science in front of the public. We can get a moderator to facilitate the discussion. If not willing to do this, please refrain from disrespectful, cowardly behaviours. Definitely don't attempt to slander me if you are unwilling to invest the time into investigating the four sources of information that I listed above. Better yet, consider trying to argue that the inventor of mRNA vaccines and the WHO have no clue what they are talking about. As for me, I remain committed to the tenet of academic freedom and standing behind it to advance the truth.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

---

From: Byram Bridle <bbridle@uoguelph.ca>
Sent: Tuesday, June 15, 2021 1:28 PM
Subject: COVID-19 Vaccines: A Guide for Parents

Please see the attached [full] guide for parents. Please circulate it as widely as you feel comfortable. I am receptive to respectful discussions with those who believe that scientists, physicians, and other professionals should be able to openly discuss the science and medicine underpinning COVID-19 policies.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

This is Exhibit " Q " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

CPSO

Complaint Form

INSTRUCTIONS

If you have a question or concern, we encourage you to first speak with your doctor, the patient advocate at your hospital or a College Public Advisor (1-800-268-7096 ext. 603). Please refer to the CPSO's for assistance and more information.

To make a complaint, you may complete this form electronically, print it out and mail it to the address at the end of this form, or submit it online to .

Once the College has received your complaint, we will aim to contact you within two business days.

We are required to notify the doctor and may provide him/her a copy of your complaint.

Consent for the release of confidential medical information

The investigator handling your complaint will need relevant personal health information. The investigator may need to get written consent from you or the patient to get certain records.

Person Registering Complaint

Last name	Bridle	First name	Byram
Street	Rm. 4834, Bldg. 89, Dept. of Pathobiology, University of Guelph 50 Stone Rd. E.	Apt#	
City	Guelph	Province	ON
Postal code	N1G 2W1		
Daytime telephone	1-519-824-4120 x54657	Alt telephone	1-519-362-5637
Email	bbridle@uoguelph.ca		

(●) I am the patient ( )

Relationship to patient: I am an independent academic researcher and faculty member.

Obtaining Records

If you are the patient, your doctor is permitted, under the *Personal Health Information Protection Act, 2004*, to disclose your medical information to the CPSO so it can investigate.

If you are **not** the patient, the patient needs to sign a **consent form** or, if unable to do so, their legal representative may sign this **authorization form** instead. This is necessary before the doctor can provide the patient's personal health records.

Patient Information *if different from the complainant*

Last name		First name			
Street			Apt#		
City		Province		Postal code	
Daytime telephone			Alt telephone		
Email					
Date of birth		Date of death (if deceased)			
OHIP #					

Preferred Mode of Communication

How would you like the College to communicate with you?

- [x] Telephone
- [x] E-mail
- [ ] Regular mail
- [ ] Fax (if confidential line)

Doctor(s) You Are Complaining About

Doctor Name	Address	Telephone Number
David Norman Fisman	Division of Infectious Diseases Toronto General Hospital 200 Elizabeth Street, Eaton Wing Room 220 Toronto ON M5G 2C4	416-340-3183

Summary of Concerns

Please list the key points of your complaint here.

1. Dr. Fisman has made libelous and slanderous comments about a fellow academic because he disagrees with my point of view regarding COVID-19 vaccines (I am an immunologist who develops novel vaccine technologies but have concerns about known and potential safety issues with the current mRNA-based COVID-19 vaccines; my concerns are based on a growing body of scientific literature).

2. I have suffered permanent damage to my reputation and career as a result of Dr. Fisman's public comments.
Dr. Fisman made a public claim about private and confidential medical information that belongs to my parents.

3. Damage being propagated by Dr. Fisman is ongoing and needs to be stopped as soon as possible.

Describe Your Complaint

Please tell us in the box below:

- What happened
- Who was involved
- When and where it happened
- Any other information that may help the CPSO in its review
- What you hope will happen as a result of this complaint

In the fulfillment of my responsibility as a public servant at a publicly funded academic institution I gave an interview, when invited. I answered a question posed by a radio show host to the best of my ability. It was an honest, unbiased answer that I could back-up with multiple peer-reviewed scientific papers. Following this interview, Dr. Fisman began a series of Tweets that appear to have been part of or initiated a very public smear campaign against me. Notably, his initial Tweet pointed people to a libelous website that was created using my domain name "byrambridle.com". The host of the radio show was also slandered on this website. Also a slanderous Twitter account was made ("Not Byram Bridle" @ByramBridle). Dr. Fisman has actively made and promoted slanderous comments about me. I have appended some screenshots to provide examples. For example, many of the negative conversations in his Twitter feed revolve around attacking the 'scientific references' for the statements I made on the radio show. However, I never had a chance to state what my references were. I obviously could not show people the science via the air waves. No attempt was made by Dr. Fisman to engage me in respectful scientific discussion; he did not ask me what my evidence was. The appended comments likely represent only a partial list of Dr. Fisman's commentary on Twitter. For maintenance of my mental health, I have stopped following and documenting his Twitter feeds. This is the account in question:
https://twitter.com/DFisman/status/1398756044004802565
Dr. Fisman's Twitter feeds began at 5:40 P.M. on May 29, 2021.
As a result of the smear campaign that Dr. Fisman is participating in I have had to cancel major academic commitments, including service this and next week on a grant review panel for the Canadian Institutes of Health Research. I have also had to contact three journal editors to request extensions to deadlines for three invited manuscripts. I am receiving some malicious e-mails and phone messages from members of the public. Dr. Fisman's role in this is contrary to the foundational tenet of academic freedom. It is also unbecoming of a physician to engage in activities that promote negative influences on another person's mental and physical health. Notably, since his first Tweet, I have averaged only ~2 hours of sleep for three consecutive nights. I cannot currently fulfill my work responsibilities. I have had to remove my trainees names from my website to try to protect them from defamation. I felt compelled to right a report to circulate on social media to show that my comments on radio were backed up by science. Of great concern, Dr. Fisman made public claims about confidential medical information regarding the vaccination status of my parents.
My hope with this complaint is: 1. That the slandering being done by Dr. Fisman will be stopped as soon as possible. 2. That Dr. Fisman will be disciplined in a manner befitting of someone that is actively harming a fellow academic and attempting to suppress open respectful scientific debate. 3. That Dr. Fisman's fitness to serve on Ontario's COVID-19 Science Advisory Table be assessed. Members of this committee should respect the basic tenets of academic conduct. 4. That it be determined if Dr. Fisman was involved in setting up the libelous website. 5. That it be determined if Dr. Fisman played in role in the creation of the fake Twitter account that is slandering me. 6. That I can return to conducting my academic work without being harassed by Dr. Fisman and others that he is inciting. 7. That Dr. Fisman will issue a public apology to me. 8. That Dr. Fisman will issue a public apology to my parents for making claims about their private medical information. 9. That Dr. Fisman will undertake sensitivity training to promote respectful academic and medical conduct.

*If more space is required, please attach additional printed pages.

Other Information

Please give the names of any other people who were involved and can provide information.

Name	Contact Information	Their role/why they might have information to contribute
Dr. Glen Pyle, Professor, University of Guelph	gpyle@uoguelph.ca 1-519-824-4120 x54772	Has interacted with Dr. Fisman in some capacity and shares his views that differ from mine. Notably, Dr. Pyle made numerous slanderous comments about me in Dr. Fisman's Twitter feed. Dr. Pyle has contributed to my harassment in the workplace.
Dr. Scott Weese, Professor, University of Guelph	jsweese@uoguelph.ca 1-519-824-4120 x54064	Has interacted with Dr. Fisman in some capacity and shares his views that differ from mine. Notably, Dr. Weese made at least one slanderous comment about me in Dr. Fisman's Twitter feed. Dr. Weese has contributed to my harassment in the workplace.

Please enclose or attach copies of any documents you feel would be relevent to your case. Please list any documents you are providing so that we can be sure we have received everything.

Supporting Documents:

Screenshots of representative portions Dr. Fisman's Twitter feed. The involvement of Dr. Pyle can be seen in this twitter feed. The second-to-last page shows that Dr. Weese was involved. The last page that is appended shows some of the libel propagated by Dr. Fisman. The Tweet at the top of the last page shows his support for the libelous website. The Tweet immediately below this makes a claim that my parents did not get vaccinated. I can attest to this being an outright lie because they did get vaccinated, although I should not have to disclose this because it represents private medical information (so please respect this confidentiality for the sake of my parents).

☑ **By checking this box and submitting, I understand that I am complaining to the College of Physicians and Surgeons of Ontario against a doctor. The doctor will be notified.**

When you have completed this Complaint Form, please submit it:

E-MAIL ir@cpso.on.ca
or
MAIL **The Registrar/CEO**
College of Physicians and Surgeons of Ontario
80 College Street
Toronto ON M5G 2E2

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
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twitter.com/DFisman/status/1398756044004802565

Apps · COMC · Bridle lab orders · Bridle Lab Folder · SAS eRequest · AUP · FRS · ECS · eCV · OSCAR · CourseLink · 2nd Cup eGift · MDPI · COVID19 Test · Conv · COVID19 screen · Gym

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Tweet

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David Fisman ✓
@DFisman

I've had questions over the past 48 h about vaccine safety concerns aired Dr Byram Bridle at @UofGuelphOAC in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here: byrambridle.com

5:40 PM · May 29, 2021 · Twitter Web App

34 Retweets **6** Quote Tweets **166** Likes

Peggy Blair @peggy_blair · 23h
Replying to @DFisman and @UofGuelphOAC
Question for you. I am one of those people who had a delayed adverse reaction to Moderna (small fibre neuropathy) and probably an immune reaction to one of the ingredients. Since I can't take Moderna or Pfizer which has the same ingredients, how will I get a second dose?

4 · 8

David @DavidJacobMBA · 23h
Replying to @DFisman and @UofGuelphOAC
Yup, the study he quoted actually demonstrates mRNA vaccines work as designed.

Ultrasensitive blood test detects viral protein, confi...
In series of samples collected from individuals vaccinated against COVID-19, an ultrasensitive test ...
sciencedaily.com

1 · 1 · 17

Jocelyne Bridle
@BridleJocelyne

Relevant people

David Fisman ✓
@DFisman
Professor, interested in plagu pestilences and politics. I am a Fish who needs a bicycle.

Ontario Agricultural ...
@UofGuelphOAC
The Ontario Agricultural Colle University of Guelph. Innovati education & research in agric food, communities and the environment. Est. 1874.

What's happening

NBA · 1 hour ago
Knicks at Hawks
Trending with Knicks, Hawks

Sports · Trending
Marc Gasol
1,125 Tweets

Sports · Trending
Anthony Davis
4,662 Tweets

Fun · Last night
Friends star Matt LeBlanc gets the meme treatment as a beloved Irish uncle

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Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
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twitter.com/DFisman/status/1398756044004202565

Apps · COMC · Bridle lab orders · Bridle Lab Folder · SAS eRequest · AUP · FRS · ECS · eCV · OSCAR · CourseLink · 2nd Cup eGift · MDPI · COVID19 Test · Conv · COVID19 screen · Gym

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Tweet

Jocelyne Bridle
@BridleJocelyne

Tweet

1 · 1 · 17

Elli @Booperkit · 3h
Replying to @DFisman and @UofGuelphOAC
@pdfmakerapp grab this

1

Glen Pyle | #GetVaccinated @glenpyle · 19h
Replying to @DFisman and @UofGuelphOAC
I hate to do this because this is my college, but Dr Bridle is not in OAC. He is a faculty member at @OntVetCollege

3 · 10

Show replies

E. David Klonsky PhD @KlonskyLab · 22h
Replying to @DFisman
Thank you for this, I was wondering but didn't want to message you yet again with a question.

1 · 1

Show replies

JDI
@DFisman and @UofGuelphOAC
This: "It's interesting to note that Bridle's lab was given $230,000 from the Ontario government to develop a competing vaccine he hoped to have ready in 4 years, that likely won't be needed if the existing vaccines succeed."

2 · 1

Show replies

@DFisman and @UofGuelphOAC

Search Twitter

@UofGuelphOAC
The Ontario Agricultural Colle
University of Guelph. Innovati
education & research in agric
food, communities and the
environment. Est. 1874.

What's happening

NBA · 1 hour ago
Knicks at Hawks
Trending with Knicks, Hawks

Sports · Trending
Marc Gasol
1,127 Tweets

Sports · Trending
Anthony Davis
4,662 Tweets

Fun · Last night
Friends star Matt LeBlanc gets the meme treatment as a beloved Irish uncle

MotoGP · This morning
19-year-old MotoGP rider Jason Dupasquier dies from injuries after crash at Italian GP

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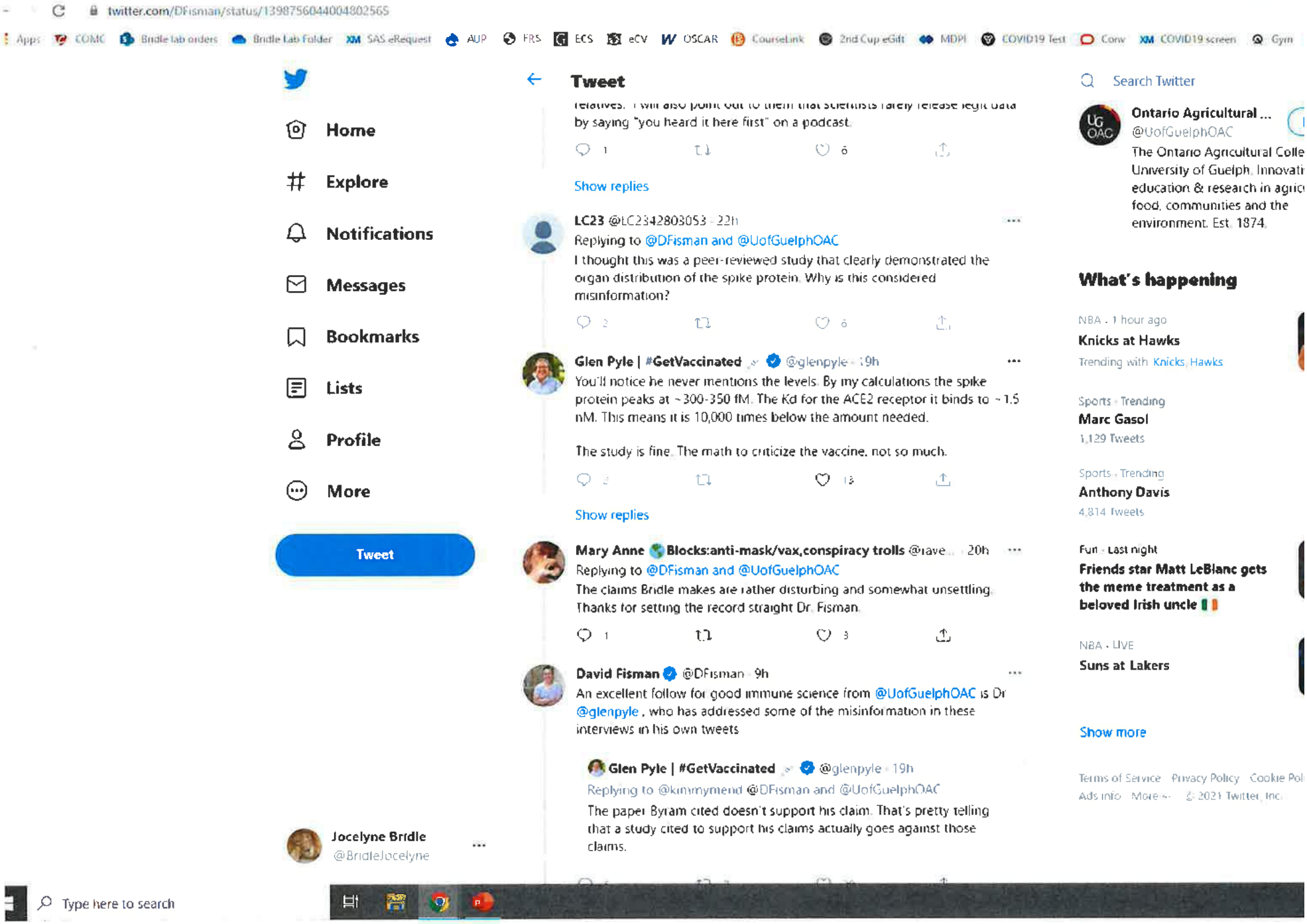

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twitter.com/DFisman/status/1398756044004802565

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that a study cited to support his claims actually goes against those claims.

5 7 29

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@DFisman and @UofGuelphOAC

J Scott Weese @weese_scott · 2h
Prevention is better than treatment

Vaccines are much more effective than antivirals or other treatments (early tx isn't prophylaxis)

Even if treatments were highly effective, you have to get sick first, transmission and healthcare burden.

Focus has to be on prevention.

1

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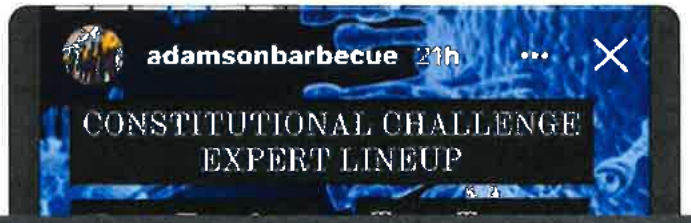
Renny Ronson @RennyRonson · 21h
Replying to @DFisman and @UofGuelphOAC
Look into it @DFisman I started to about a month ago when I noticed he is going to be an expert for Adam Skelly of Adamsons BBQ.
whatsupcanada.org/latest/premier...



Jocelyne Bridle
@BridleJocelyne

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Renny Ronson @RennyRonson · 21h
It concerns me that he is associating with these folks.

> **Police on Guard for Thee**
>
> **Police on Guard for Thee**
> Apr 17 ·
> Watch the Canadian Professionals Unite Panel, recorded on April 15th, 2021. Dr. Dolores Cahill, Dr. Byram Bridle, Rocco Galati, Dr. Stephen Malthouse and Len Faul, answered the questions sent in by you

2 · 1 · 1

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ScienceGuru @ScienceGuruMam · 7h
Replying to @DFisman and @UofGuelphOAC
There are no pharmacokinetic studies of the spike protein. Byram may be referring to a preprint by Ogata wherein spike protein was detected in the plasma of 3 of 13 subjects after Moderna vaccination...for up to 29 days in one of them.

Jocelyne Bridle
@BridleJocelyne
Circulating SARS-CoV-2 Vaccine Antigen Detected i...
Abstract: SARS-CoV-2 proteins were measured in

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ScienceGuru
@DFisman and @UofGuelphOAC
I appreciate that the spike protein isn't supposed to be getting into circulation...but this was never investigated and pk studies of the spuke protein were not required by any of the regulators. Which is completely insane to me.

ScienceGuru @ScienceGuruMam · 7h
Replying to @DFisman and @UofGuelphOAC
Correction, David, Ogata study showing detectable plasma levels of spike protein in 3 of 13 subjects and the S1 subunit which contains the ACE2 receptor binding domain, in 11 of 13 subjects is now ACCEPTED in Clinical Infectious Diseases. No longer a preprint.
1 9

Control_Group @ControlGroup9 · 7h
Will only take the MSM 2 months to report it...how many young adults will have been vaccinated ? How many "rare" side affects?
2

NCameron @CamNichelle · 3h
Replying to @DFisman and @UofGuelphOAC
Do your posts usually fill up with conspiracy type information? Seems like a red flag here and concerning given that Dr Bridle is a "legit immunologist". Why are professionals not held to a higher standard when making claims to the public without facts?

Jocelyne Bridle
@BridleJocelyne

Adventureover40 @cwwhitehead · 5h
Replying to @DFisman and @UofGuelphOAC

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MotoGP · This morning
19-year-old MotoGP rider Jason Dupasquier dies from injuries after crash at Italian GP

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Jocelyne Bridle
@BridleJocelyne

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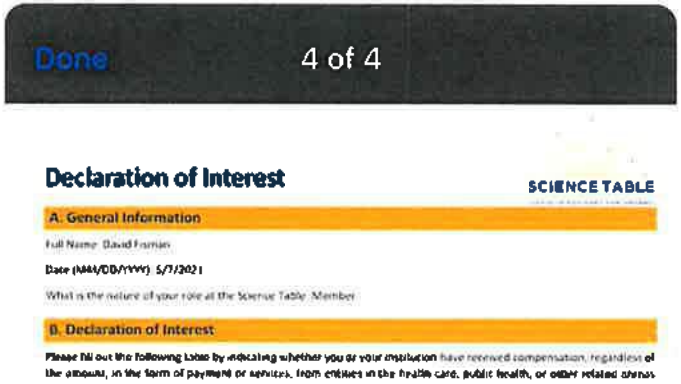
Adventureover40 @cwwhitehead · 5h
Replying to @DFisman and @UofGuelphOAC
I wonder if @DFisman would like to discuss his own conflicts of interest?



4

Jennifer Drogell @JenDrogell · 3h
Replying to @DFisman and @UofGuelphOAC
I am pro science and pro vaccine. But I don't understand why you'd direct us to an attack style website created to discredit Dr. Bridle instead of providing scientific data to reassure? Who is this website even authored by?

2

BC Think Tank : Covid Chapter @COVIDUpdate2020 · 22h
Replying to @DFisman and @UofGuelphOAC
There seems to be a not insignificant number of qualified people in public health, ID, immunology, and virology who are magical thinkers. It's certainly interesting. And hella dangerous.

2 · 1 · 9

Eve Examines @EveCritical · 21h
Yes, they have a big clot of them at Stanford.

1 · 1

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Canada national news · 2 hours ago
Indigenous community mourns and demands action following discovery of 215 children's remains at a former residential school
Trending with Indigenous, #215children

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Matt Unruh @matthewunruh · 3h
Replying to @DFisman and @UofGuelphOAC
@BogochIsaac would be interested for you to weigh in on this one too...

> In short, the conclusion is, we made a big mistake. We didn't realize it until now. We thought the spike protein was a great targeted antigen. We never knew the spike protein itself was a toxin and was a pathogenic protein. So by vaccinating people we are inadvertently inoculating them with a toxin. [For] some people this gets into circulation and when that happens, in some people that can cause damage especially in the cardiovascular system and I have many other, I don't have time, but many other legitimate questions about the long-term safety there

Dave @justice_4_yall · 23h
Replying to @DFisman and @UofGuelphOAC
It is absolutely right for the vulnerable to be vaccinated, but I worry that the message coming from someone who has just advocated masks for 3 year olds and ventilation in schools as a mental wellness measure might be somewhat ... counter-productive

4

TraumaaaNurse
@DFisman and @UofGuelphOAC
Odd that this appears to have only happened in Norway???? According to the hijacker of the domain name :The Seniors who have been vaccinated are 'perfectly healthy' post vaccination??? Where is the study to support this claim?

Jocelyne Bridle
@BridleJocelyne

Covid-19: Pfizer-BioNTech vaccine is 'likely' respon...
The Pfizer-BioNTech covid-19 vaccine is 'likely' to

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Jocelyne Bridle
@BridleJocelyne

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@CamNichelle · 21h
Replying to @DFisman and @UofGuelphOAC

Glen Pyle | #GetVaccinated @glenpyle · May 28
Replying to @Wontevertweet27 @Aly_Meek and @WesternU
No, this is a hypothesis, and nothing is reviewed or published. A few points:

1. Claims the first access to biodistribution studies. In fact EMA reported these data last year & updated in Feb 2021. (ema.europa.eu/en/documents/a...)

Eli @elroberton · 21h
Replying to @DFisman and @UofGuelphOAC
Thanks for addressing this. I know his radio interview scared a lot of people, and it's good to confront bad science.

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Thread Reader App @threadreaderapp · 3h
Sorry we only unroll consecutive tweets from the same author, but if you want to grab the whole convo try @pdfmakerapp!
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@pdfmakerapp · Aug 4, 2020

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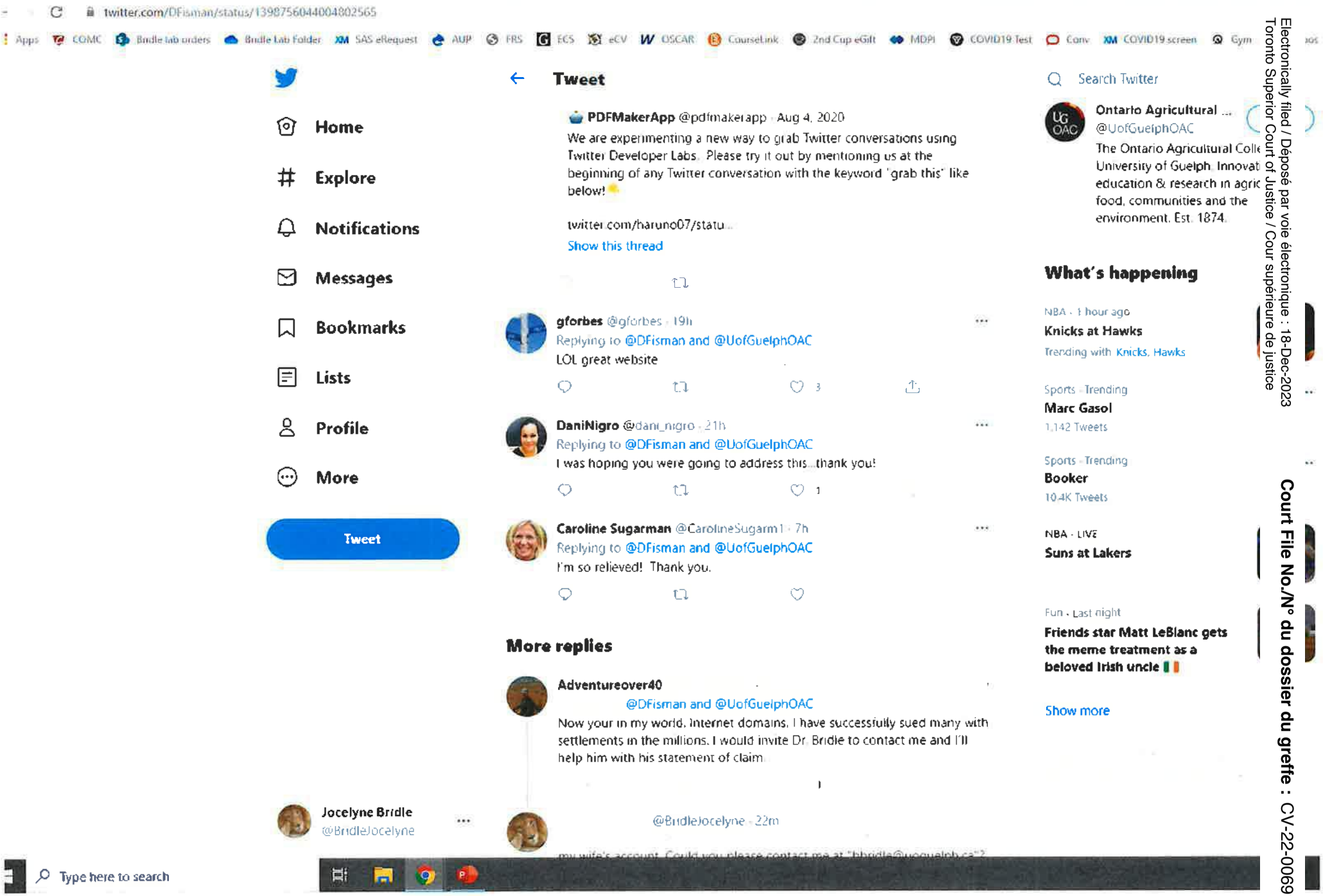

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Jocelyne Bridle @BridleJocelyne · 23m
Dear Adventureover40, I do not usually use social media, hence my use of my wife's account. Could you please contact me at "bbridle@uoguelph.ca"? Thank-you. Byram (Bridle)

Thebodylibrary @thebodylibrary · 23h
Replying to @DFisman and @UofGuelphOAC
You mention the spike does not accumulate in the spleen, liver, etc. Any data on this please?
2 · 5

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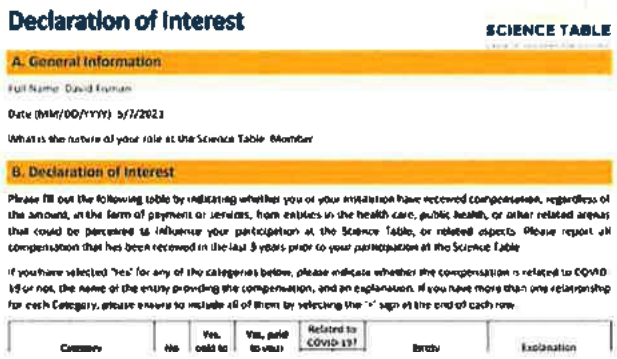
Wolf @Wolf_3141_59 · 7h
Replying to @DFisman and @UofGuelphOAC



Declaration of Interest

SCIENCE TABLE

A. General Information

Full Name: David Fisman

Date (MM/DD/YYYY): 5/7/2021

What is the nature of your role at the Science Table: Member

B. Declaration of Interest

Please fill out the following table by indicating whether you or your institution have received compensation, regardless of the amount, in the form of payment or services, from entities in the health care, public health, or other related areas that could be perceived to influence your participation at the Science Table, or related aspects. Please report all compensation that has been received in the last 5 years prior to your participation at the Science Table.

If you have selected "Yes" for any of the categories below, please indicate whether the compensation is related to COVID-19 or not, the name of the entity providing the compensation, and an explanation. If you have more than one relationship for each category, please ensure to include all of them by selecting the "+" sign at the end of each row.

Category	No	Yes, paid to me	Yes, paid to me/my institution	Related to COVID-19?	Entity	Explanation

1 · 2

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Evita Siu @EvaSiu21 · 17m
Replying to @DFisman and @UofGuelphOAC

Jocelyne Bridle
@BridleJocelyne

Spike Protein Behavior
I've been getting a lot of questions in the last few

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Spike Protein Behavior

Evita Siu @EvaSiu21 · 15m
Consider what happens when you re infected by actual coronavirus. We know that huge majority of infections R spread by inhalation of virus-laden droplets from other infected people,so route of admin. is via nose &/or lungs & cells lining ur airway R thus 1st ones 2 get infected.

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Jordan @method_4747 · 6h
Replying to @DFisman and @UofGuelphOAC
Wait, so you or someone under you set up a website, under Dr Bridle's name to discredit him? Wow.

Declaration of Interest — SCIENCE TABLE

A. General Information

Full Name: Dávid Fisman

Date (MM/DD/YYYY): 5/7/2021

What is the nature of your role at the Science Table: Member

B. Declaration of Interest

Please fill out the following table by indicating whether you or your institution have received compensation, regardless of the amount, in the form of payment or services, from entities in the health care, public health, or other related arenas that could be perceived to influence your participation at the Science Table, or related aspects. Please report all compensation that has been received in the last 3 years prior to your participation at the Science Table.

If you have selected "Yes" for any of the categories below, please indicate whether the compensation is related to COVID-19 or not, the name of the entity providing the compensation, and an explanation if you have more than one relationship for each category. Please ensure to include all of them by selecting the "+" sign at the end of each row.

Category	No	Yes, used to	Yes, going to/now	Related to COVID-19?	Entity	Explanation

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@BridleJocelyne

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Evita Siu @EvaSiu21 · 6h
Replying to @DFisman and @UofGuelphOAC
David, could you Comment on this study and if this phenomena is limited to adenovirus delivery and why it would not be present in mRNA vaccines? #covide #cdnpoli

Research Square — During the la t n onths many ountrie have started the i in inization f n illi n of people by ... re ear h quare om

Evita Siu @EvaSiu21 · 6h
These soluble Spike variants initiate severe side effects when binding 2 ACE2-expressing endothelial cells in blood vessels. In analogy 2 thromboembolic events caused by Spike protein encoded by SARS-CoV-2,we termed underlying mechanism "Vaccine-Induced Covid-19 Mimicry" syndrome

2 1 2

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Kimmymend @kimmymend · 19h
Replying to @DFisman and @UofGuelphOAC
Not surprising that you are trying to discredit him. He doesn't support vaccines are best- narrative.

2 4

Jocelyne Bridle
@BridleJocelyne

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Julius Randle
Knicks fans are reacting to Julius Rand performance in Game 4 against the Ha
Trending with Derrick Rose, Thibs

Canada national news · 2 hours ago
Indigenous community mourns and demands action following discovery of 215 children's remains at a former residential school
Trending with Indigenous

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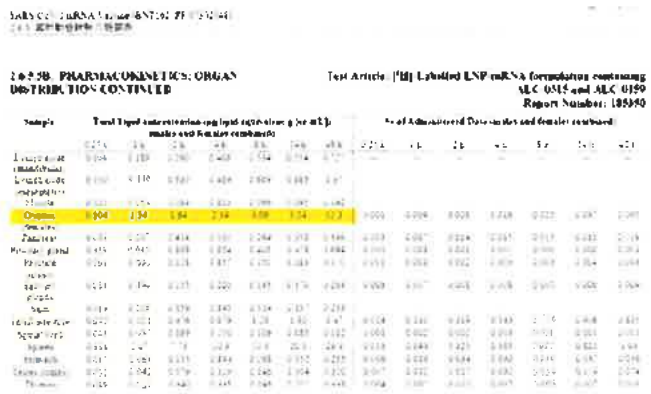
Sam W. @datavibe_io · 6h
Replying to @DFisman and @UofGuelphOAC
Seems like Dr. Byram Bridle's concerns are data based. More to come.



Pat @Pat_nebraska · 47m
Replying to @DFisman and @UofGuelphOAC
Did you read his latest research/data from the study in Japan yet? It's not really refuting when all you say is "it doesn't". You both should be showing your data. Otherwise it's just 1 person's opinion and people are gonna pick between the two.

Liam McKinnon @liam_p_mckinnon · 16h
Replying to @DFisman and @UofGuelphOAC
Strange to link to a website that uses Dr. Bridle's name only to discredit each of his data-backed claims, and yet offer no data in return. Where are the footnotes, sources?

Evita Siu @EvaSiu21 · 23m
Replying to @DFisman and @UofGuelphOAC

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Jocelyne Bridle
@BridleJocelyne

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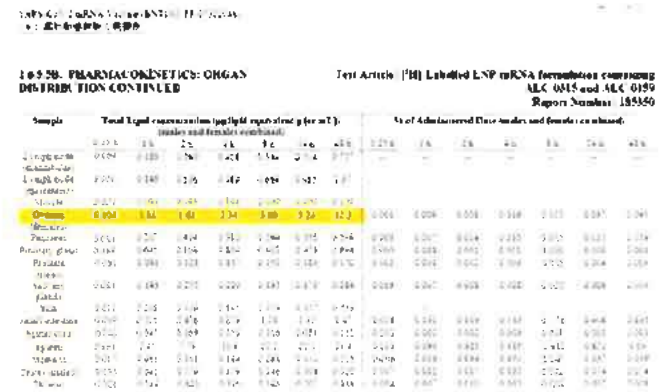
Sam W. @datavibe_io · 6h
Replying to @DFisman and @UofGuelphOAC
Seems like Dr. Byram Bridle's concerns are data based. More to come.



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Strange to link to a website that uses Dr. Bridle's name only to discredit each of his data-backed claims, and yet offer no data in return. Where are the footnotes, sources?

1 1 9

Jocelyne Bridle
@BridleJocelyne

Evita Siu @EvaSiu21 · 23m
Replying to @DFisman and @UofGuelphOAC

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twitter.com/DFisman/status/1398756044004802565

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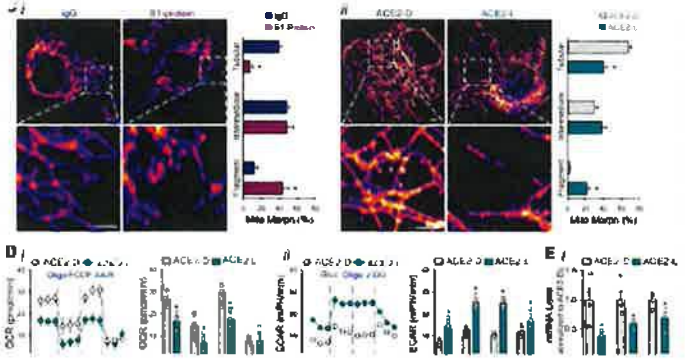

SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2
ahajournals.org

1

cm @cm93967811 · 23h
Replying to @DFisman and @UofGuelphOAC
Isn't Dr. Bridle an animal doctor?
If he was given research money to find a different kind of vax, is that not automatically SUS?

1

Glen Pyle | #GetVaccinated @glenpyle · 20h
No. He works at @OntVetCollege but we are not all veterinarians. Many of us do research focused on human health.

7

Evita Siu @EvaSiu21 · 23m
Replying to @DFisman and @UofGuelphOAC

Spike Protein of SARS-CoV-2 Virus Alone Can Caus...
Exposure to a segment of the viral spike protein

Jocelyne Bridle
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@BridleJocelyne

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Spike Protein of SARS-CoV-2 Virus Alone Can Caus...
Exposure to a segment of the viral spike protein induced COVID-19 like symptoms and caused lung...
contagionlive.com

2

nolan pine @nthnbtnt · 23h
Replying to @DFisman and @UofGuelphOAC
RE:
'He says the spike protein from the vaccine leaves the deltoid (your arm muscle), and...
accumulates in the blood, spleen, and liver (it doesn't)
accumulates in the bone marrow, and the adrenal glands (it doesn't)
accumulates in the ovaries (it really doesn't)'

2 · 1 · 1

nolan pine @nthnbtnt · 23h
From what I understand, it's too early to say 'it doesn't' about any of these things...

3

Lesley - I do not consent! @CountryMom_07 · 21h
Replying to @DFisman and @UofGuelphOAC
Okay you took the time to secure his name as a URL and then explain why he's wrong. Maybe he is. But please explain the deaths, strokes, heart attacks, seizures, paralysis, sepsis and blood clots etc that tens of thousands (that we know of) are experiencing. Details please.

1 · 1 · 3

Lesley - I do not consent! @CountryMom_07 · 8h
And crickets...

If only you took as much time to answer these questions for the vaccine injured. The people that have died are voiceless and WE are speaking for them. We will remember those who were complicit in this crime against humanity.

1

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Gasol
7,076 Tweets

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Canada national news · 3 hours ago
Indigenous community mourns and demands action following discovery of 215 children's remains at a former residential school
Trending with Indigenous, #215children

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@BridleJocelyne

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humanity.

Honor Barnes UK @HonorUkb · 22h
Replying to @DFisman and @UofGuelphOAC
How many deltoid injections end up in a vein? Hardly any. But not zero.

Denmark have a policy of aspirating vax injections to avoid the risk of injecting into a vein.

Why isn't this policy elsewhere?

I asked my vaccinator to aspirate the injection and they had no clue.

V. Oden @Padhskr · 7h
Replying to @DFisman and @UofGuelphOAC
Who is the author of the article you cited please? The author of byrambridle.com? There is no attribution. Thanks.

Interstellar Angel ✨ 🇨🇦 @Tickety05965929 · 12h
Replying to @DFisman and @UofGuelphOAC
How do we know Dr. Byram Bridle is over the target? David Fisman discredits him.

The irreversible biomedical experimental gene editing injection is dangerous, as is David Fisman.

It is what it is @Linda59836531 · 23h
Replying to @DFisman and @UofGuelphOAC
I heard it and I fully agree with him. He has our backs. If this vax is gonna harm down the road it needs to be banned

Maggie 🇨🇦 @maggieoutabout · 23h
Replying to @DFisman and @UofGuelphOAC
wait 48 hours and you'll see the evidence to back his claims.

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@BridleJocelyne

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Maggie 🇨🇦 @maggieoutabout · 23h
Replying to @DFisman and @UofGuelphOAC
wait 48 hours and you'll see the evidence to back his claims.

Kirstin Adam @roxxishaker · 9h
I'll be interested to see this. No one here seems to be mentioning the FOI request from Japan that he cited. That's where he said the info re: spleen, bone marrow etc came from.

Gnosys @GnosysAwakening · 6h
Replying to @DFisman and @UofGuelphOAC
Science is actually on Dr. Bridle's side.

PMC
SARS-CoV-2 Spike Protein Elicits Cell Signaling in ...
The world is suffering from the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute...
ncbi.nlm.nih.gov

1

Lawrence Gold @LawrenceGold12 · 19h
Replying to @DFisman and @UofGuelphOAC
This is not evidence based and a bit odd. He says "there have been reports of infant bleeding". This is unsubstantiated info. @UofGuelphOAC @UofGuelphNews @am640

2

It is what it is @Linda59836531 · 23h
Replying to @DFisman and @UofGuelphOAC
And Toronto is planning a youth vax blitz?!? This is a disgusting reality

5

Maggie 🇨🇦 @maggieoutabout · 23h

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Maggie @maggieoutabout · 23h
Replying to @DFisman and @UofGuelphOAC
Wait, you're citing a website, created by an Icelandic hacker who hijacked Byram's name & put it as a web domain, as your rebuttal that Dr. Bridle's claims are not supported by data?

Gosh, maybe too much Harðfiskur & Brennivín being passed around the Ontario Science Table?

This Tweet was deleted by the Tweet author. Learn more

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nolan pine @nthnbtnt · 22h
Replying to @DFisman and @UofGuelphOAC
The linked website doesn't provide any sources for its claims, so all we're doing is playing 'he said she said'

@glenpyle · 9h

Circulating SARS-CoV-2 Vaccine Antigen Detected i...
Abstract. SARS-CoV-2 proteins were measured in longitudinal plasma samples collected from 13 ...
academic.oup.com

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Covid Sense @sense_covid · 1h
Replying to @DFisman and @UofGuelphOAC
Dave, aren't you an epidemiologist? Isn't vaccine development a bit out of your area of expertise? Scientific debate would be welcome but a dummy website? Byram's hypothesis explains a lot of what we are seeing in the

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Indigenous community mourns and demands action following discovery of 215 children's remains at a former residential school
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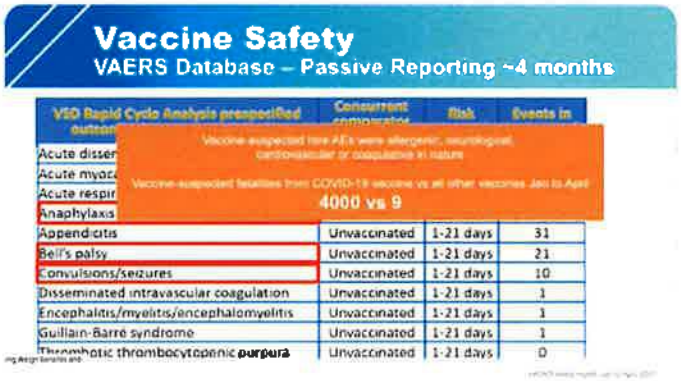
Dave, aren't you an epidemiologist? Isn't vaccine development a bit out of your area of expertise? Scientific debate would be welcome but a dummy website? Byram's hypothesis explains a lot of what we are seeing in the database #SafetyFirst



Seraphina @seraphina416 · 22h
Replying to @DFisman and @UofGuelphOAC
How kind of you to purchase Dr. Bridle's .com domain name for that greasy "takedown."

Is this your come back after deleting your @RufusValhalla account?

> **Amy** @skepticalzebra · May 27
> So, I was gonna do this thread later. But so many people have picked up on this- I think it's time to have a look:
>
> THREAD: @RufusValhalla What is this account?
>
> To start, as many ppl have gathered, the profile is a stock photo. But that's only the beginning of the weirdness
>
> 1/
> Show this thread

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@BridleJocelyne

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Eva Migdal @WellSchool · 17h
Please tell more...

SovietRepublicofOntario @PravdaDC · 23h
Replying to @DFisman and @UofGuelphOAC
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@BridleJocelyne

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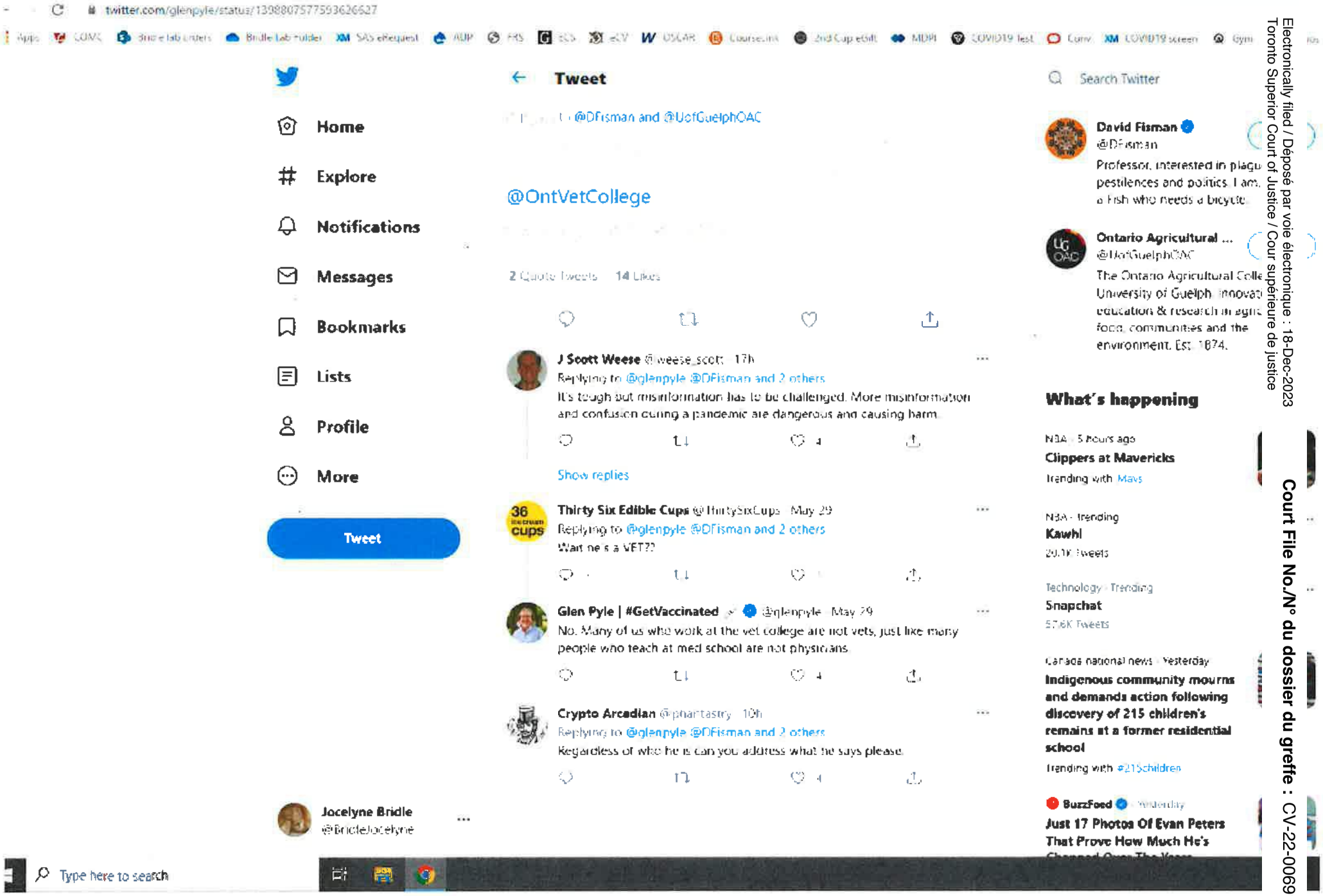

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This is Exhibit " R " to the Affidavit of

Byram Bridle, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

inventor of mRNA vaccine technology

Byram Bridle <bbridle@uoguelph.ca>
Sat 6/12/2021 11:39 PM

Bcc:Glen Pyle <gpyle@uoguelph.ca>;J. Scott Weese <jsweese@uoguelph.ca>;david.fisman@utoronto.ca <david.fisman@utoronto.ca>;Maya Goldenberg <mgolden@uoguelph.ca>;jbettinger@bcchr.ubc.ca <jbettinger@bcchr.ubc.ca>; abraham.al-ahmad@ttuhsc.edu <abraham.al-ahmad@ttuhsc.edu>

I thought you might be interested in what the inventor of mRNA vaccine technology had to say...

https://www.youtube.com/watch?v=U1pEtrEr2_s&t=326s

Respectfully,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

---

Re: inventor of mRNA vaccine technology

Byram Bridle <bbridle@uoguelph.ca>

Mon 6/14/2021 6:06 PM

To:Byram Bridle <bbridle@uoguelph.ca>
Bcc:Glen Pyle <gpyle@uoguelph.ca>;J. Scott Weese <jsweese@uoguelph.ca>;david.fisman@utoronto.ca <david.fisman@utoronto.ca>;Maya Goldenberg <mgolden@uoguelph.ca>;jbettinger@bcchr.ubc.ca <jbettinger@bcchr.ubc.ca>; abraham.al-ahmad@ttuhsc.edu <abraham.al-ahmad@ttuhsc.edu>

Here is another video that might be of interest...

https://www.youtube.com/watch?v=Du2wm5nhTXY

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

---

From: Byram Bridle
Sent: Saturday, June 12, 2021 11:39 PM
Subject: inventor of mRNA vaccine technology

I thought you might be interested in what the inventor of mRNA vaccine technology had to say...

https://www.youtube.com/watch?v=UtpEtrEr2_s&t=32s

Respectfully,
Byram

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E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

---

COVID-19 vaccines for children; what does the inventor say

Byram Bridle <bbridle@uoguelph.ca>

Wed 6/23/2021 7:17 PM

To:Byram Bridle <bbridle@uoguelph.ca>
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1 attachments (160 KB)

Dr. Bridle LOS 18June2021 RWMalone.pdf;

You might be interested in the attached open letter that was written by the inventor of the mRNA vaccine technology. Feel free to distribute widely.

Sincerely,
Byram

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COVID-19 vaccines for children; the tide is changing

Byram Bridle <bbridle@uoguelph.ca>

Tue 6/22/2021 6:54 PM

Bcc:Jocelyne Bridle <canoekeen@rogers.com>;lighthouse.wc@wightman.ca <lighthouse.wc@wightman.ca>;Rachael Bridle <rachaelofrivia@gmail.com>;Ralph Hoffer <ralphhoffer57@gmail.com>;Jennifer Harrison <jharrison110@cogeco.ca>;Julie Galbraith <juliegalbraith1963@gmail.com>;benbridle2@gmail.com <benbridle2@gmail.com>;Cara Weisenbluth <cwspirit@hotmail.com>;Becky Pritchard <missfergie1@hotmail.com>;Colin Williams <colin@wightman.ca>;Terry Bridle <ta.bridle@sympatico.ca>;Favrin, Steve (stevefavrin@hotmail.com) <stevefavrin@hotmail.com>;Douglas Patay <dpatay@pr.uoguelph.ca>;Jeff Roy <jeff@3crosses.ca>;brian (brian@parkwoodgardens.ca) <brian@parkwoodgardens.ca>; Shayan Sharif <shayan@uoguelph.ca>;Brandon Lillie <blillie@uoguelph.ca>;Jeffrey Wichtel <jwichtel@uoguelph.ca>;Karen Mantel <kmantel@uoguelph.ca>;Jane Dawkins <jdawkins@uoguelph.ca>;Deirdre Healey <healeyd@uoguelph.ca>;Philip Oldfield <philip.oldfield@poldfieldbc.com>;St.Philip, Elizabeth <Elizabeth.St.Philip@bellmedia.ca>;Favaro, Avis <Avis.Favaro@bellmedia.ca>;Paul Elias Alexander <elias98_99@yahoo.com>;Glen Pyle <gpyle@uoguelph.ca>;Sheldon Cumming <sheldonc4@gmail.com>;ksmeltzer@cbsc.ca <ksmeltzer@cbsc.ca>;asha.ross@corusent.com <asha.ross@corusent.com>;karen.gifford@corusent.com <karen.gifford@corusent.com>;simone.sammut@corusent.com <simone.sammut@corusent.com>;plavoie@bcchr.ca <plavoie@bcchr.ca>;david.fisman@utoronto.ca <david.fisman@utoronto.ca>;Nicola.mercer@wdgpublichealth.ca <Nicola.mercer@wdgpublichealth.ca>;Nicole De Francesco <nicole.defrancesco@wellingtoncdsb.ca>;Sandra Cummings <sandra.cummings@wellingtoncdsb.ca>;Lovell, Jessica <jlovell@guelphmercurytribune.com>;Ted Arnott <ted.arnottco@pc.ola.org>;Michael Chong <michael.chong@parl.gc.ca>; lloyd.longfield@parl.gc.ca <lloyd.longfield@parl.gc.ca>;doug.fordco@pc.ola.org <doug.fordco@pc.ola.org>; justin.trudeau@parl.gc.ca <justin.trudeau@parl.gc.ca>;Mark Paralovos <mparalovos@gmail.com>;Furey, Anthony <AFurey@postmedia.com>;Glenn Bragonier <glenn.bragonier@corusent.com>;ALEX PIERSON <piersona@hotmail.com>;Anna Vanderlaan <Anna.Vanderlaan@wdgpublichealth.ca>;katherine.kenny@wellingtoncdsb.ca <katherine.kenny@wellingtoncdsb.ca>;generalinquiries@wellingtoncdsb.ca <generalinquiries@wellingtoncdsb.ca>; inquiry@ugdsb.on.ca <inquiry@ugdsb.on.ca>;Mschreiner@ola.org <Mschreiner@ola.org>;mayor@guelph.ca <Mayor@guelph.ca>;dominique.orourke@guelph.ca <dominique.orourke@guelph.ca>;mark.mackinnon@guelph.ca <mark.mackinnon@guelph.ca>;leanne.caron@guelph.ca <leanne.caron@guelph.ca>;cathy.downer@guelph.ca <cathy.downer@guelph.ca>;mike.salisbury@guelph.ca <mike.salisbury@guelph.ca>;christine.billings@guelph.ca <christine.billings@guelph.ca>;June Hofland <june.hofland@guelph.ca>;phil.allt@guelph.ca <phil.allt@guelph.ca>;Rodrigo Goller <rodrigo.goller@guelph.ca>;dan.gibson@guelph.ca <dan.gibson@guelph.ca>;christine.elliott@pc.ola.org <christine.elliott@pc.ola.org>;newsroom@guelphmercurytribune.com <newsroom@guelphmercurytribune.com>; news@wellingtonadvertiser.com <news@wellingtonadvertiser.com>;George Bridge <gbridge@town.minto.on.ca>;Jessica Minott <minott@uoguelph.ca>;Elaine Klafuric <eklafuri@uoguelph.ca>;Ashley Stegelmeier <astegelm@uoguelph.ca>;Khalil Karimi <kkarimi@uoguelph.ca>;Lily Chan <lchan12@uoguelph.ca>;Jason Knapp <jknapp03@uoguelph.ca>;David Marom <dmarom@uoguelph.ca>;Yeganeh Mehrani <ymehrani@uoguelph.ca>;Julia Kakish <jkakish@uoguelph.ca>;Sierra Vanderkamp <vanderka@uoguelph.ca>;Trinity Lougheed <lougheet@uoguelph.ca>;Christina Napoleoni <napoleoc@uoguelph.ca>;J. Scott Weese <jsweese@uoguelph.ca>;Maya Goldenberg <mgolden@uoguelph.ca>;jbettinger@bcchr.ubc.ca <jbettinger@bcchr.ubc.ca>;abraham.al-ahmad@ttuhsc.edu <abraham.al-ahmad@ttuhsc.edu>;Anne-Marie Zajdlik <azajdlik@sentex.net>;Mark Paralovos <mparalovos@gmail.com>;mark <mark@trialsitenews.com>; newsroom@guelphmercurytribune.com <newsroom@guelphmercurytribune.com>;gmcnaughton@guelphmercurytribune.com <gmcnaughton@guelphmercurytribune.com>

1 attachments (5 MB)

2021-06-15 - Children and COVID-19 Vaccines - full guide_ FINAL.pdf;

Some people on this e-mail have been steadfast supporters, others have remained neutral (which I also respect), others have tried to brutalize me via a cowardly smear campaign. Particularly for the latter, before you judge me further, I would ask that you first do four things: 1. Read my attached report if you have not done so already (to get a full understanding of why I have concerns about children receiving experimental COVID-19 vaccines). 2. Listen to this podcast, in which Dr. Robert Malone, the inventor of the mRNA vaccine technology clearly states that my interpretation of the science is 100% correct: https://podcasts.apple.com/ng/podcast/mrna-inventor-robert-malone-backs-up-byram-bridle-on/id1513237951?i=1000526212312. 3. See the latest posting on the website of the World Health Organization (https://www.who.int/emergencies/diseases/novel-coronavirus-

should not be vaccinated for the moment. "...because children and adolescents tend to have milder disease compared to adults, so unless they are part of a group at higher risk of severe COVID-19, it is less urgent to vaccinate them than older people, those with chronic health conditions and health workers. More evidence is needed on the use of the different COVID-19 vaccines in children to be able to make general recommendations on vaccinating children against COVID-19." 4. View this interview in which I provide rebuttals to all opposing statements that I was aware of, including addressing the libelous website that was made in my domain name: https://www.facebook.com/WhatsUpCanadians/videos/206400258023039

The need for this e-mail came to my attention when a local article in the Guelph MercuryTribune was released yesterday (https://www.thestar.com/local-guelph/news/2021/06/21/immunologists-raise-concerns-on-u-of-guelph-prof-s-views-on-covid-19-vaccine-safety.html). It is a very poorly researched, imbalanced, and highly biased article that seems to do nothing other than contribute to the smear campaign against me. Among many things, the reporter failed to mention the reason why I did not agree to go on record after a ~1 hr discussion (that was ignored); which was because the reporter refused to allow me to see a draft to ensure they would not misquote me (the end-product justifies why I made this request). They also failed to interview anyone representing the side opposite the narrow public health narrative. Of those they interviewed, all but one remained cowardly and refused to be named, making the statements of the reporter no more than hearsay. Of note, a federal MP invested time to write a lengthy e-mail to this local reporter to give them a slap on the wrist for such poor reporting and to highlight their numerous omissions that would have made the story somewhat balanced. The fact that this disrespectful behaviour is ongoing indicates to me that people still have not placed my views into an appropriate context. The above four sources of information should help to do this.

Note that I previously contributed to an open letter expressing concerns about the safety of the AstraZeneca vaccine just after Health Canada authorized its use. That vaccination program has now largely ended after being declared too dangerous for Canadians. This, and the fact that the WHO and the inventor of mRNA vaccine technology agree with me about concerns regarding vaccinating youth, should alleviate concerns raised by so-called 'fact-checkers' and others that I have no clue what I am talking about.

If anyone remains intent upon trying to defame me and harm my career, I kindly ask, out of respect, that you try to do so in a public forum where you and I can openly discuss the science in front of the public. We can get a moderator to facilitate the discussion. If not willing to do this, please refrain from disrespectful, cowardly behaviours. Definitely don't attempt to slander me if you are unwilling to invest the time into investigating the four sources of information that I listed above. Better yet, consider trying to argue that the inventor of mRNA vaccines and the WHO have no clue what they are talking about. As for me, I remain committed to the tenet of academic freedom and standing behind it to advance the truth.

Sincerely,
Byram

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From: Byram Bridle <bbridle@uoguelph.ca>
Sent: Tuesday, June 15, 2021 1:28 PM
Subject: COVID-19 Vaccines: A Guide for Parents

Please see the attached [full] guide for parents. Please circulate it as widely as you feel comfortable. I am receptive to respectful discussions with those who believe that scientists, physicians, and other professionals should be able to openly discuss the science and medicine underpinning COVID-19 policies.

Sincerely,
Byram

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This is Exhibit " S " to the Affidavit of

Byram Bridle, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

COVID-19 Vaccines and Children:

A Scientist's Guide for Parents

by

Dr. Byram W. Bridle, PhD

Associate Professor of Viral Immunology

June 15, 2021

Canadian Covid Care Alliance
Alliance canadienne pour la prévention et prise-en-charge de la covid

https://www.canadiancovidcarealliance.org/

EXECUTIVE SUMMARY

Pfizer BioNTech's COVID-19 mRNA vaccine has been *Authorized under an Interim Order* by Health Canada for use in Canadians as young as 12 years old, with mandatory commitments for the monitoring of long-term safety and efficacy. Authorization under an Interim Order means additional information is needed on the safety, efficacy, and quality of the vaccine, including in children and adolescents, to support the future full market approval and licensing of the vaccine.

There is some uncertainty regarding the long-term safety of Pfizer BioNTech's COVID-19 vaccine in all individuals, and especially in children, youth, and younger adults of child-bearing age. Indeed, some key safety studies appear to have been missed in the rush to roll out the vaccines, and more is being learned about the vaccines every day. For example, there was a previously wide-held assumption that vaccination with the mRNA vaccines is safe because it is a localized event in the body, with the vaccine remaining limited to the shoulder muscle following injection and triggering an immune response in the local lymph nodes. However, there is evidence that Pfizer's COVID-19 vaccine does not remain at the injection site. In fact, once injected, the vaccine contents appear to travel extensively throughout the body, to the brain and other sensitive tissues, such as bone marrow, spleen, liver, adrenal glands, ovaries *etc.* Whether these body sites are involved in producing the spike protein is not known, as this was never studied. Nonetheless, new data have been published that, following vaccination with the Moderna vaccine (an mRNA vaccine very similar to Pfizer's mRNA vaccine), the spike protein can enter the circulatory system. Presumably, this means the spike protein can travel extensively throughout the body. It is important to understand which organs are producing the spike protein, what factors result in the spike protein entering the circulation, how long the spike protein circulates, and in which body fluids (*e.g.*, semen, saliva, breast milk, urine) the spike protein is present. This information is incredibly important because recent data have come to light that the spike protein is "biologically active". This means that the spike protein is not just an antigen that is recognized by the immune system as being foreign. It means that the spike protein, itself, can interact with receptors throughout the body, called ACE2 receptors, potentially causing undesirable effects such as damage to the heart and cardiovascular system, blood clots, bleeding, and neurological effects. Although some might argue that the risk of the spike protein causing this type of damage is only a theoretical risk, when we are mass vaccinating a population of predominantly healthy people, including children, adolescents, and adults of child-bearing age, there is absolutely no room for avoidable error.

The current scientific uncertainties demand that the administration of Pfizer's COVID-19 vaccine to children, adolescents, and young adults of child-bearing age be paused until proper scientific studies that focus on the safety and pharmacokinetics and biodistribution of the vaccines and the vaccine-encoded spike protein can be conducted. Halting the vaccination can be done safely because:

- The risk of severe and potentially lethal COVID-19 in these specific populations is so low that we need to be very certain that risks associated with mass vaccination are not higher;
- Asymptomatic members of this population are not a substantial risk for passing COVID-19 to others; and

- There are effective early-treatment strategies for the very few children, adolescents, and young adults of child-bearing age who may be at risk of developing severe COVID-19, such as ivermectin, fluvoxamine, and budesonide.

It is not appropriate to use an "experimental" vaccine in a population group unless the benefit of vaccination exceeds the risk of vaccination in that population group. With risk of severe COVID-19 in children, adolescents, and young adults of child-bearing age already so low, the benefit of vaccinating these population groups with a vaccine for which neither the long-term safety nor efficacy is known cannot be concluded to exceed the risk. In other words, the risk of serious COVID-19 is so low in children, adolescents, and young adults of child-bearing age that the standards for safety must be set much higher for them.

Contents

Who is Dr. Bridle?

I am an Associate Professor of Viral Immunology in the Department of Pathobiology at the University of Guelph in Canada. My research program focuses on the development of vaccines to prevent infectious diseases and treat cancers, as well as studying the body's immune response to viruses. I teach several courses at the undergraduate and graduate levels on the topics of immunology, virology, and cancer biology. The overall aim of my research efforts is to develop safe and effective new therapies for people. Indeed, one of my previous cancer therapies progressed into four human clinical trials. I am also involved in training Canada's next generation of multidisciplinary researchers, especially in vaccinology. I received funding from the Ontario Government (COVID-19 Rapid Research Fund, Ministry of Colleges and Universities) and Government of Canada (Pandemic Response Challenge Program, National Research Council of Canada) to develop vaccines against COVID-19. The scope of this research is limited to the pre-clinical realm and is years away from being ready for testing in a clinical trial. Since I do not hold any commercial interests, this is not considered a conflict of interest that would preclude me from publishing my research findings. If that were the case, most researchers could never comment on topics relevant to their area of expertise, because they receive funding in that area. Further, my laboratory's vaccine vectors also express the spike protein of SARS-CoV-2. As such, what I am presenting here affects my vaccines as much as anyone else's. I also hold numerous grants in support of my cancer research and basic viral immunology research programs, including, but not limited, to the Canadian Institutes for Health Research, Natural Sciences and Engineering Research Council of Canada, Canadian Cancer Society, and Cancer Research Society. Since the COVID-19 pandemic was declared, I have been actively involved in providing fact-based; balanced, scientific answers to questions posed by the public to help them make fully informed decisions. This has included ~150 media engagements ranging from radio shows, published articles, and appearances on televised news programs, spanning the local to international scope. I was also an invited keynote speaker for two international conferences that focused on COVID-19 and served as an invited member of several COVID-19-focused discussion panels. Vaccinology is a sub-discipline of immunology. I teach the value of high-quality, well-validated, robustly safety-tested vaccines and promote their use. I consider vaccines that have been developed on a foundation of sound science to be the most efficient type of medicine; they have cost-effectively saved millions of people from sickness and/or death. However, I am concerned that the risk-benefit profile of SARS-CoV-2 vaccines currently being used in Canada and elsewhere may not be appropriate for the mass immunization of children, youth, and young adults of child-bearing age. My scientific reasoning substantiated by the peer-reviewed literature is contained within this guide.

What is the Canadian COVID Care Alliance (CCCA)?

The CCCA is an alliance of independent Canadian scientists, physicians and other health professionals, committed to providing top-quality and balanced evidence-based information to

the Canadian public about COVID-19 so that hospitalizations can be reduced, lives can be saved, and our country can be safely restored as quickly as possible.

Disclaimer

The comments in this guide are mine alone and do not necessarily reflect the opinions held by my academic institution or the agencies funding my research program. Nevertheless, these comments have been vetted and supported by many like-minded researchers and physicians associated with the CCCA.

Preamble

Although I have tried to be reasonably comprehensive in my presentation of relevant facts about COVID-19 vaccines, I could have written much more; hundreds of pages, in fact. However, I feel that the current content represents the most important information that parents will need to make informed decisions about vaccinating their children. As children in Canada who are 12 and older can be vaccinated without parental consent, this guide also serves to share information and encourage open discussions between parents and their older children, so that the choice to consent or not consent is truly "informed". There will be many people who will challenge the content of this guide. I respect others' opinions and decisions. I simply ask for similar respect in return. I am a public servant providing information for which I have substantial expertise. It is being done from the perspective of having a genuine concern for the well-being of Canadian youth. I urge everyone to follow the weight of validated scientific data. I ask you to challenge information that is accompanied by loose claims of being 'data from on the ground' or 'data from the front lines', which often lack scientific rigor and a 'big picture' perspective, especially in an era of extensive social media censorship. Follow the weight of the validated data when deciding which evidence is relevant and reliable in your decision-making process.

Important note: many treasured colleagues from within and outside Canada have helped me piece together this story. Without them, we would not have made all the scientific links that are described in this guide. As such, **I can take only partial credit for this work**. Instead, I am fronting a larger group of physicians and researchers; consolidating our conversations and sharing of scientific articles into my own words. Sadly, many of these experts and professionals currently feel the need to remain anonymous to protect themselves from potentially career-ending reprisals when objective scientific evidence is presented publicly.

I have included some citations and links for important statements to show that they are backed by sound science. In many cases, there are other scientific articles that could have been referenced. However, the purpose of this document is not to provide an exhaustive list of references, but rather to provide sufficient evidence to support my concerns. My goal is not to prove that Canada's COVID-19 vaccines are unsafe, but to highlight the substantial uncertainties that exist in the current base of safety evidence and my consequent discomfort with the mass

vaccination of our youth. The proper scientific process dictates that the burden of proof of safety is on vaccine manufacturers and health protection agencies. Most importantly, a lack of proof of harm is not proof of safety.

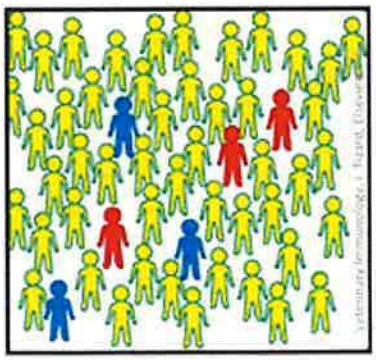
I first presented some of the information that is in this guide during a radio interview on May 27, 2021. This was a truncated ~five-minute sound bite that triggered a public smear campaign, including a slanderous website, a fake Twitter account, and harassment in the workplace. Nobody involved in the establishment of the smear campaign reached out to me to respectfully discuss the science. As a result, I wrote, along with collaborators, a brief two-page 'guide' to provide some key scientific references. Here, I have assembled a much more comprehensive guide, written with the goal of trying to communicate complex scientific principles to a lay person, yet with sufficient scientific rigour to also address experts. As I have often done with presentations and articles over the past year, I have set up this guide to answer the most common questions that I have received from the public. It is with sincere concern, and with the best interests of my fellow Canadians in mind, that I present you with the information that follows.

The problem: COVID-19

"COVID-19" is a disease that develops in a subset of individuals infected with a virus that is known as 'severe acute respiratory syndrome-coronavirus-2' (SARS-CoV-2). In the vast majority of cases of SARS-CoV-2 infections, people remain healthy (*i.e.* they are 'asymptomatic') or develop only mild to moderate symptoms of illness. However, in some cases, severe, and potentially lethal pneumonia, occasionally accompanied by other inflammatory events causing bleeding, clotting and/or neurological impairment, can develop in people in high-risk demographics, which includes the frail elderly and individuals who are immunocompromised (*i.e.* their immune systems do not function properly). Many people who become infected with SARS-CoV-2 do not develop the disease called COVID-19.

What is 'herd immunity'?

The concept of 'herd immunity' means that a virus will stop spreading among a population once most of the people in that population acquire a protective immune response. Importantly, this does not require every person to become immune, just a large majority. There are two ways for people to acquire immunity to SARS-CoV-2 and thus avoid the debilitating effects of COVID-19:



1. Natural infection:

When infected with SARS-CoV-2, most people clear this virus from their body by mounting a robust, long-lasting immune response that targets multiple components of the virus[1]. These people will be protected from re-infection with the same variant of SARS-CoV-2 and, due to the breadth of a natural immune response, will also likely have some degree of protection against emerging new variants of SARS-CoV-2. Indeed, most people who have naturally acquired immunity should not be at risk of developing severe disease even if variants arise that can effectively bypass the narrower immunity conferred by COVID-19 vaccines that are focused on a single component of SARS-CoV-2, such as the spike protein[2]. Interestingly, a landmark study in Canada suggested that a majority of healthy adults in British Columbia have evidence of pre-existing or naturally acquired immunity to SARS-CoV-2[3].

2. Vaccination:

Vaccines that have undergone properly conducted preclinical studies and the full suite of clinical trials to ensure they are (i) effective; and (ii) have excellent short-term and long-term (*i.e.* a minimum of two years; preferably longer) safety profiles, can allow an individual to become immune to a virus without having to be naturally infected.

How do vaccines work?

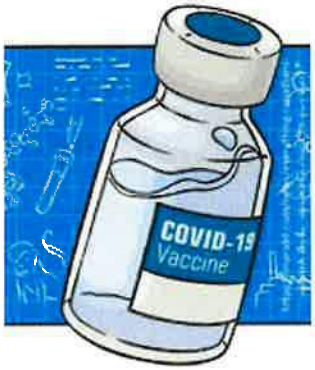
A successful vaccine must provide two things:

Thing 1: The virus or a piece(s) of the virus (*i.e.* a target for the immune system).

Thing 2: A danger signal (*i.e.* something that tells the person's immune system that the target it is seeing is dangerous and, therefore, worth responding to).

An effective vaccine simulates just enough of a natural infection, to trigger a person's body to develop an appropriate immune response without causing disease. Then, when the person becomes infected the first time by the natural virus, their body's immune system senses it is seeing the virus for the second time. This is because an immune response triggered by successful vaccination involves the body's development of 'immunological memory'. Therefore, the person's vaccine-primed immune response to the natural viral exposure will be faster and more robust, and the virus will be cleared without the person experiencing disease. Mass vaccination can accelerate progress of a population towards herd immunity.

How do Canada's COVID-19 vaccines work?



Canada currently has four COVID-19 vaccines that Health Canada has "Authorized by Interim Order". The Interim Orders enable the widespread deployment of the vaccines while the Phase 3 clinical studies (experiments in people) are being conducted. In the Phase 3 studies, all vaccine recipients must be followed for two years following the administration of the second vaccine dose. As long-term effects of the vaccine have yet to be understood, the vaccine is largely investigational. This is why the authorizations are "interim" and continued use is contingent on the collection of additional data from the Phase 3 studies, as well as other surveillance systems to assess the safety and effectiveness of the vaccines. Because the COVID-19 vaccines are being administered in Canada under experimental trial conditions, people receiving these vaccines should provide informed consent prior to being immunized. Informed consent demands that people be provided with all the known pros and cons, in an objective fashion and without undue pressure or coercion. This is a basic tenet of bioethics. Anyone administering a COVID-19 vaccine should be able to explain the benefits and risks based on the weight of the evidence provided in peer-reviewed, published scientific papers. Lay persons are encouraged to ask public health officials to explain the rationale for any statements made regarding COVID-19 vaccines and to have the sources of this information identified. Numbers in printed documents that do not contain citations do not necessarily reflect the robustness of the scientific literature.

The four COVID-19 vaccines currently being used in Canada include:

1. AstraZeneca/COVISHIELD vaccine (ChAdOx1-S):

These are two different names for the same vaccine (COVISHIELD is the brand name of AstraZeneca's vaccine that is manufactured by Verity Pharmaceuticals Inc. with the Serum Institute of India). Developed by AstraZeneca and Oxford University, the backbone of this vaccine is an adenovirus that does not cause disease in people. This adenovirus virus carries genetic material that provides instructions for a cell to manufacture a piece of SARS-CoV-2 (*i.e.*, the spike protein). When this adenovirus-based vaccine gets injected into the shoulder muscle, it is intended to infect cells and use the 'machinery' in these cells to manufacture small amounts of the SARS-CoV-2 spike protein. The SARS-CoV-2 spike protein and the adenovirus backbone provide the 'thing 1' and 'thing 2', respectively, that are needed to trigger an immune response.

Unfortunately, the rollout of the AstraZeneca vaccine in Canada proved to be a frustrating and complicated series of ever-changing, safety-triggered, recommendations given to a growing number of confused and distrusting members of the public. While many other countries paused their AstraZeneca vaccination programs to investigate safety issues related to potentially fatal blood clots, Canadians were told the AstraZeneca vaccine was safe for some population segments

and vaccinations with the AstraZeneca vaccine were initiated. After other countries practiced due diligence and confirmed that blood clotting was an adverse event associated with this vaccine, Canadians were then told that it was too unsafe for those under 55 years of age. Then Canadians between 40-55 years of age were told it was safe enough for them to use. Several weeks later, the message changed again, and the current messaging is that it is too unsafe to use as a first does in much of Canada. Millions of Canadians who received a single dose of this vaccine have since been wondering what to do. This highlights why the scientific method exists and why it should not be over-ridden by zealous public health officials. Safety testing should never be cut short. In many parts of Canada, the AstraZeneca vaccine is generally being used only for second doses for individuals who have had a first dose of the AstraZeneca vaccine and do not wish to have a second dose of another vaccine. The vaccine is irrelevant to Canadian children, youth, and young adults of child-bearing age, as it was never authorized for use in these population groups.

2. Janssen vaccine (Ad26.COV2.S):

This vaccine is made by Johnson & Johnson. Like the AstraZeneca vaccine, the Johnson & Johnson vaccine uses an adenovirus, albeit a different one. The way this vaccine works is similar to the AstraZeneca vaccine. After injection, cells infected with the adenovirus start to manufacture a spike protein that is very similar to that of the SARS-CoV-2 spike protein. There has been some public acknowledgement that this vaccine might also be associated with blood clots, and Health Canada has noted in their website notices of April 26th 2021 to healthcare professionals that "[v]ery rare cases of thrombosis in combination with thrombocytopenia, in some cases accompanied by bleeding, have been observed following vaccination with Janssen COVID-19 vaccine. A causal relationship with the vaccine is considered plausible." In considering the request for the Janssen vaccine to be Authorized Under Interim Order, Health Canada yet again acknowledged that "[i]mportant limitations of the data at this time include the lack of information on the long-term safety and effectiveness of the vaccine, interactions with other vaccines, and the lack of data in sub-populations (*e.g.* pregnant/breastfeeding women, pediatric population <18 years of age, patients with autoimmune or inflammatory disorders, immunocompromised patients and frail patients with comorbidities)." At the timing of writing this article, this vaccine has not been authorized for use in Canadian children, youth, and young adults of child-bearing age.

3. Pfizer BioNTech vaccine (BNT162b2):

This vaccine relies on technology that, prior to the COVID-19 pandemic, was not previously used in humans, except in small-scale clinical trials (such as a clinical trial of a rabies mRNA vaccine)[4]. The backbone of the Pfizer BioNTech vaccine is a lipid nanoparticle (a small bubble of fat). Inside the nanoparticle is a 'messenger ribonucleic acid' (mRNA). This is a tiny piece of genetic material that provides the instructions for a cell to manufacture a modified version of the SARS-CoV-2 spike protein. When these nanoparticles are injected into the body, they are

intended to fuse with cells with which they come into contact. When this happens, the mRNA migrates from the lipid nanoparticle and into the cell and the cell 'machinery' then uses this mRNA 'blueprint' to manufacture the modified version of the SARS-CoV-2 spike protein. This protein is the 'thing 1' that provides one of the two signals required for the immune system to become activated. It is not entirely clear what provides 'thing 2'. However, mRNA vaccines promote inflammation that can cause injury to normal tissue. When cells are injured, they release 'danger signals'. This might be what is providing the second signal ('thing 2') needed to induce an immune response.

Pfizer's vaccine has been associated with anaphylactic reactions in a small subset of individuals. These are serious allergic reactions that can be life-threatening. At the time of writing this guide, **the Pfizer vaccine is the only one that has received Authorization under Interim Order for Canadian children and adolescents 12 to 15 years of age.** In its decision-making process, Health Canada declared; "Health Canada has conducted a rigorous scientific review of the available medical evidence to assess the safety of the Pfizer-BioNTech COVID-19 vaccine. No major safety concerns have been identified in the data that we reviewed" [emphasis added]. Health Canada also acknowledged that "One limitation of the data at this time is the lack of information on the long-term safety and efficacy of the vaccine. The identified limitations are managed through labelling and the Risk Management Plan. The Phase 3 Study is ongoing and will continue to collect information on the long-term safety and efficacy of the vaccine. There are post-authorization commitments for monitoring the long-term safety and efficacy of Pfizer-BioNTech COVID-19 vaccine." Specifically related to the authorization for adolescents 12 to 15 years of age, "Health Canada declared, Health Canada has placed terms and conditions on this authorization requiring Pfizer-BioNTech to continue providing information to Health Canada on the safety, efficacy and quality of the vaccine in this younger age group to ensure its benefits continue to be demonstrated once it is on the market."

4. Moderna vaccine (mRNA 1273 SARS-CoV-2):

The Moderna vaccine also is an mRNA-based vaccine and, therefore, works the same way as Pfizer's COVID-19 vaccine. This vaccine has also been associated with anaphylactic reactions in a small subset of individuals. On June 7th 2021, Moderna had filed an application to extend the Authorization under an Interim Order to adolescents aged 12 to 17 years. At the time of writing this guide, Health Canada had not issued its decision.

None of Canada's COVID-19 vaccines can, in and of themselves, infect people with the SARS-CoV-2 virus, per se. Rather, these vaccines trigger the cells in a person's own body to manufacture one of the proteins that is a component part of SARS-CoV-2, and all the vaccines cause a person to make a modified version of the spike protein from SARS-CoV-2. The AstraZeneca vaccine contains the manufacturing blueprint for the exact same spike protein as is found on SARS-CoV-2. In contrast, the other three vaccines in use in Canada contain the manufacturing blueprint for a modified version that scientists refer to as the 'prefusion-stabilized spike'. All four vaccines are

designed to use the body's internal capability to manufacture the spike protein to then trigger the body's immune response.

What are the known serious adverse events that are associated with COVID-19 vaccines?

Using the United States Vaccine Adverse Event Reporting System (U.S. VAERS), as of June 11th 2021, the 20 most frequently reported adverse events (presented in descending order) were headache, pyrexia (fever), fatigue, chills, pain, nausea, dizziness, pain in extremity, injection site pain, myalgia (muscle pain), injection site erythema (redness), arthralgia (joint stiffness), pruritus (itching), rash, dyspnoea (difficulty breathing), injection site swelling, injection site pruritus (itching), vomiting, and asthenia (weakness). These side effects are common side effects and are similar to those reported in the Phase 3 clinical trials. Although these symptoms can be severe in some people and can result in an inability to perform daily activities, they usually subside over one to three days.

The mRNA vaccines (Pfizer and Moderna) can, in rare cases, cause anaphylaxis. Since this can be potentially fatal, these vaccines are often administered in special vaccine clinics that are staffed with personnel trained to treat people who may experience anaphylactic shock. The reason this problem is thought to be limited to the mRNA vaccines is likely due to a pre-existing allergy against something present in the liposome nanoparticles (the small bubble of fat) that are the part of the vaccine that envelopes the mRNA material. One of the liposome ingredients that might be the culprit is polyethylene glycol (PEG).

Based on data from international regulatory agencies (such as the Norwegian Medicines Agency), the adenovirus-based vaccines (*i.e.* AstraZeneca and Janssen) have been implicated in causing a very serious type of blood clot (a cerebral venous sinus thrombosis) that is simultaneously associated with a low platelet count and bleeding following vaccination. This is one of the reasons the AstraZeneca vaccine has largely been suspended for use in Canada, with the exception of use for second doses in those who received the AstraZeneca as their first dose and wish to stay with the same vaccine brand.

Are there other serious adverse events associated with COVID-19 vaccines that are being investigated?

Side effects that are rarer, including those that are serious or life-threatening, are still being learned about. For example, the United States Centers for Disease Control and Prevention (CDC) announced, only on June 11th 2021, that an Emergency Meeting would be held on June 18th 2021 to discuss reports of inflammation of the heart resulting from use of the Pfizer and Moderna vaccines in young males 16 to 24 years of age. It has been approximately six months since the vaccines were authorized under an emergency use in the U.S., and only now is this

association being recognized. There are many reasons why it is difficult to identify serious side effects that are rare or that occur only over a longer period of time or in a specific population group or sex. These difficulties are described below.

Difficulty #1: Too Soon to Tell for Sure

Pfizer and Moderna each initiated large, Phase 3 trials that were randomized, double-blind, and placebo-controlled. The placebo group is important because it serves as the reference group and helps in the interpretation of side effects experienced in the vaccine group. At the time that the vaccines were granted emergency use authorization, each company had safety and efficacy data for an average of only two months following the administration of the second vaccine dose; in the study in adolescents, most subjects had safety and efficacy data for either one or two months. According to the original protocols, every individual in the study is supposed to be followed for a total of two years following their second dose.

Difficulty #2: Abandoning the Control Group

The vaccines have been authorized under emergency use in many key countries, globally; and fear-based pressures imposed by public health agencies to vaccinate everyone has triggered study participants to want to know which study group they had been allocated to, so that those in the placebo group could be vaccinated. The studies have therefore been unblinded, meaning there is no longer a placebo group. This means that a rigorous assessment of safety in the context of a well-controlled clinical study is no longer possible, and there must be increased reliance on vaccine post-deployment, passive surveillance systems. Of course, this, itself, is challenging, given that there is uncertainty in both the numerator (the number of vaccine-related adverse events) and the denominator (the number that is typical for that event, otherwise referred to as the "background incidence" of the event). Moreover, it is extremely difficult to prove definitively that an event is caused by (and not just associated with) vaccination when using passive surveillance systems.

Difficulty #3: Under-Reporting of Adverse Events

The problem with passive adverse event reporting systems, which is the type of system that both Canada and the U.S. are relying on, is that there is a notorious problem of adverse event under-reporting. This is because reporting is voluntary; people may be unaware there are ways to report adverse events; people are often discouraged from reporting adverse events; people (including attending physicians) assume the condition is not related to vaccination; or people may not be able to report their adverse events (if they are severely disabled, ill, or deceased). Most disconcerting is the situation, as we see in Canada, where adverse event reports attempted to be submitted by medical professionals are pre-screened and sometimes rejected by pre-screening authorities. Consequently, adverse event databases can easily fail to identify potential concerns, or underestimate problems to an unknown degree and are, therefore, not a source of

accurate numbers to calculate true risk. For example, using the U.S. VAERS, it was estimated that the risk of anaphylaxis was 4.7 per million for the Pfizer vaccine and 2.5 per million for the Moderna vaccine[5]; however, in an active surveillance study of 64,900 healthcare workers who had been vaccinated, the rate was actually 216 per million[5], representing a potential rate of under-reporting of 46- to 86-fold. Despite these limitations, passive surveillance systems are useful for identifying potential risks that could then be investigated in properly designed safety studies.

Difficulty #4: Lack of Global Consistency and Thoroughness in Defining Events of Special Interest

Using the U.S. VAERS and similar adverse event reporting systems around the world, there is continuous monitoring of adverse events of special interest. But each jurisdiction is left to their own discretion to decide which, if any, particular adverse events of special interest will receive closer scrutiny. For example, the European Medicines Agency has compiled a list of important medical events (IMEs) which are always to be classified as serious (the IME list). The IMEs that are most frequently reported following COVID-19 vaccination (in descending order) are:

- Fainting (syncope)
- Blood clot(s) in the lungs
- Anaphylactic reaction
- Deep vein thrombosis
- Pneumonia
- Low blood platelet count (thrombocytopenia)
- Blood clot(s) or bleeding in the brain
- Hallucinations
- Cerebral stroke
- Loss of consciousness

Definitive cause-and-effect relationships for these events have not yet been established; it is hoped that with additional surveillance and time, clarity on the role of the vaccines in the cause of these events will be better understood. In the meantime, given that the spike protein is biologically active and there are mechanisms that could potentially explain some of these IMEs (discussed further below), there is good reason for genuine concern.

Why weren't serious adverse events identified before vaccines were rolled out?

Problems like anaphylactic shock (a severe allergic reaction) and potentially fatal blood clots were not identified until most of the experimental COVID-19 vaccines were used widely among the public[5, 6]. Janssen's study of the Johnson & Johnson vaccine did suggest some propensity for blood clotting. As for anaphylactic reactions, people with a history of allergies were excluded from the earlier clinical trials.

Another reason why some problems were not identified earlier is because short-cuts were taken with the traditional approach to vaccine research. Specifically, **the time taken to assess safety was too short**. Instead of taking the usual ~4-10 years to undergo thorough *in vitro* (*i.e.*, benchtop) tests, pre-clinical (*i.e.*, animal) studies, and then sequential clinical testing (*i.e.*, human Phase 1, 2 and 3 trials), COVID-19 vaccines were developed and assessed for safety and efficacy in less than one year. This meant that only very short-term safety scenarios could be evaluated. Of equal concern, **the number of people that were evaluated in clinical trials was too small** to capture rare but dangerous side-effects. This is unfortunate, because we have seen in Canada that rare but serious problems can lead to a vaccine program being suspended. Indeed, in Canada, a risk of blood clots for the AstraZeneca vaccine of 1 out of every 55,000 people vaccinated was deemed to be too dangerous, leading to its use being halted. Authorization under Interim Order for COVID-19 vaccines was granted after they were evaluated for a short duration in about 20,000 people. This means these studies could, at best, detect serious side effects that would occur in at least 1 out of every 20,000 people. In other words, the study design included a test population that was too small to identify vaccines that may be too dangerous for Canadians.

A clinical trial was conducted to justify using the Pfizer vaccine in Canadian children and adolescents; was it flawed as well?

Yes. First, it was far too short in duration to have any chance of assessing anything other than short-term harm. Also, in light of the information provided above, one needs to consider the following: only 1,131 adolescents between the ages of 12 and 15 received the vaccine in this study. This means that the study would have only been able to detect a serious side effect that occurs in 1 out of every 1,131 adolescents that are vaccinated; but a 1 in 55,000 risk was deemed to be too dangerous for adults for whom SARS-CoV-2 represents a greater risk. Furthermore, based on the recent observation of increased risk of heart inflammation following immunization with either the Pfizer or Moderna vaccine in young males, it appears serious side effects may be a function of both age and sex. In this regard, the Pfizer study of only 1,131 subjects provides even less robust data...enough to detect a serious gender-differentiating side effect that occurs in one out of approximately 565 (*i.e.*, 1,131÷2) males vaccinated and one out of approximately 565 females vaccinated.

But we have been told that adolescents and children can: (a) die from COVID-19, (b) suffer severe disease, and (c) be asymptomatic spreaders of SARS-CoV-2 and, therefore, kill others. Don't these risks suggest that children, youth, and young adults of child-bearing age should be vaccinated?

No, they don't. Let's break this down...

(a) Deaths due to COVID-19 are extremely rare in young Canadians. In sixteen months 13 Canadians under the age of 20 have died of 266,852 with confirmed SARS-CoV-2 infection (data from the Government of Canada, as of June 11, 2021). Because many children have asymptomatic infections, the true denominator is likely greater. This loss of 13 lives is indeed a tragedy, but no more so than the ~2,266 Canadians under the age of 20 who die from other causes every 16 months. Basic cost-benefit analyses have been largely ignored during the pandemic. The fear of young people dying from SARS-CoV-2 has reached a point where we seem to have placed a much higher value on lives lost due to COVID-19 than lives lost to any other causes.

SARS-CoV-2 is not a problem of pandemic proportions for all demographics. Infection fatality rate (IFR) is a way to assess how dangerous a pathogen is. The IFR is calculated based on the number of people who die, from among the total number infected. Early in the declared COVID-19 pandemic, it was estimated that the IFR for SARS-CoV-2 was ~10-fold higher than for a serious outbreak of an influenza virus, or ~1%; maybe even as high as 10%. Indeed, the IFR for a bad 'flu' season can be as high as ~0.1%[7]. This IFR for influenza is calculated despite the high use of influenza vaccines that are commonly given seasonally to target populations. It is important to note that calculating an accurate IFR requires having accurate data for the denominator in the equation, which is the total number of people that have been infected.

Exacerbated by Canada's lack of testing for evidence of seroconversion (*i.e.* when virus-specific antibodies are present in an individual, which indicates they were infected) against SARS-CoV-2, it has been impossible to ascertain how many Canadians have been infected. However, as data have accumulated in countries that did practice due diligence in this area, the total number of infections that have occurred keeps getting re-adjusted to higher numbers. This is due to phenomena such as the large number of people who were infected but did not realize it, because they never became ill (they never developed COVID-19). As a result, the actual calculated IFR for SARS-CoV-2 has been steadily declining. Remarkably, as the data regarding total infections have become more accurate, the IFR for SARS-CoV-2 has most recently been estimated to be only ~0.15%[8]. It is likely that this IFR will drop even further as the extent of unnoticed infections is further elucidated.

Indeed, a recent study found that ~90% of randomly tested healthy adults in British Columbia had evidence of natural immunity to SARS-CoV-2[9]. This indicates that the denominator for determining the true IFR is likely substantially higher than previously appreciated, which would mean the IFR is less than 0.15%[9]. Further, this IFR includes the high-risk frail elderly, immunocompromised, smokers, highly obese people, and those with diabetes, pulmonary and cardiovascular disease. For Canadians who are outside of these high-risk demographics, the IFR would be much less than 0.15%, especially for children. Therefore, COVID-19 does not represent a substantial risk to children, youth, and young adults of child-bearing age[10].

(b) Very few children are at risk of developing severe COVID-19. It is challenging to know how small this risk is because public health officials have refused to differentiate the nature of the 'cases' of COVID-19 that have been reported. Many estimates of children in hospital with COVID-19 include children who were admitted for other reasons but had tested positive with SARS-CoV-2. The reality is that most cases in children and adolescents are mild. In fact, most children do not get sick at all after being infected with SARS-CoV-2. Children have a lower risk of developing disease, especially severe forms, compared to adults. This is in large part because they express in their lungs and airways lower concentrations of the "ACE2 receptor", a protein on the surface of various cells in the body that serves as a point of attachment for the SARS-CoV2 spike protein, and that when "docked" enables entry of the virus into the cell for subsequent replication and spread of infection.

(c) Asymptomatic transmission of SARS-CoV-2 is negligible. The definition of an asymptomatic individual is a person who is known to be infected with a microorganism but fails to develop symptoms associated with a disease. Indeed, we are all 'asymptomatic carriers' in the sense that we harbor trillions of bacteria and viruses in and on our bodies. However, these normal microbiomes usually do not cause us any disease, unless we become immunosuppressed or unless 'safe' microbes get transferred to anatomical locations where they can potentiate disease (*e.g.* fecal-to-oral transfer of some strains of *Escherichia coli*). So, in the context of SARS-CoV-2, an asymptomatic carrier would be defined as an individual who is infected with the virus but fails to develop COVID-19. A colleague of mine recently asked this rhetorical question: "didn't we previously call an asymptomatic person 'healthy'?"

A study of the prevalence of SARS-CoV-2 in ~10 million people in Wuhan, China found no evidence of asymptomatic transmission[11]. In the United Kingdom, the 'Scientific Advisory Group for Emergencies' recommended that "Prioritising rapid testing of symptomatic people is likely to have a greater impact on identifying positive cases and reducing transmission than frequent testing of asymptomatic people in an outbreak area"[12]. Consequently, they have asked their government to change their testing policy by moving away from asymptomatic testing. The World Health Organization notes that "Most PCR assays are indicated as an aid for diagnosis, therefore, health care providers must consider any result in combination with timing of sampling, specimen type, assay specifics, clinical observations, patient history, confirmed status of any contacts, and epidemiological information"[13].

On its own, a positive result on a PCR test to detect SARS-CoV-2 is insufficient to diagnose COVID-19, yet this has become routine in Canada. In addition to the potential for false positive tests, true positive results can also be obtained from genomes of SARS-CoV-2 particles that are no longer infectious. An example of the latter would be an individual who has mounted an effective immune response and may have remnant replication-incompetent viral particles or partially degraded viral genetic material. Indeed, following clearance of SARS-CoV-2 from the body, full and/or partial genomes of SARS-CoV-2 can remain for up to several weeks. One key reason for this is that some phagocytic cells, which are a component of the innate immune

system, can be long-lived. Phagocytosis, which is the engulfment and digestion of SARS-CoV-2, is a mechanism to kill and remove the virus from the body and to activate other white blood cells. As such, these can be a source of SARS-CoV-2 genetic material that could be amplified by a PCR test. However, this genetic material would not have the potential to cause COVID-19. Persistence of whole or partial genetic material that is not associated with infectious particles is well-documented for a variety of other viruses, including measles[14], Middle East Respiratory Syndrome (MERS)-coronavirus[15], and other coronaviruses[16].

Too often, a positive PCR test for the presence of SARS-CoV-2, is being used, on its own, to define positive cases of COVID-19. However, the presence of a portion of the viral genome in an individual, on its own, does not necessarily equate with disease (*i.e.* COVID-19). To be declared a COVID-19 "case", the infection would also have to be associated with expected signs such as antibody development and/or symptoms of disease. This is known as a clinical diagnosis and would be based on evaluation by a physician, in conjunction with test results. A gold-standard test for infectivity of a virus is a cell-based functional assay that determines the potential for the virus sample to cause cell death. However, such an assay is not in routine use in Canada. Absence of such an assay further confounds any meaningful interpretation of positive results in asymptomatic people. Drawing conclusions based solely on the results of laboratory tests, would take the diagnosis of diseases out of the hands of physicians, and place the onus for this on technicians employed by testing laboratories. Further confounding this issue is the fact that cases of COVID-19 can be claimed in the absence of confirming infection with SARS-CoV-2 (this is known as "ICD code U07.2 COVID-19, virus not identified")[17]. Worse, the definition of a case of COVID-19 has changed over time in Canada. Indeed, the government of Canada has stated the following on their website: "Previous versions of the COVID-19 case definition are available upon request. Please email COVID19Surveillance@canada.ca to request a copy or for more information."[17]

Positive PCR tests for SARS-CoV-2 in asymptomatic people are often based on what scientists call 'high cycle numbers' (also called "cycle thresholds" or Ct"). PCR tests that only yield a positive result at high cycle numbers brings into question whether or not these individuals actually harbor infectious viral particles. This, combined with the absence of a functional cell-based assay to prove infectivity, renders results of asymptomatic testing nearly impossible to interpret accurately. Indeed, the World Health Organization, agreeing with many health professionals around the world, has emphasized that spreading of SARS-CoV-2 by asymptomatic individuals is rare and an emphasis should be placed, therefore, on testing people with signs or symptoms of illness, not those who are apparently healthy[18]. Of particular concern is the high cycle numbers being used by labs in Ontario (*i.e.* up to 38 cycles being defined as 'positive' by Public Health Ontario[19]), to define a COVID-19 positive "case." Several studies have been conducted to determine the highest number of PCR cycles at which live SARS-CoV-2 from a sample could be successfully cultured in cells. These studies suggest that appropriate cycle thresholds were 25[20], 22-27[21], and 30[22] cycles. This indicates that tests with positive results obtained above 22-30 cycles are not clearly supportive of the presence of live (*i.e.* replication-competent) SARS-CoV-2. The logical conclusion is that it is erroneous to declare samples that test

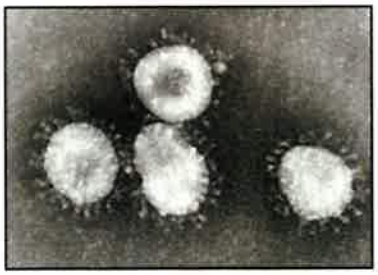
positive at high cycle numbers, especially those above 30, as being "positive" for infectious SARS-CoV-2. Appendix 1 shows results of a published study that depicts the numbers of PCR cycles at which asymptomatic people tested positive for SARS-CoV-2 relative to that observed for people with symptomatic infections[23]. Remarkably, if the cut-off for positive test results was set to Ct values of 22 or 30 (*i.e.* the point beyond which samples fail to yield potentially infectious virus particles), the vast majority of 'positive test results' would be rendered negative. It was even concluded in a study by La Scola B, *et al.*, that patients testing 'positive' at cycle numbers above 33 could likely be discharged from hospitals[24]. This means that an unknown number of positive cases reported in Ontario were likely not true positives of COVID-19. This is further supported by evidence that asymptomatic people have detectable SARS-CoV-2-specific memory T immune cells after exposure to the virus, which would be inconsistent with a risk of them harboring and spreading the virus to others[25].

Importantly, false positive test results, which have a greater risk of happening among asymptomatic people, have been shown to have numerous negative consequences in terms of physical and mental health, and causes financial losses[26]. Testing of asymptomatic people for the presence of portions of the SARS-CoV-2 genome makes neither medical nor economic sense. Positive test results from asymptomatic individuals cannot be interpreted in a clinically meaningful way. Although asymptomatic transmission is theoretically possible, it is improbable that it is occurring in substantial numbers and does not represent a significant risk of causing COVID-19-related hospitalizations or deaths in others.

For all the aforementioned reasons, **it is wrong to label children as being asymptomatic spreaders of SARS-CoV-2** that will sicken and kill others. Indeed, as reported by L. T. Brandal *et al.*, "under 14 year olds are not the drivers of SARS-CoV-2 transmission"[27]. A study in England concluded "SARS-CoV-2 infections and outbreaks were uncommon in educational settings", with staff (adults), not students (children) being the primary source of infections[28].

Now that the reasons that were used to justify using an experimental COVID-19 vaccine in children have been put into a reasonable perspective, let's continue talking about the vaccine technology.

Why was the spike protein from SARS-CoV-2 chosen as a target for the immune system?



Electron micrograph of a coronavirus

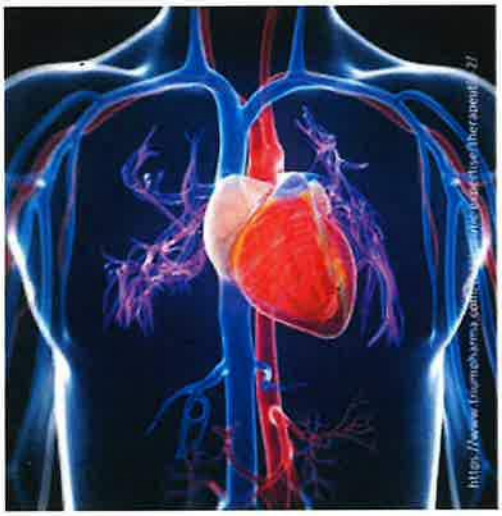
The spike protein gives SARS-CoV-2 its 'crown-like' appearance, which means it looks like it has a 'corona'. This protein allows the virus to attach to our cells and then infect them. If antibodies can bind to and 'block' all the spike proteins on the surface of the virus, then it could not infect our cells. Moreover, the binding of antibodies to even a part of the virus can tag it for attack by cells of our immune system. As such, COVID-19

vaccines currently being used in Canada instruct our cells to manufacture the spike protein in order to trigger our bodies to mount an immune response against this protein with the hope that the ensuing antibodies will get into our lungs and airways and block the virus, should we be infected in the future.

What should we know about the SARS-CoV2 spike protein?

Before we go any further with the story about COVID-19 vaccines, there is important information that you need to know about the spike protein from SARS-CoV-2.

The spike protein from SARS-CoV-2 has the potential to damage cells in the body



In cases of severe COVID-19, problems can extend well beyond pneumonia and the associated inflammation in the lungs. The disease can progress beyond the lungs and into other parts of the body. In severe infections, SARS-CoV-2 can cause damage to the cardiovascular system (*i.e.* heart and blood vessels). In fact, some have referred to severe COVID-19 as largely being a vascular disease[29, 30, 31]. Blood clots, bleeding and/or damage to the heart have all been linked to severe COVID-19. Severe COVID-19 can also cause neurological problems (*i.e.* damage in the brain). A series of recent scientific publications provide some evidence that this damage throughout the body may not require an intact SARS-CoV-2 particle. Instead, the spike protein from SARS-CoV-2 might be responsible for at least some of the damage that occurs in severe cases of COVID-19[32]. This is because there are many cells other than those in the lungs and airways that feature the receptor for the spike protein, known as the ACE2 receptor. Most notably, platelets and cells lining blood vessels can express high concentrations of this receptor. Importantly, autopsies performed on patients who died from severe COVID-19 revealed that free spike protein from SARS-CoV-2, not the intact virus, was responsible for substantial damage throughout the body. Notably, blood vessels in the skin, fat, and the brain were found to express high concentrations of the ACE2 receptor that the spike protein binds to. There was a lot of spike protein found in these tissues, with little to no evidence of the intact virus being present. Indeed, the authors of the study that described these autopsies concluded "COVID-19 represents a viral infection with limited sites of infectious virions but deadly sequelae due to the effective manner in which pseudovirions in the context of released viral proteins activate synergistic microvascular pathways of tissue destruction throughout the body."[33] In lay language, proteins like the spike protein, not the intact virus, appear to mediate

much of the damage in the body in people who suffer from severe COVID-19. When the spike protein binds to these receptors, there are several events that can take place:

1. Proteins (called 'complement proteins') that are part of our innate immune system can get activated, causing inflammation that can damage or destroy the cells lining blood vessels and/or platelets[34]. Platelets that are required for clotting of blood also express ACE2 receptors that can bind with spike protein with dire consequences. Damage and destruction of platelets can cause their numbers to go down (a condition known as "thrombocytopenia"), and if platelet counts get too low and blood vessels are damaged, bleeding cannot be stopped. Therefore, the spike protein can potentiate bleeding.

2. Binding of the spike protein to platelets can also cause the platelets to become activated[35]. Activated platelets tend to clump, which can lead to the formation of clots. There is evidence that the spike protein can interact with other proteins in the blood to promote clotting[36]. As such, the spike protein can promote blood clotting.

3. Spike proteins binding to the cells that line our blood vessels can cause these cells to express proteins (known as 'caspases') that can cause the cells to die[33]. This is similar to findings from the 2002-2004 SARS outbreak where the spike protein from the original SARS-CoV could cause cells to die when it was being manufactured inside of them[37]. Dying cells that have been manufacturing the vaccine-encoded spike protein would release free spike protein or portions thereof.

4. Spike proteins binding to the cells that line our blood vessels can cause these cells to over-produce cell-signalling cytokines that can potentially contribute to dangerous 'cytokine storms' (overly robust and severe inflammation)[33, 38].

Of additional concern is the knowledge that the spike protein is capable of dissociating into two parts and these smaller subunits (S1 and S2) can cross the blood-brain barrier where they can potentially cause damage in the brain[39]. Indeed, people who have died from severe COVID-19 with neurological signs were found to have the spike proteins but not the intact virus in their brains[40]. These neurological signs could be seen in laboratory studies when spike proteins were injected into the blood of mice.

Conclusion: The spike protein, if it gets into circulation, has the potential to cause damage to the cardiovascular system and other tissues.

Back to the vaccines

Now that there is a clear understanding that the spike protein from SARS-CoV-2 is a dangerous toxin when it gets into the blood and is distributed throughout the body, we can continue with the story about COVID-19 vaccines.

Evidence that mRNA-based COVID-19 vaccines can get distributed throughout the body

When the COVID-19 vaccines were designed, it was not appreciated that the spike protein could potentially damage cells in the body. As a consequence, administration of the current COVID-19 vaccines can put people at risk of damaging their cells, especially if expression of the spike protein is not limited to the vaccine injection site. An assumption was made with these vaccines that has proven to be incorrect. The assumption was that mRNA vaccines, which are a new technology, would behave the same as traditional vaccines. It was thought by many that mRNA vaccines would stay at the injection site and the only other place they would go is to the draining lymph nodes in the immediate vicinity of the injection site. More specifically, it was thought that cells of the immune system would come to the site of injection and create pieces of the virus and take these pieces to the lymph nodes where they would be shown to B and T cells (*i.e.*, B and T lymphocytes). The B and T cells would then get activated, multiply to large numbers (this is why lymph nodes swell when a person is mounting an immune response) and then head out into the body to search for the pathogen. Notably, B cells are the source of antibodies. Unfortunately, researchers have come to learn that **the mRNA vaccines do not stay in the shoulder muscle**. In fact, **they have the potential to spread far and wide throughout the body via the blood**. Obviously, this is a very serious conclusion to draw, so let's walk through the solid scientific evidence that demonstrates this potential for biodistribution.

A report that Pfizer provided to the Japanese government (see Appendix 2) was published as reference #25 in an article[41] published in *BMJ* that can be found at this link. In section 2.6.5.5B of the report to the Japanese government there is a table containing lipid nanoparticle biodistribution data. This table shows where their surrogate "vaccine" (*i.e.* represented in the laboratory test by little bubbles of surrogate fat containing an analytical detection marker) ended up in the body of immunized rats, used in the laboratory as surrogates for humans. A portion of the table is reproduced below. Please review the data so you can get the full picture. I would like to highlight some observations. First, as shown in the blue rectangle that I added to the table, a lot of the surrogate vaccine dose remained at the injection site, as one would expect. Remarkably, however, most of the vaccine dose had gone elsewhere. The right side of the table (shown in the report to the Japanese government but not below) shows that 50-75% of the vaccine dose failed to remain the site of injection. The big question is, where did it go? Looking at the other tissues shows some of the places it went and accumulated. The red rectangle shows that **the surrogate vaccine was circulating in the blood**. There is also evidence that a substantial amount of the vaccine went to places like the spleen (green rectangle), liver (brown rectangle), ovaries (yellow

rectangle), adrenal glands (purple rectangle), and bone marrow (orange rectangle). The vaccine went to other places as well, such as testes, lungs, intestines, kidneys, thyroid gland, pituitary gland, uterus, *etc*. **The surrogate vaccine tested in a laboratory setting was widely distributed throughout the laboratory animals' bodies.**

Species (Strain):
Sex Number of Animals: Male and female 5 animals set
Feeding Condition:
Method of Administration: I
Dose: 50 µg [^{3}H]
Number of Doses:
Detection: Radioactivity quant
Sampling Time (hour): 0.25, 1, 2, 4,

Sample	Mean total lipid concentration (µg lipid equivalent g (or mL) (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365
Bone (femur)	0.091	0.195	0.260	0.276	0.340	0.342	0.687
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77
Brain	0.045	0.100	0.138	0.115	0.075	0.069	0.068
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546
Injection site	128	394	311	338	213	195	165
Kidneys	0.391	1.16	2.05	0.923	0.590	0.426	0.425
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED **Test A**

Sample	Total Lipid concentration (µg lipid equivalent g (or mL)) (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.405	0.534	0.554	
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	
Skin	0.013	0.208	0.159	0.145	0.119	0.157	
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	
Spinal cord	0.045	0.097	0.169	0.250	0.106	0.085	0.112
Spleen	0.354	2.47	7.73	10.3	22.1	20.1	23.4
Stomach	0.017	0.065	0.115	0.144	0.208	0.152	0.215
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320
Thymus	0.055	0.243	0.340	0.335	0.196	0.207	0.331
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.09
Uterus (females)	0.043	0.203	0.305	0.140	0.257	0.259	0.456
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805
Blood:Plasma ratio[a]	0.515	0.515	0.550	0.510	0.555	0.530	0.540

Based on the results of this biodistribution test, further tests should have been required in order to assess the impacts on more tissues and for a longer time before the vaccine was authorized for use, especially in growing children, adolescents, and young adults of child-bearing age. The vaccine manufacturer, researchers and regulatory authorities alike should have also looked more comprehensively at the potential for the test animals to shed the vaccine by assessing saliva, urine, and feces. Note that there was evidence of some trafficking of the vaccine to the salivary gland and bladder, which indicates there is potential for some degree of shedding of the vaccine from the body. Further, the biodistribution of the spike protein that is created by the body after vaccination should be carefully mapped. Studies such as these should be performed in at least two animal models, with one of these not being a rodent model since rodents have levels of ACE2 receptor binding affinity that is far less than that of humans and may, as a result, underestimate the impact of spike protein on humans. There should also have been an evaluation of where the vaccine and the spike protein were going in humans in a very limited Phase 1 clinical safety trial. **This may not have mattered as much if the protein encoded by the mRNA was inert, although the risks of autoimmunity with the deposition of the lipid nanomaterials at different organs are certainly worthy of consideration. But now that we know the spike protein encoded by the mRNA has**

its own biological activities of concern, there is even greater potential for damage to organs and tissues arising from circulating vaccine material.

Although not as detailed as the data in the report to the Japanese government, Pfizer's report to the European Medicines Agency states similar findings regarding the broad distribution of their vaccine platform throughout the body. The report is in Appendix 3. Of great concern is the following excerpt from section 2.3.2 on page 45: **"No traditional pharmacokinetic or biodistribution studies have been performed with the [Pfizer-BioNTech] vaccine candidate BNT162b2"**. If this is the first time this vaccine technology platform has been rolled out for wide distribution to humans, and if the Japanese biodistribution data showed evidence of spread of the surrogate vaccine material, one must ask **why was this experimental vaccine allowed to be used in people without it having undergone a crucial biodistribution study first?** This would have told us where the vaccine was going in the body before its use in people.

Supporting the need to address uncertainties and concerns regarding the biodistribution of the vaccine and the resulting spike protein is a peer-reviewed scientific paper that has just been accepted for publication. It describes a study in which 13 healthcare workers were assessed for the presence of the spike protein in their blood after receiving Moderna's vaccine (an mRNA vaccine with essentially identical platform technology as the Pfizer-BioNTech vaccine). Notably, the spike protein, (or the portion of it that binds to ACE2 receptor), could be found in the circulation in 3 out of the 13 people (and in 11 out of the 13 people), respectively[42]. The spike protein could be detected in the blood up to two weeks post-vaccination in most individuals and at 28 days post-vaccination in one individual. Some may argue that the concentration of the protein was low in most of the people studied. However, a protein circulating at a low concentration for up to two or more weeks could accumulate on cells over time as the blood constantly perfuses *(i.e.*, flows through) bodily tissues. Further, the biodistribution studies in the appendices suggest the spike protein could potentially be concentrated in many tissues that would not be evident by looking in blood alone. The possibility also exists that there were spike proteins already bound to ACE2 on the cells lining the blood vessels, but this was not investigated. Regardless, low concentrations of the spike protein in circulation would be expected in this small-scale study. High concentrations of a protein that can cause damage to blood vessels in a large number of people would not be consistent with a low incidence of severe adverse events. Remember, the AstraZeneca vaccination program was suspended in Canada due to a 1:55,000 incidence of blood clots. If spike proteins in blood were responsible for a severe side-effect, one would expect to see high concentrations of this protein in only one out of many thousands of people; a phenomenon that would likely not be detected in an analysis of only 13 people. Clearly, more work is needed here to assess the biodistribution of spike proteins in the human body after vaccination.

In a pre-print article (note: this means the paper has not yet undergone independent scientific peer review), there are data that indicate mRNA can even be detected in breast milk post-vaccination. This aspect of the study was downplayed but provides proof-of-principle that

this can happen. Knowing what we now know, it would not be surprising to have the spike protein in the breast milk of some lactating women if they were to be vaccinated. Proteins circulating in the blood usually get concentrated in breast milk. Notably, there have been some adverse events reported of infants experiencing bleeding in their gastrointestinal tracts after suckling from mothers who had received a COVID-19 vaccine. Here are some examples from the U.S. VAERS (I haven't checked for more since May 2021):

Serious Adverse Events Related to Breastfeeding After Receiving a COVID-19 Vaccine

- VAERS ID #945282; a 32-year-old mother had her 2-month-old breastfeeding daughter die 7 days after the mother had received the Pfizer-BioNTech vaccine
- VAERS ID #949926; a 34-year-old mother had her 4-month-old breastfeeding boy pass blood and mucous in the stools starting 2 days after the mother had received the Moderna vaccine
- VAERS ID #992676; a 30-year-old mother had her 2-month-old breastfeeding boy experience anorexia, spitting up, discoloured bloody feces, vomiting of blood, ulceration of the stomach, and bleeding in the gastrointestinal tract starting 2 days after the mother had received the Moderna vaccine

There were also other types of adverse events in infants associated with breastfeeding from mothers who had recently received a COVID-19 vaccine. For the sake of brevity, I have listed the VAERS ID #s here; anyone can look them up in the publicly available VAERS database.

- VAERS ID #s: 903355, 911226, 913968, 913971, 918972, 921052, 927664, 936865, 939409, 974519, 978085, 978485, 984448 (mother) - 984602 (infant), 1049482, 1105816, 1168901, 1171284

There is also a pre-print article that describes how an adenovirus-based vaccine can result in spike proteins damaging the vascular system. These types of vaccines are currently not being given to children in Canada. The mechanism is different from the mRNA-based vaccines, but the outcome is similar. The authors of this paper have coined an interesting term to describe the effect of a COVID-19 vaccine causing the same damage to the body that SARS-CoV-2 does; they called it "vaccine-induced COVID-19 mimicry syndrome".

It turns out that the suggested wide distribution of mRNA vaccines throughout the body has a historical precedent, such as for immunizing against influenza for example[43]. However, many people do not realize that lipid nanoparticles were not designed to function as vaccines. They were designed to serve as gene therapies or carry drug cargo throughout the body[44], including into the brain where attempts could be made to treat diseases such as Alzheimer's disease, Parkinson's disease, and brain cancers. Of substantial concern is the use of PEG, which has been associated with anaphylactic shock in some people after receiving a mRNA vaccine. PEG was added to lipid nanoparticles in the early days of drug development to promote much wider distribution throughout the body. Specifically, when PEG is added to lipid nanoparticles, it helps

the particles avoid being consumed by cells throughout the body, especially cells of the immune system, that would limit the distribution of the mRNA cargo[45, 46]. Indeed, addition of PEG to lipid nanoparticles was hailed as a breakthrough because "This effect is substantially greater than that observed previously with conventional liposomes and is associated with a more than 5-fold prolongation of liposome circulation time in blood"[45]. In retrospect, it seems that another mistake may have been made in the rush to get these vaccines into people: Arguably, the PEG component should have been removed from the lipid nanoparticle formulation. This likely would have resulted in lipid nanoparticles with a greater tendency to remain at the injection site and be picked up by the very cells of the immune system that we want to induce an immune response.

Conclusion: The assumption that COVID-19 vaccines remain at the injection site (*i.e.* the shoulder muscle) is not borne by the evidence. Laboratory studies have shown that the vaccine itself, and the spike protein that it encodes, may get into the blood, and be distributed widely throughout the body. Vaccines targeting the spike protein from SARS-CoV-2 were designed to induce antibodies that would bind to this protein to prevent the virus from being able to infect our bodies. The spike protein was supposed to be the 'first thing' that a vaccine must provide; a target for the immune system. We did not appreciate the potential for the spike protein alone to cause damage to cells in the body. We now understand that the current COVID-19 mRNA vaccines have the potential to be distributed throughout the body, thereby potentially and inadvertently inoculating many tissues with a protein that is possibly harmful. If unknown damage is being caused in some organs, this might not be clearly evident until years after vaccination. The data presented here do not provide proof of long-term harm. However, it provides the rationale for asking a number of safety questions. These questions should be thoroughly investigated in safety studies prior to using COVID-19 vaccines in children, adolescents, and young adults of child-bearing age.

A concern beyond circulating spike proteins: the potential for induction of autoimmunity

Some scientists have proposed that the spike protein from SARS-CoV-2 might have portions that are very similar to proteins in our own bodies[47]. If true, inducing immunity against the spike protein could theoretically promote autoimmune disorders. Indeed, two researchers found there was cross-reactivity between antibodies induced against the spike protein and several 'self' proteins[48]. This led to the recommendation almost one year ago to avoid targeting the entire spike protein in vaccines and instead target only portions of the protein that are not

similar to proteins in our own bodies. Unfortunately, autoimmune diseases can be insidious and take years for symptoms to become apparent.

The broad distribution of an mRNA vaccine throughout the body implicates other mechanisms that could lead to autoimmune disease. First, the mRNA vaccines promote robust inflammation. This is why many people have sore shoulders after being immunized. Promotion of inflammation in critical tissues, such as the ovaries, after being seeded with the vaccine could have dire consequences. Tissues like the ovaries are not supposed to become inflamed. This is because inflammation causes a lot of bystander damage to normal tissues, which is unwanted in an organ designed for reproduction. Also, the vaccine-encoded spike protein is designed to remain anchored on the surface of the cell that has manufactured it. If antibodies are present, such as would be the case several days after vaccination or natural infection, they could bind to the spike proteins on cells throughout our body, resulting in their destruction. Let's take the ovaries, again, as a theoretical scenario. If they were to undergo any type of tissue destruction, there is the possibility of proteins being released that the immune system has never seen before. This is because our immune systems learn to tolerate 'self' at a very young age. However, organs like the ovaries and testes start to express new proteins during puberty that the immune system has not been tolerized against. If these get released due to tissue damage, this could provide the same two signals that a vaccine needs to activate the immune system; signal 1 (target protein) and signal 2 (damage-associated danger signals). This could result in an autoimmune response against the organ. In this example (ovaries), such damage might not become apparent until years later when attempting to have a baby. This is speculation but is based on a huge body of scientific literature looking at how autoimmune diseases get started. Notably, this could potentially happen in any of the tissues seeded with the vaccine if they start to express the spike protein. This is certainly worthy of investigation before the mass vaccination of children, adolescents, and young adults of child-bearing age.

Even the fact that the current COVID-19 vaccines cause muscle cells in the shoulder to express the spike protein, is a potential problem. This could potentially result in immune responses being mounted against muscle tissue. This is of particular concern, because Israel has started to suspect a link between COVID-19 vaccines and inflammation in the heart muscle (a condition known as myocarditis). Indeed, this potential link is being actively investigated by the European Medicines Agency, as well as by the U.S. CDC. Again, with these kinds of concerns being raised in the global community, one must wonder why these vaccines are pushed so hard upon Canadian youth who are not at high risk of severe COVID-19. It will be a tragedy if we repeat something similar to or even worse than the AstraZeneca vaccine fiasco with our young people.

Why doesn't everyone who gets vaccinated experience a severe side-effect?

The spike protein likely does not get into circulation in every person. Indeed, in the study of 13 people vaccinated with the Moderna vaccine, ten had no evidence of the spike protein and

two had no evidence of the S1 subunit (a fragment of the spike protein) in their blood[42]. Also, it is important to remember that following vaccination, people manufacture the spike protein in their own cells. The amount and quality of mRNA in each dose of the vaccine can vary from batch to batch. The stability of the mRNA is also dependent on its handling as it is very temperature sensitive. So different people will receive different amounts of the active mRNA. People that receive the same amount of mRNA can produce different amounts of the spike protein depending on how metabolically active their cells are. And there are likely numerous other factors, including body size, *etc.* All of this could contribute to substantial variability in the concentration of spike proteins that a person produces. Notably, a standard vaccine injection might be expected to have a different impact in a 75-pound youth than in a 200-pound adult. The adverse events that we know about seem relatively rare. Some adverse events may go undetected. For example, knowing that the spike protein gets into circulation and knowing that it can kill platelets, it would not be surprising if most people have some loss of platelets after getting vaccinated. Also, platelets could pick up the mRNA from the circulating lipid nanoparticles and then display the spike protein on their surface, which would tag them for destruction by the ensuing antibody response. However, platelet counts are not being routinely monitored after people leave vaccination clinics, nor have the vaccine companies publicly released their data showing platelet counts post-immunization. Indeed, in a first-in-human study of BNT162b1, an earlier prototype of the Pfizer BioNTech BNT162b2 vaccine in use today, that encoded the S1 subunit of the spike protein (which contains the portion of the spike protein that binds to ACE2 receptors, called the receptor binding domain), platelet numbers dropped following vaccination in both the young and older adults studied[49]. Unfortunately, clinical chemistry and haematology values following vaccination with the BNT162b2 vaccine, which is the one currently being used to vaccinate people, were not published in Pfizer's first-in-human study[50].

One would be unaware if they were experiencing a loss of platelets unless their platelet count became dangerously low and they suffered trauma that would cause bleeding. Of greater concern is the potential for serious adverse events that we may not know about for quite some time. For example, damage to the ovaries or testicles might result in infertility that would not become apparent until attempting to have children. The oocytes that are present in the ovaries of newborn baby girls represent that female's life-long fixed supply of oocytes, which are the precursor of eggs. These oocytes cannot reproduce or regenerate if damaged or destroyed. Damage to the uterus could potentiate spontaneous abortions or miscarriages during pregnancy. The fact is, there is a clearly established set of biological mechanisms that raise numerous legitimate scientific concerns about COVID-19 vaccines. **We can't simply hope that none of these concerns end up being realized**. Instead, we must return to following the scientific method. We should stop the roll-out of the vaccination program for children, youth and young adults of child-bearing age, and ask the manufacturers of COVID-19 vaccines to take the time to conduct the proper biodistribution and safety studies to answer these emerging questions, and then conduct an accurate re-evaluation of the risk of COVID-19 versus the risks associated with the experimental COVID-19 vaccines.

Is the Pfizer BioNTech vaccine losing its effectiveness?

The stated purpose of vaccinating children, youth, and young adults of child-bearing age is to protect them from infection and reduce the risk of them transmitting SARS-CoV-2 to older adults. Therefore, it is important to note that the current COVID-19 vaccines fail to induce what we call 'sterilizing immunity'. This means that vaccinated individuals can still get infected with SARS-CoV-2, potentially become ill, and potentially transmit the virus to others. This is why vaccinated individuals are not exempt from lockdown policies and are still encouraged to wear masks. Importantly, there is evidence that the 'Delta variant' of SARS-CoV-2 has changed enough to be able to start evading the immunity conferred by the Pfizer BioNTech vaccine[51]. Indeed, the earlier 'South African' variant rendered AstraZeneca's vaccine only 10% effective[52]. With new variants on the horizon that will almost inevitably be able to bypass vaccine-induced immunity, this raises another question about whether the potential risks associated with the current vaccines are worth the minimal protection they will confer in the long-term to children, youth, and young adults of child-bearing age.

The Pfizer BioNTech vaccine might cause an excessive number of serious side-effects in young Canadians

As noted previously, Pfizer conducted an extremely small and very short-term clinical trial to test their vaccine in adolescents between the ages of 12-15 years. The results were reported in a fact sheet to the U.S. Food and Drug Administration. In this document, Pfizer defined severe adverse events as follows:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above

No deaths occurred in this small study, but Pfizer did note the following on page 27 of their fact sheet: "Serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.1% of placebo recipients." Much larger numbers of adolescents would have to be studied to provide conclusive evidence, but these limited data suggest the risk of serious adverse events

may have been 0.3% higher in the vaccinated group (not statistically significant in this small study).

As discussed previously, adverse events of special interest are being monitored, although the thoroughness is questionable, and the transparency of such activity is spotty at best. For example, the European Medicines Agency has compiled a list of important medical events (IMEs) which are always to be classified as serious (the IME list). The IMEs that are most frequently reported following COVID-19 vaccination include (in descending order):

- Fainting (syncope)
- Blood clot in the lungs
- Anaphylactic reaction
- Deep vein thrombosis
- Pneumonia
- Low blood platelet count (thrombocytopenia)
- Blood clots or bleeding in the brain
- Hallucinations
- Cerebral stroke
- Loss of consciousness

As the number of adolescents studied in the Pfizer trial was so small, it remains unclear whether adolescents also will experience these IMEs. It is not appropriate or ethical to experiment with youth, especially when their risk of severe COVID-19 is so low.

A side note about blood donations

Although not directly related to vaccinating children, adolescents, and young adults of child-bearing age, it is important to recognize that if the spike protein, which can cause substantial damage, gets into the blood after vaccination, this could have implications for donating blood. It would be unwise to infuse a blood product into a potentially fragile patient if it is contaminated with the spike protein. Worse, Pfizer's own biodistribution data demonstrate that the vaccine itself, not the spike protein, circulates in blood for at least two days post-immunization. Intravenous infusion of mRNA that can produce the spike protein in cells of the recipient should not be infused into patients who require blood. Remember, not only is there a risk of free-floating and cell-expressed spike proteins, but the lipid nanoparticles themselves can promote anaphylactic shock in a small subset of people. Of concern, Canadian Blood Services currently states their approval for receiving blood donations from people who have received a COVID-19 vaccine, without deferral. This is based on assumptions made using traditional vaccines that remain at the injection site, not novel mRNA-based vaccines that have been shown in laboratory studies to travel throughout the body. **This practice should be halted immediately** until it can be determined how long it takes for the lipid nanoparticles, and spike proteins to disappear from the blood. Canadian Blood Services should then recommend deferring blood

donations from vaccinated individuals until there is no risk of transferring lipid nanoparticles, mRNA, or spike proteins. The small-scale study that has looked at circulating levels of spike proteins suggests that it might not be safe to use blood products from a vaccinated individual for at least 4-5 weeks post-immunization[42]. In the United Kingdom, the National Health Service Blood and Transplant has recommended that, "COVID-19 vaccine – please wait 7 full days from your vaccine before donating on the 8th day. If you had side effects from the vaccine such as headache, temperature, aches, and chills, please wait 28 days from your recovery". It is unfortunate that there is not international collaboration with regards to recommendations for the donation of blood after COVID-19 vaccination.

What options are we left with if we pause the vaccination roll-out for children, adolescents, and young adults of child-bearing age?

Canada abandoned the original goal of learning to live with SARS-CoV-2 after the initial 2-3-week 'flattening of the curve' of daily cases of COVID-19 early in the year 2020. A massive amount of scientific data about COVID-19 has been compiled over the past 16 months. But we have not been following the accumulating science. It can direct us towards what one of my colleagues likes to call a 'rapid but soft landing.' The purpose of this guide was not to build a detailed exit strategy. However, I have also been closely following the scientific literature about strategies that can be used to effectively treat COVID-19, especially if they are implemented as an early out-patient, at-home treatment before the disease progresses to a level requiring hospitalization. Some, but all too few Canadian physicians, are aware of, or using, these early at-home treatment protocols. These protocols include safe and highly effective drugs like ivermectin, fluvoxamine, budesonide, zinc, melatonin, vitamin C, vitamin D, and many others. Several cocktails of approved drugs have proven to be particularly effective and are described in a variety of websites including TreatEarly.org, c19protocols.com, and FLCCC.net. There is now an avalanche of scientific data in support of these treatment options, but this digresses into an area beyond the scope of this guide. Unfortunately, the use of these effective therapies has never been promoted in Canada even though they could have prevented a lot of sickness and deaths and would have reduced the burden on intensive care units. Many people do not realize that the Interim Order or emergency use authorization of COVID-19 vaccines would have been contraindicated if there was acknowledgement of effective treatment strategies. This rule is in place to protect Canadians from being experimented on when there are viable alternatives that are known to be safe. However, it is never too late to do the right thing. Canada panicked and threw out pandemic preparedness plans at all its public institutions. Sometimes poor decisions occur when being made during a crisis and in the absence of established guidelines. It is time to move on. By promoting widespread use of effective treatments for COVID-19, Canada can safely narrow its experimental vaccination program and call for the science to catch up before subjecting our children, adolescents, and young adults of child-bearing age to potential harm.

Concluding remarks

Looking back through this report, it is clear that there are too many warning signals to ignore. Each individual signal may present a particular level of uncertainty, but when all the signals are considered together, the alert is deafening and must not be ignored. We must halt the vaccination of our children, adolescents, and young adults of child-bearing age. This can be done safely and expeditiously because:

- The risk of severe and potentially lethal COVID-19 in these specific populations is so low that we need to be very certain that risks associated with mass vaccination are not higher;
- Asymptomatic members of this population are not a substantial risk for passing COVID-19 to others; and
- There are effective early-treatment strategies and considerations for the very few children, adolescents, and young adults of child-bearing age who may be at risk of developing severe COVID-19.

Our younger generations of Canadians are our treasures and our future. Let's not put their futures at unnecessary risk by forcing upon them experimental vaccines that present newly identified and still-to-be-clarified dangers. Proof-of-principle now exists to demonstrate the current crop of vaccines may be dangerous. This risk, no matter how theoretical, must be further investigated and all concerns put to rest prior to the vaccination of our youth. It's time to sort out the science and reduce the pressures on parents and their children so they can make truly informed decisions. It is time to pass the torch from the pharmaceutical companies and hand it to the leaders and innovators among our community of physicians and researchers who have the skills, knowledge and experience to optimize excellent treatment strategies encompassing repurposed drugs that can be deployed to reduce the future casualties of this war against COVID-19.

What to do next?

If interested in obtaining more information relevant to COVID-19, please go to the Canadian COVID Care Alliance (CCCA) website at https://www.canadiancovidcarealliance.org/. There is an option to join an e-mail list if you are interested in receiving news from the CCCA.

An example of the expertise represented within CCCA's membership and their balanced scientific messaging with an emphasis on charting a safe but rapid exit from the cycles of lockdowns can be found here: https://trialsitenews.com/covid-19-expert-panel-the-path-forward-for-canadians-trialsite-webinar/. This discussion panel was set-up after the governments of Alberta, Saskatchewan, and Ontario failed to respond to invitations to engage scientists and physicians in respectful public discussions of the scientific knowledge that has accumulated about COVID-19.

Interviews that include one of the original inventors of mRNA vaccine technology (Dr. Robert Malone) opining on findings described in this guide can be found here and here.

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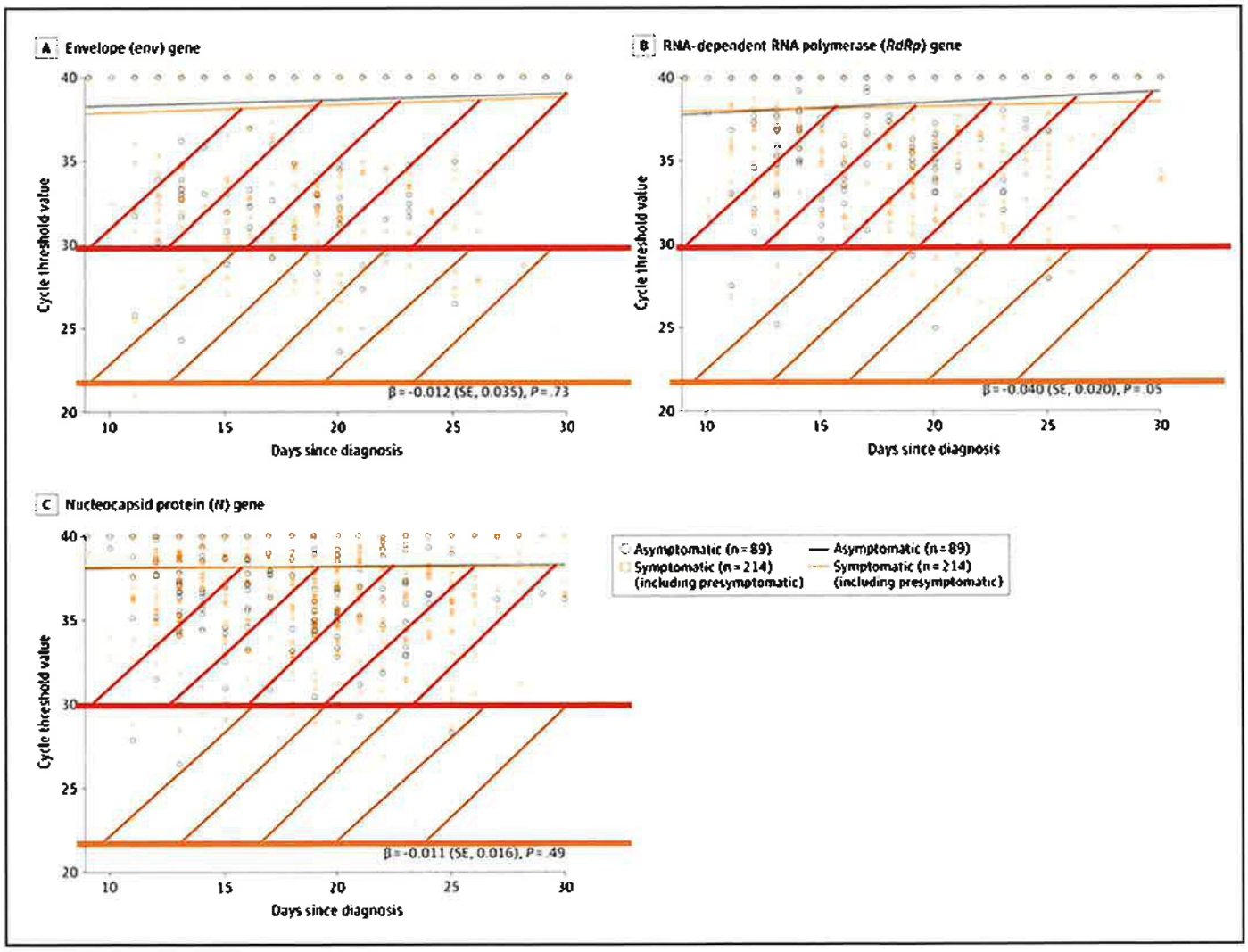
Appendix 1

Most 'positive' results for the SARS-CoV-2 PCR test are negative based on the gold standard virology assay. Shown are graphs from Figure 2 of a paper published in the *Journal of the American Medical Association* (*JAMA Intern Med.* 2020; 180(11): 1447-1452. doi:10.1001/jamainternmed.2020.3862). The argument being made was that the frequency at which asymptomatic people tested positive for SARS-CoV-2 was like that observed for people with symptomatic infections. However, new cut-offs for a positive test result were placed at 22 (orange line) and 30 (red line) PCR cycles. These are the limits (depending on the laboratory) at which replication-competent SARS-CoV-2 can no longer be recovered from samples according to the gold standard functional virology assay. When this is done, it is apparent that most of the results would be negative (*i.e.* these samples would fail to transmit infectious SARS-CoV-2).



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本項で使用する用語・略語

用語・略号	省略していない表現または定義
ALC-0159	本剤に添加される PEG 脂質
ALC-0315	本剤に添加されるアミノ脂質
[^{3}H]-CHE	Radiolabeled [Cholesteryl-1,2-^{3}H(N)]-Cholesteryl Hexadecyl Ether : 放射性標識 ［コレステリル-1, 2-^{3}H(N)］ヘキサデシルエーテル
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine：1,2-ジステアロイル-sn-グリセロ-3-ホスホコリン
GLP	Good Laboratory Practice：医薬品の安全性に関する非臨床試験の実施の基準
LNP	Lipid-nanoparticle：脂質ナノ粒子
modRNA	Nucleoside-modified mRNA：修飾ヌクレオシド mRNA
mRNA	Messenger RNA：メッセンジャーRNA
m/z	m/z（m・オーバー・z）：イオンの質量を統一原子質量単位（＝ダルトン）で割って得られた無次元量をさらにイオンの電荷数の絶対値で割って得られる無次元量
PEG	Polyethylene glycol：ポリエチレングリコール
PK	Pharmacokinetics：薬物動態
RNA	Ribonucleic acid：リボ核酸
S9	Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g：肝ホモジネートを 9000 g で遠心分離した上清画分
WHO	World Health Organization：世界保健機関

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1. まとめ

BNT162b2（BioNTech コード番号：BNT162，Pfizer コード番号：PF-07302048）は，重症急性呼吸器症候群コロナウイルス 2（SARS-CoV-2）のスパイク糖タンパク質（S タンパク質）全長体をコードする修飾ヌクレオシド mRNA（modRNA）であり，SARS-CoV-2 による感染症に対する mRNA ワクチンの本質として開発が進められている。BNT162b2 の製剤化にあたっては，2 つの機能脂質である ALC-0315（アミノ脂質）および ALC-0159（PEG 脂質）ならびに 2 つの構造脂質として DSPC（1,2-distearoyl-sn-glycero-3-phosphocholine）およびコレステロールと混合することで BNT162b2 を封入する脂質ナノ粒子（LNP）が形成される（以降，「BNT162b2 封入 LNP」）。

BNT162b2 封入 LNP の非臨床薬物動態を評価するために，LNP に含まれる ALC-0315 および ALC-0159 の吸収(PK)，代謝および排泄を評価する in vivo および in vitro 試験ならびに BNT162b2 の代替レポーターとしてルシフェラーゼまたは放射能標識した脂質を利用した生体内分布試験を実施した。

感染症予防を目的としたワクチンの開発では全身曝露量の評価を必要としないことを踏まえ（WHO, 2005；感染症予防ワクチンの非臨床試験ガイドライン）[1,2]，BNT162b2 封入 LNP の筋肉内投与による PK 試験は実施しなかった。また，本剤に含有される他の 2 種類の脂質（コレステロールおよび DSPC）は天然に存在する脂質であり，内在性脂質と同様に代謝，排泄されると考えられる。加えて，BNT162b2 は取り込んだ細胞中のリボヌクレアーゼにより分解されて核酸代謝され，BNT162b2 由来の S タンパク質はタンパク分解を受けると予想される。以上のことから，あらためてこれらの成分の代謝および排泄を評価する必要はないと考えられた。

BNT162b2 の代替レポーターとしてルシフェラーゼをコードする RNA を封入した LNP(ルシフェラーゼ RNA を BNT162b2 封入 LNP と同一の脂質構成を持つ LNP に封入：以降，「ルシフェラーゼ RNA 封入 LNP」）を Wistar Han ラットに静脈内投与した PK 試験では，血漿，尿，糞および肝臓試料を経時的に採取して，各試料中の ALC-0315 および ALC-0159 濃度を測定した。その結果，ALC-0315 および ALC-0159 は血中から肝臓にすみやかに分布することが示された。また，ALC-0315 および ALC-0159 はそれぞれ投与量の約 1%および約 50%が未変化体として糞中に排泄され，尿中においてはいずれも検出限界未満であった。

生体内分布試験では，ルシフェラーゼ RNA 封入 LNP を BALB/c マウスに筋肉内投与した。その結果，ルシフェラーゼの発現が投与部位でみられ，それより発現量は低値であったものの肝臓でも認められた。ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現も投与後 6 時間に認められ，投与後 48 時間までに消失した。また，ルシフェラーゼ RNA 封入 LNP の放射能標識体をラットに筋肉内投与して生体内分布を定量的に評価したところ，放射能濃度は投与部位で最も高値であった。投与部位以外では肝臓が最も高かった（投与量の最大 18%）。

ALC-0315 および ALC-0159 の代謝を CD-1/ICR マウス，Wistar Han または Sprague Dawley ラット，カニクイザルもしくはヒトの血液，肝ミクロソーム，肝 S9 画分および肝細胞を用いて in vitro で評価した。また，上記のラット静脈内投与 PK 試験で採取した血漿，尿，糞および肝臓試料を用いて in vivo 代謝についても検討した。これら in vitro および in vivo 試験から，ALC-0315 および ALC-0159 は，試験したいずれの動物種でも，それぞれエステル結合およびアミド結合の加水分解により緩徐に代謝されることが示された。

以上の非臨床薬物動態評価より，循環血中に到達した LNP は肝臓に分布することが示された。また，ALC-0315 および ALC-0159 の消失には，それぞれ代謝および糞中排泄が関与することが示唆された。

2. 分析法

報告書番号：PF-07302048_06[redacted]_072424

GLP 非適用のラット静脈内投与 PK 試験（M2.6.4.3 項）で LNP の構成脂質である ALC-0315 および ALC-0159 濃度を定量するために適切な性能を有する LC/MS 法を開発した。すなわち，20 µL の血漿，肝ホモジネート（肝臓の 3 箇所から採取した切片を用いてホモジネートを調製し，それらをプールしたものを適宜，ブランクマトリクスで希釈），尿および糞ホモジネート（適宜，ブランクマトリクスで希釈）試料をそれぞれ内部標準物質（PEG-2000）を含有するアセトニトリルで除タンパクした後，遠心分離し，その上清を LC-MS/MS 測定に供した。

3. 吸収

報告書番号：PF-07302048_06[redacted]_072424，概要表：2.6.5.3

ALC-0315 および ALC-0159 の体内動態を検討するため，ルシフェラーゼ RNA 封入 LNP を雄性 Wistar Han ラットに 1 mg RNA/kg の用量で単回静脈内投与し，経時的（投与前，投与後 0.1，0.25，0.5，1，3，6 および 24 時間ならびに投与後 2，4，8 および 14 日）に血漿および肝臓をスパースサンプリングにより採取（3 匹/時点）した。血漿中および肝臓中の ALC-0315 および ALC-0159 濃度を測定し，PK パラメータを算出した（Table 1）。血中の ALC-0315 および ALC-0159 は，投与後 24 時間までにすみやかに肝臓へ分布した。また，投与後 24 時間の血漿中濃度は最高血漿中濃度の 1%未満であった（Figure 1）。見かけの終末相消失半減期（t½）は血漿中および肝臓中で同程度で，ALC-0315 は 6～8 日，ALC-0159 は 2～3 日であった。本試験の結果から，肝臓が血中からの ALC-0315 および ALC-0159 を取り込む主要組織の 1 つであることが示唆された。

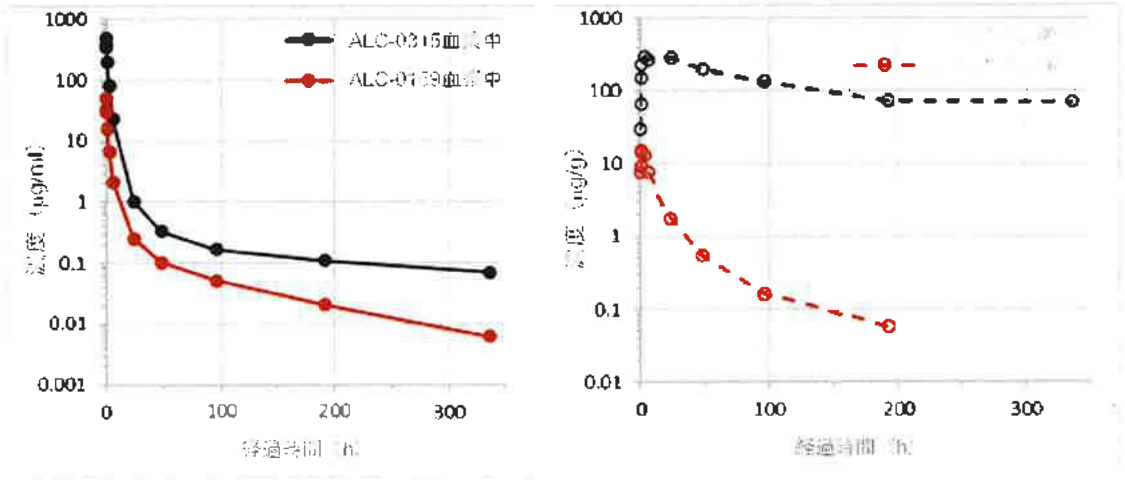
本試験において実施した ALC-0315 および ALC-0159 の尿中および糞中濃度の検討結果については M2.6.4.6 項で述べる。

Table 1 ルシフェラーゼ RNA 封入 LNP を Wistar Han ラットに 1 mg RNA/kg の用量で静脈内投与したときの ALC-0315 および ALC-0159 の薬物動態

分析物	分析物の投与量 (mg/kg)	性/N	t½ (h)	AUC_{inf} (µg•h/mL)	AUC_{last} (µg•h/mL)	肝臓への分布割合 (%)[a]
ALC-0315	15.3	雄/3[b]	139	1030	1020	60
ALC-0159	1.96	雄/3[b]	72.7	99.2	98.6	20

a. ［最高肝臓分布量 (µg)］/［投与量 (µg)］として算出。
b. 各時点 3 匹。スパースサンプリング。

Figure 1 ルシフェラーゼ RNA 封入 LNP を Wistar Han ラットに 1 mg RNA/kg の用量で静脈内投与したときの ALC-0315 および ALC-0159 の血漿および肝臓中濃度

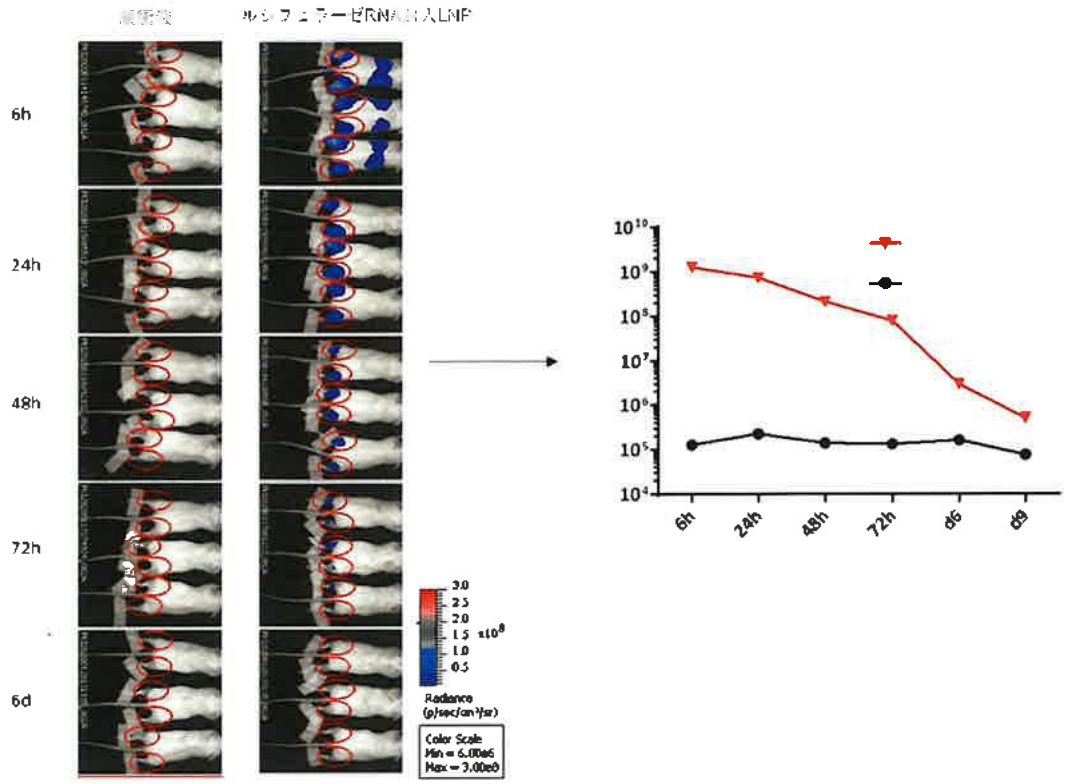


4. 分布

報告書番号：R-[redacted]-0072，185350，概要表：2.6.5.5A，2.6.5.5B

雌性 BALB/c マウス（3 匹）にルシフェラーゼ RNA 封入 LNP を投与し，ルシフェラーゼ発光を代替マーカーとして BNT162b2 の生体内分布を検討した。すなわち，ルシフェラーゼ RNA 封入 LNP をマウスの左右の後肢に各 1 µg RNA（計 2 µg RNA）の用量で筋肉内投与した。その後，ルシフェラーゼ発光検出の 5 分前に発光基質であるルシフェリンを腹腔内投与し，イソフルラン麻酔下，in vivo における発光を Xenogen IVIS Spectrum を用いて投与後 6 および 24 時間ならびに 2，3，6 および 9 日に測定することにより，ルシフェラーゼタンパクの同一個体での経時的な発現推移を評価した。その結果，ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現も投与後 6 時間からみられ，投与後 48 時間までに消失した。肝臓への分布は局所投与したルシフェラーゼ RNA 封入 LNP の一部が循環血中に到達し，肝臓で取り込まれたことを示すものと考えられた。M2.6.4.3 項で詳述したように，ラットにルシフェラーゼ RNA 封入 LNP を静脈内投与した場合には，肝臓が ALC-0315 および ALC-0159 の主要な分布臓器であることが示唆されており，このことはマウスに筋肉内投与した本試験結果の所見と符合するものであった。なお，ラット反復投与毒性試験で肝障害を示す毒性所見は認められていない（M2.6.6.3 項）。

Figure 2 ルシフェラーゼ RNA 封入 LNP を筋肉内投与した BALB/c マウスにおける生体内発光



雌雄 Wistar Han ラットに，[^{3}H]-コレステリルヘキサデシルエーテル（[^{3}H]- CHE）で標識した LNP を用いたルシフェラーゼ RNA 封入 LNP を 50 µg RNA の用量で筋肉内投与し，投与後 15 分ならびに 1，2，4，8，24 および 48 時間の各時点において雌雄各 3 匹から血液，血漿および組織を採取し，液体シンチレーション計数法により放射能濃度を測定することで LNP の生体内分布を評価した。雌雄ともに，放射能濃度はいずれの測定時点においても投与部位が最も高値であった。血漿中の放射能濃度は投与後 1～4 時間で最も高値を示した。また，主に肝臓，脾臓，副腎および卵巣への分布がみられ，これらの組織において放射能濃度が最も高くなったのは投与後 8～48 時間であった。投与部位以外での投与量に対する総放射能回収率は肝臓で最も高く（最大 18%），脾臓（1.0%以下），副腎（0.11%以下）および卵巣（0.095%以下）では肝臓と比較して著しく低かった。また，放射能の平均濃度および組織分布パターンは雌雄でおおむね類似していた。

BNT162b2 がコードする抗原の生体内発現分布は LNP 分布に依存すると考えられる。本試験で用いたルシフェラーゼ RNA 封入 LNP の脂質の構成は，BNT162b2 の申請製剤と同一であることから，本試験結果は BNT162b2 封入 LNP の分布を示すと考えられる。

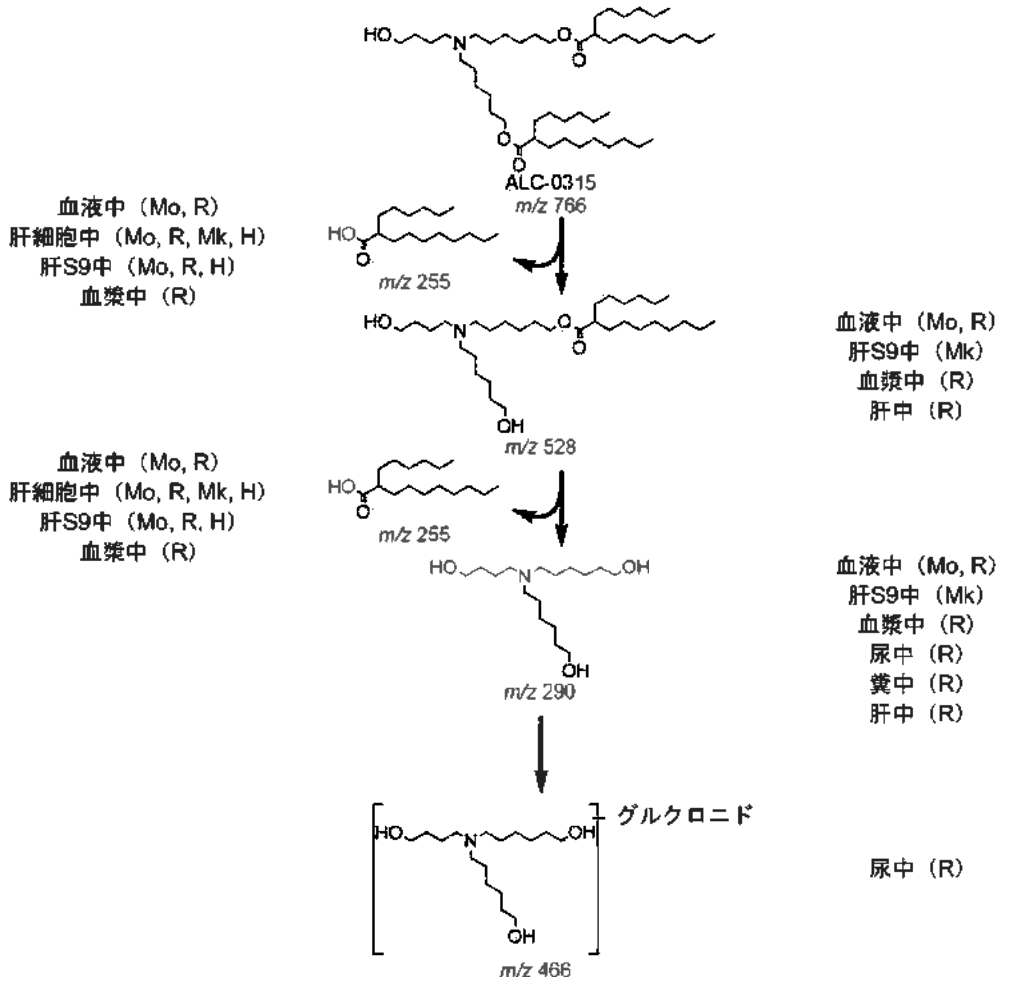
5. 代謝

報告書番号：01049-[redacted]008，01049-[redacted]009，01049-[redacted]010，01049-[redacted]020，01049-[redacted]021，01049-[redacted]022，PF-07302048_05[redacted]_043725，概要表：2.6.5.10A，2.6.5.10B，2.6.5.10C，2.6.5.10D

CD-1/ICR マウス，Wistar Han または Sprague Dawley ラット，カニクイザルならびにヒトの肝ミクロソーム，肝 S9 画分および肝細胞を用いて，ALC-0315 および ALC-0159 の in vitro 代謝安定性を評価した。ALC-0315 または ALC-0159 を各動物種の肝ミクロソームまたは肝 S9 画分（120 分間インキュベーション）もしくは肝細胞（240 分間インキュベーション）に添加して，インキュベーション後の未変化体の割合を測定した。その結果，ALC-0315 および ALC-0159 はいずれの動物種・試験系でも代謝的に安定であり，未変化体の最終的な割合は 82%超であった。

さらに ALC-0315 および ALC-0159 の代謝経路について in vitro および in vivo で評価した。これらの試験では，CD-1 マウス，Wistar Han ラット，カニクイザルおよびヒトの血液，肝 S9 画分および肝細胞を用いて in vitro での代謝を評価した。また，ラット PK 試験で採取した血漿，尿，糞および肝臓試料を用い，in vivo での代謝を評価した（M2.6.4.3 項）。試験結果から，ALC-0315 と ALC-0159 の代謝はいずれも緩徐であり，それぞれエステル結合およびアミド結合の加水分解により代謝されることが明らかになった。Figure 3 および Figure 4 に示した加水分解による代謝は，評価したすべての動物種でみられた。

Figure 3 種々の動物種での ALC-0315 の推定生体内代謝経路



H：ヒト，Mk: サル，Mo：マウス，R：ラット

ALC-0315 はエステル加水分解を 2 回連続で受けることにより代謝される。この 2 回の加水分解により，最初，モノエステル代謝物（*m/z* 528），次に二重脱エステル化代謝物（*m/z* 290）が生成される。この二重脱エステル化代謝物はさらに代謝され，グルクロン酸抱合体（*m/z* 466）となるが，このグルクロン酸抱合体はラット PK 試験で尿中にのみ検出された。また，2 回の加水分解の酸性生成物がいずれも 6-ヘキシルデカン酸（*m/z* 255）であることも確認された。

Figure 4 種々の動物種での ALC-0159 の推定生体内代謝経路

H：ヒト，Mk: サル，Mo：マウス，R：ラット

ALC-0159 は，アミド結合の加水分解により *N,N*-ジテトラデシルアミン（*m/z* 410）が生成される経路が主要な代謝経路であった。この代謝物は，マウス・ラットの血液ならびにマウス・ラット・サル・ヒトの肝細胞および肝 S9 画分中に検出された。In vivo 試料からは ALC-0159 の代謝物は確認されなかった。

3

Figure 3

7. 薬物動態学的薬物相互作用

本ワクチンの薬物動態学的薬物相互作用試験は実施していない。

8. その他の薬物動態試験

本ワクチンのその他の薬物動態試験は実施していない。

9. 考察および結論

ラット PK 試験において，血漿および肝臓中 ALC-0315 濃度は，投与後 2 週間までに最高濃度のそれぞれ約 7000 分の 1 および約 4 分の 1 に減少し，ALC-0159 濃度はそれぞれ約 8000 分の 1 および約 250 分の 1 に減少した。t½は血漿中および肝臓中で同程度で，ALC-0315 は 6～8 日，ALC-0159 は 2～3 日であった。血漿中 t½値は，それぞれの脂質が LNP として組織中に分布し，その後，消失過程で血漿中に再分布したことを表すと考えられる。

ALC-0315 の未変化体は尿中と糞中のいずれにもほとんど検出されなかったが，ラット PK 試験で採取した糞および血漿試料からモノエステル代謝物，二重脱エステル化代謝物および 6-ヘキシルデカン酸が，尿からは二重脱エステル化代謝物のグルクロン酸抱合体が検出された。この代謝過程が ALC-0315 の主要消失機序と考えられるが，この仮説を検証する定量データは得られていない。一方，ALC-0159 は投与量の約 50%が未変化体として糞中に排泄された。In vitro 代謝実験において，アミド結合の加水分解により緩徐に代謝された。

BNT162b2 がコードする抗原の生体内発現分布は LNP 分布に依存すると考えられることから，BALB/c マウスにルシフェラーゼ RNA 封入 LNP を筋肉内投与し，代替レポータータンパク質の生体内分布を検討した。その結果，ルシフェラーゼの発現が投与部位においてみられ，それより発現量は低値であったものの肝臓でも認められた。ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現は投与後 6 時間から認められ，投与後 48 時間までに消失した。肝臓への分布は局所投与したルシフェラーゼ RNA 封入 LNP が循環血中に到達し，肝臓で取り込まれたことを示すものと考えられた。また，ラットにルシフェラーゼ RNA 封入 LNP の放射能標識体を筋肉内投与したところ，放射能濃度は投与部位で最も高値を示した。投与部位以外では，肝臓で最も高く，次いで脾臓，副腎および卵巣でも検出されたが，これらの組織における投与量に対する総放射能回収率は肝臓より著しく低かった。この結果は，マウス生体内分布試験において肝臓でルシフェラーゼ発現がみられたことと符合した。なお，ラット反復投与毒性試験で肝障害を示す毒性所見は認められなかった（M2.6.6.3 項）。

以上の非臨床薬物動態評価より，循環血中に到達した LNP は肝臓に分布することが示された。また，ALC-0315 および ALC-0159 の消失には，それぞれ代謝および糞中排泄が関与することが示唆された。

10. 図表

図表は本文中および概要表に示した。

参考文献

1 World Health Organization. Annex 1. Guidelines on the nonclinical evaluation of vaccines. In: WHO Technical Report Series No. 927, Geneva, Switzerland. World Health Organization; 2005:31-63.

2 感染症予防ワクチンの非臨床試験ガイドラインについて（薬食審査発 0527 第 1 号，平成 22 年 5 月 27 日）

2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test item	Method of Administration	Testing Facility	Report Number
Single Dose Pharmacokinetics					
Single Dose Pharmacokinetics and Excretion in Urine and Feces of ALC-0159 and ALC-0315	Rat (Wistar Han)	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	IV bolus	Pfizer Inc[a]	PF-07302048_06[redacted]_072424
Distribution					
In Vivo Distribution	Mice BALB/c	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	IM Injection	[redacted][b]	R-[redacted]-0072
In Vivo Distribution	Rat (Wistar Han)	modRNA encoding luciferase formulated in LNP comparable to BNT162b2 with trace amounts of [^{3}H]-CHE as non-diffusible label	IM Injection	[redacted][c]	185350
Metabolism					
In Vitro and In Vivo Metabolism					
In Vitro Metabolic Stability of ALC-0315 in Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	ALC-0315	In vitro	[redacted][d]	01049-[redacted]008
In Vitro Metabolic Stability of ALC-0315 in Liver S9	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 liver fractions	ALC-0315	In vitro	[redacted][d]	01049-[redacted]009

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test item	Method of Administration	Testing Facility	Report Number
In Vitro Metabolic Stability of ALC-0315 in Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	ALC-0315	In vitro	[redacted][d]	01049-[redacted]010
In Vitro Metabolic Stability of ALC-0159 in Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	ALC-0159	In vitro	[redacted][d]	01049-[redacted]020
In Vitro Metabolic Stability of ALC-0159 in Liver S9	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 fractions	ALC-0159	In vitro	[redacted][d]	01049-[redacted]021
In Vitro Metabolic Stability of ALC-0159 in Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	ALC-0159	In vitro	[redacted][d]	01049-[redacted]022
Biotransformation of ALC-0159 and ALC-0315 In Vitro and In Vivo in Rats	In vitro: CD-1 mouse, Wistar Han rat, cynomolgus monkey, and human blood, liver S9 fractions and hepatocytes In vivo: male Wistar Han rats	ALC-0315 and ALC-0159	In vitro or IV (in vivo in rats)	Pfizer Inc[e]	PF-07302048_0[redacted]_043725

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test item	Method of Administration	Testing Facility	Report Number

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; IM = Intramuscular; IV = Intravenous; LNP = lipid nanoparticles; S9 = Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g.

a. La Jolla, California.
b. [redacted], Germany.
c. [redacted], UK.
d. [redacted], China.
e. Groton, Connecticut.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

2.6.5.3. PHARMACOKINETICS: PHARMACOKINETICS AFTER A SINGLE DOSE

Test Article: modRNA encoding luciferase in LNP
Report Number: PF-07302048_06[redacted]_072424

Species (Strain)	Rat (Wistar Han)	
Sex/Number of Animals	Male/ 3 animals per timepoint[a]	
Feeding Condition	Fasted	
Method of Administration	IV	
Dose modRNA (mg/kg)	1	
Dose ALC-0159 (mg/kg)	1.96	
Dose ALC-0315 (mg/kg)	15.3	
Sample Matrix	Plasma, liver, urine and feces	
Sampling Time Points (h post dose):	Predose, 0.1, 0.25, 0.5, 1, 3, 6, 24, 48, 96, 192, 336	
Analyte	ALC-0315	ALC-0159
PK Parameters:	Mean[b]	Mean[b]
AUC_{inf} (µg•h/mL)[c]	1030	99.2
AUC_{last} (µg•h/mL)	1020	98.6
Initial $t_{½}$ (h)[d]	1.62	1.74
Terminal elimination $t_{½}$ (h)[e]	139	72.7
Estimated fraction of dose distributed to liver (%)[f]	59.5	20.3
Dose in Urine (%)	NC[g]	NC[g]
Dose in Feces (%)[h]	1.05	47.2

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; AUC_{inf} = Area under the plasma drug concentration-time curve from 0 to infinite time; AUC_{last} = Area under the plasma drug concentration-time curve from 0 to the last quantifiable time point; BLQ = Below the limit of quantitation; LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA; PK = Pharmacokinetics; $t_{½}$ = Half-life.

a. Non-serial sampling, 36 animals total.
b. Only mean PK parameters are reported due to non-serial sampling.
c. Calculated using the terminal log-linear phase (determined using 48, 96, 192, and 336 h for regression calculation).
d. ln(2)/initial elimination rate constant (determined using 1, 3, and 6 h for regression calculation).
e. ln(2)/terminal elimination rate constant (determined using 48, 96, 192, and 336 h for regression calculation).
f. Calculated as follows: highest mean amount in the liver (µg)/total mean dose (µg) of ALC-0315 or ALC-0159.
g. Not calculated due to BLQ data.
h. Fecal excretion, calculated as: (mean µg of analyte in feces/ mean µg of analyte administered) × 100

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

2.6.5.5A. PHARMACOKINETICS: ORGAN DISTRIBUTION

Test Article: modRNA encoding luciferase in LNP
Report Number: R-[redacted]-0072

Species (Strain):	Mice (BALB/c)
Sex/Number of Animals:	Female/3 per group
Feeding Condition:	Fed ad libitum
Vehicle/Formulation:	Phosphate-buffered saline
Method of Administration:	Intramuscular injection
Dose (mg/kg):	1 µg/hind leg in gastrocnemius muscle (2 µg total)
Number of Doses:	1
Detection:	Bioluminescence measurement
Sampling Time (hour):	6, 24, 48, 72 hours; 6 and 9 days post-injection

Time point	Total Mean Bioluminescence signal (photons/second)		Mean Bioluminescence signal in the liver (photons/second)
	Buffer control	modRNALuciferase in LNP	modRNALuciferase in LNP
6 hours	1.28×10^{5}	1.26×10^{9}	4.94×10^{7}
24 hours	2.28×10^{5}	7.31×10^{8}	2.4×10^{6}
48 hours	1.40×10^{5}	2.10×10^{8}	Below detection[a]
72 hours	1.33×10^{5}	7.87×10^{7}	Below detection[a]
6 days	1.62×10^{5}	2.92×10^{6}	Below detection[a]
9 days	7.66×10^{4}	5.09×10^{5}	Below detection[a]

LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA.
a. At or below the background level of the buffer control.

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Species (Strain):	Rat (Wistar Han)
Sex/Number of Animals:	Male and female/3 animals/sex/timepoint (21 animals/sex total for the 50 µg dose)
Feeding Condition:	Fed ad libitum
Method of Administration:	Intramuscular injection
Dose:	50 µg [^{3}H]-08-A01-C0 (lot # NC-0552-1)
Number of Doses:	1
Detection:	Radioactivity quantitation using liquid scintillation counting
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, and 48 hours post-injection

Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL) (males and females combined)							% of administered dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	--	--	--	--	--	--	--
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2	0.001	0.007	0.010	0.015	0.035	0.066	0.106
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	--	--	--	--	--	--	--
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77	--	--	--	--	--	--	--
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030
Injection site	128	394	311	338	213	195	165	19.9	52.6	31.6	28.4	21.9	29.1	24.6
Kidneys	0.391	1.16	2.05	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34	0.008	0.025	0.065	0.192	0.405	0.692	0.762
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3	0.602	2.87	7.33	11.9	18.1	15.4	16.2
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09	0.052	0.101	0.178	0.169	0.122	0.101	0.101

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Sample	Total Lipid concentration (µg lipid equivalent/g [or mL]) (males and females combined)							% of Administered Dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	--	--	--	--	--	--	--
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37	--	--	--	--	--	--	--
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	--	--	--	--	--	--	--
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	--	--	--	--	--	--	--
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4	0.013	0.093	0.325	0.385	0.982	0.821	1.03
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420	--	--	--	--	--	--	--
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805	--	--	--	--	--	--	--
Blood:Plasma ratio[a]	0.815	0.515	0.550	0.510	0.555	0.530	0.540	--	--	--	--	--	--	--

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

-- = Not applicable, partial tissue taken; [^{3}H]-08-A01-C0 = An aqueous dispersion of LNPs, including ALC-0315, ALC-0159, distearoylphosphatidylcholine, cholesterol, mRNA encoding luciferase and trace amounts of radiolabeled [Cholesteryl-1,2-3H(N)]-Cholesteryl Hexadecyl Ether, a nonexchangeable, non-metabolizable lipid marker used to monitor the disposition of the LNPs; ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N--ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4--hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; LNP = Lipid nanoparticle; mRNA = messenger RNA.
a. The mean male and female blood:plasma values were first calculated separately and this value represents the mean of the two values.

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2.6.5.9. PHARMACOKINETICS: METABOLISM IN VIVO, RAT

Test Article: modRNA encoding luciferase in LNP
Report Number: PF-07302048_05[redacted]_043725

Species (Strain):	Rat (Wistar Han)
Sex/ Number of animals	Male/ 36 animals total for plasma and liver, 3 animals for urine and feces
Method of Administration:	Intravenous
Dose (mg/kg):	1
Test System:	Plasma, Urine, Feces, Liver
Analysis Method:	Ultrahigh performance liquid chromatography/ mass spectrometry

Biotransformation	m/z	Metabolites of ALC-0315 Detected			
		Plasma	Urine	Feces	Liver
N-dealkylation, oxidation	102.0561[a]	ND	ND	ND	ND
N-Dealkylation, oxidation	104.0706[b]	ND	ND	ND	ND
N-dealkylation, oxidation	130.0874[a]	ND	ND	ND	ND
N-Dealkylation, oxidation	132.1019[b]	ND	ND	ND	ND
N-dealkylation, hydrolysis, oxidation	145.0506[a]	ND	ND	ND	ND
Hydrolysis (acid)	255.2330[a]	+	ND	ND	ND
Hydrolysis, hydroxylation	271.2279[a]	ND	ND	ND	ND
Bis-hydrolysis (amine)	290.2690[b]	+	+	+	+
Hydrolysis, glucuronidation	431.2650[a]	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	464.2865[a]	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	466.3011[b]	ND	+	ND	ND
Hydrolysis (amine)	528.4986[b]	+	ND	ND	+
Hydrolysis (amine), Glucuronidation	704.5307[b]	ND	ND	ND	ND
Oxidation to acid	778.6930[a]	ND	ND	ND	ND
Oxidation to acid	780.7076[b]	ND	ND	ND	ND
Hydroxylation	782.7232[b]	ND	ND	ND	ND
Sulfation	844.6706[a]	ND	ND	ND	ND
Sulfation	846.6851[b]	ND	ND	ND	ND
Glucuronidation	940.7458[a]	ND	ND	ND	ND
Glucuronidation	942.7604[b]	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = minor metabolite as assessed by ultraviolet detection.
a. Negative ion mode.
b. Positive ion mode.

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2.6.5.10A. PHARMACOKINETICS: METABOLISM IN VITRO

Test Article: ALC-0315
Report Numbers: 01049-[redacted]008
01049-[redacted]009
01049-[redacted]010

Type of Study:	Stability of ALC-0315 In Vitro		
Study System:	Liver Microsomes + NADPH	S9 Fraction + NADPH, UDPGA, and alamethicin	Hepatocytes
ALC-0315 Concentration:	1 µM	1 µM	1 µM
Duration of Incubation (min):	120 min	120 min	240 min
Analysis Method:	Ultra-high performance liquid chromatography-tandem mass spectrometry		

Incubation time (min)	Percent ALC-0315 remaining													
	Liver Microsomes					Liver S9 Fraction				Hepatocytes				
	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
15	98.77	94.39	96.34	97.96	100.24	97.69	98.85	99.57	95.99	--	--	--	--	--
30	97.78	96.26	97.32	96.18	99.76	97.22	99.62	96.96	97.32	101.15	97.75	102.70	96.36	100.72
60	100.49	99.73	98.54	100.00	101.45	98.61	99.62	99.13	94.98	100.77	98.50	102.32	97.82	101.44
90	97.78	98.66	94.15	97.96	100.48	98.15	98.85	98.70	98.33	101.92	99.25	103.09	100.0	100.36
120	96.54	95.99	93.66	97.71	98.31	96.76	98.46	99.57	99.33	98.85	97.38	99.61	96.36	100.72
180	--	--	--	--	--	--	--	--	--	101.15	98.88	103.47	95.64	98.92
240	--	--	--	--	--	--	--	--	--	99.62	101.12	100.00	93.82	99.64
$t_{1/2}$ (min)	>120	>120	>120	>120	>120	>120	>120	>120	>120	>240	>240	>240	>240	>240

-- = Data not available; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the lipid nanoparticle formulation used in BNT162b2; Cyno = Cynomolgus; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; NC = not calculated; SD = Sprague Dawley; $t_{1/2}$ = half-life; WH = Wistar-Han; UDPGA= uridine-diphosphate-glucuronic acid trisodium salt.

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2.6.5.10B. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0159
Report Numbers: 01049-[redacted]020
01049-[redacted]021
01049-[redacted]022

Type of Study:	Stability of ALC-0159 In Vitro		
Study System:	Liver Microsomes + NADPH	S9 Fraction + NADPH, UDPGA, and alamethicin	Hepatocytes
ALC-0159 Concentration:	1 µM	1 µM	1 µM
Duration of Incubation (min):	120 min	120 min	240 min
Analysis Method:	Ultra-high performance liquid chromatography-tandem mass spectrometry		

Incubation time (min)	Percent ALC-0159 remaining													
	Liver Microsomes					Liver S9 Fraction				Hepatocytes				
	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
15	82.27	101.24	112.11	100.83	99.59	98.93	84.38	91.30	106.73	--	--	--	--	--
30	86.40	93.78	102.69	85.12	92.28	91.10	90.87	97.96	107.60	100.85	93.37	113.04	90.23	106.34
60	85.54	98.34	105.38	86.36	95.53	102.85	97.97	105.56	104.97	94.92	91.81	105.07	92.93	101.58
90	85.41	95.44	100.90	94.63	97.97	90.75	93.51	108.33	109.36	94.28	90.25	112.80	94.59	92.67
120	95.87	97.10	108.97	93.39	93.09	106.76	92.70	105.74	119.59	87.08	89.47	104.11	97.51	96.04
180	--	--	--	--	--	--	--	--	--	94.92	93.96	102.90	89.81	93.66
240	--	--	--	--	--	--	--	--	--	102.75	94.93	98.79	92.93	102.57
t½ (min)	>120	>120	>120	>120	>120	>120	>120	>120	>120	>240	>240	>240	>240	>240

-- = Data not available; ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the lipid nanoparticle formulation used in BNT162b2; Cyno = Cynomolgus; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; NC = not calculated; SD = Sprague Dawley; WH = Wistar-Han; UDPGA= uridine-diphosphate-glucuronic acid trisodium salt.

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2.6.5.10C. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0315
Report Number: PF-07302048_05[redacted]_043725

Type of study	Metabolism of ALC-0315 In Vitro		
Study system	Blood	Hepatocytes	Liver S9 Fraction
ALC-0315 concentration	10 µM	10 µM	10 µM
Duration of incubation	24 h	4 h	24 h
Analysis Method:	Ultrahigh performance liquid chromatography/ mass spectrometry		

Biotransformation	m/z	Blood				Hepatocytes				Liver S9 Fraction			
		Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human
N-dealkylation, oxidation	102.0561[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	104.0706[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-dealkylation, oxidation	130.0874[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	132.1019[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-dealkylation, hydrolysis, oxidation	145.0506[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (acid)	255.2330[a]	+	+	ND	ND	+	+	+	+	+	+	ND	+
Hydrolysis, hydroxylation	271.2279[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine)	290.2690[b]	+	+	ND	ND	ND	ND	ND	ND	ND	ND	+	ND
Hydrolysis, glucuronidation	431.2650[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	464.2865[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	466.3011[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (amine)	528.4986[b]	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	+	ND
Hydrolysis (amine), glucuronidation	704.5307[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Oxidation to acid	778.6930[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Oxidation to acid	780.7076[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydroxylation	782.7232[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sulfation	844.6706[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sulfation	846.6851[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Glucuronidation	940.7458[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Glucuronidation	942.7604[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = metabolite present.
a. Negative ion mode.
b. Positive ion mode.

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2.6.5.10D. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0159
Report Number: PF-07302048_05[redacted]_043725

Type of study		Metabolism of ALC-0159 In Vitro											
Study system		Blood				Hepatocytes				Liver S9 Fraction			
ALC-0159 concentration		10 µM				10 µM				10 µM			
Duration of incubation		24 h				4 h				24 h			
Analysis Method:		Ultrahigh performance liquid chromatography/ mass spectrometry											
Biotransformation	**m/z**	**Blood**				**Hepatocytes**				**Liver S9 Fraction**			
		Mouse	**Rat**	**Monkey**	**Human**	**Mouse**	**Rat**	**Monkey**	**Human**	**Mouse**	**Rat**	**Monkey**	**Human**
O-Demethylation, *O*-dealkylation	107.0703[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, *O*-dealkylation	151.0965[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, *O*-dealkylation	195.1227[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis, *N*-Dealkylation	214.2529[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	227.2017[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (amine)	410.4720[b]	+	+	ND	ND	+	+	+	+	+	+	+	+
N,*N*-Didealkylation	531.5849[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation	580.6396[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, oxidation	629.6853[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydroxylation	633.6931[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ω-Hydroxylation, Oxidation	637.1880[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (acid)	708.7721[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = metabolite present.
a. Negative ion mode.
b. Positive ion mode.

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Appendix 3

Pfizer's Report to the European Medicines Agency

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2021
EMA/707383/2020 Corr.1*[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Comirnaty

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] * *Correction dated 19 February 2021 to clarify ERA statement*

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Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
BDR	blinded data review
BLQ	below the level of quantitation
BMI	body mass index
CD	Circular dichroism
CDC	Centers for Disease Control and Prevention (United States)
CGE	Capillary gel electrophoresis
COVID-19	coronavirus disease 2019
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRF	case report form
CRM	Clinical Reference Material
CRO	contract research organization
CSR	clinical study report
CV	curriculum vitae
C&E	Cause and Effect Matrices
DCT	data collection tool
DLS	Dynamic Light Scattering
DMC	data monitoring committee
DOE	Design of experiments
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
e-diary	electronic diary
EU	European Union
FIH	first-in-human
FSFV	first subject first visit
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCS	human convalescent serum
HCV	hepatitis C virus
HCV	Ab hepatitis C virus antibody
HIV	human immunodeficiency virus
HPLC-CAD	High-Performance Liquid Chromatography - Charged Aerosol Detector
IA	interim analysis
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
IPT-C	In-process testing control
IPT-M	In-process testing monitoring
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IVT	in vitro transcription
IWR	interactive web response
LAL	Limulus Amebocyte Lysate
LC-UV/MS	Liquid Chromatography – Ultraviolet / Mass Spectometry
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mRNA	Messenger ribonucleic acid
modRNA	nucleoside-modified messenger ribonucleic acid

NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NMT	Not more than
NOR	Normal Operating Range
NT50	neutralizing titer 50
NT90	neutralizing titer 90
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PAR	Proven Acceptable Range
(q)PCR	(quantitative) Polymerase Chain Reaction
PD	protocol deviation
Ph.Eur.	European Pharmacopoeia
PPQ	Process Performance Qualification
PRM	Primary Reference Material
Prevax	prevaccination
PT	preferred term
QA	quality assurance
QA	Quality Attribute
QTL	quality tolerance limit
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RDC	remote data capture
RNA	ribonucleic acid
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
RT-PCR	Real Time Polymerase Chain Reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRVA	shoulder injury related to vaccine administration
SMQ	standardized MedDRA queries
SOC	system organ class
Tdap	diphtheria vaccine toxoid; pertussis vaccine acellular 3 component; tetanus vaccine toxoid

TME	targeted medical event
TSE	Transmissible Spongiform Encephalopathy
UFDF	Ultrafiltration/diafiltration
US	United States
Vax	vaccination
VE	vaccine efficacy
WBC	white blood cell count
WCB	Working Cell Bank
WHO	World Health Organization
WRM	Working Reference Material
YOA	years of age

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioNTech Manufacturing GmbH submitted on 30 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Comirnaty, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 July 2020.

The applicant applied for the following indication:

"Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older. The use of Comirnaty vaccine should be in accordance with official guidance."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0480/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0480/2020 was not yet completed as some measures were deferred.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, as it is intended for the prophylaxis of a life-threatening disease. In addition, the above-mentioned medicinal product is intended for use in an emergency situation, in response to public health threats duly recognised by the World Health Organisation and by the Union.

New active Substance status

The applicant requested the active substance Single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike

(S) protein of SARS-CoV-2 contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2. Steps taken for the assessment of the product[2]

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

The CHMP confirmed eligibility to the centralised procedure on	23 July 2020
Confirmation by ETF on the eligibly to the rolling review procedure on	24 July 2020
Agreement by ETF to start the rolling review procedure on	25 September 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	05 October 2020
The procedure (Rolling Review 1) started on	06 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	22 October 2020
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	28 October 2020
ETF discussions took place on	29 October 2020
Adoption of first Interim Opinion on the RR via 24 hour written procedure on	06 November 2020
The applicant submitted documentation as part of a rolling review on quality data to support the marketing authorisation application	06 November 2020

[2] These steps do not reflect the additional submissions made by the applicant during the active assessment phases.

The procedure (Rolling Review 2) started on	07 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, Peer Reviewer and ETF on	19 November 2020
BWP extraordinary adobe meeting was held on	24 November 2020
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF on	25 November 2020
ETF discussions took place on	26 November 2020
Adoption of the 2nd interim opinion for this rolling review on	30 November 2020
The application for the marketing authorisation was formally received by the EMA on	30 November 2020
The procedure started on	1 December 2020
BWP extraordinary adobe meeting was held on	15 December 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, peer reviewer and ETF on	16 December 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	16 December 2020
BWP extraordinary adobe meeting with an Oral Explanation by the applicant was held on	16 December 2020
ETF discussions took place on	17 December 2020
The Rapporteurs circulated the Joint Assessment Report to all CHMP members on	17 December 2020
BWP extraordinary adobe meeting was held on	18 December 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary meeting on	18 December 2020
CHMP extraordinary adobe meeting was held on	18 December 2020
The following GMP and GLP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– GMP inspections (distant assessments) of the sites Wyeth BioPharma, Andover (manufacturer DS, QC DS, QC DP) and Pfizer Inc., Chesterfield (QC DP, QC DP), both located in the USA, were carried out between 20 November 2020 and 02 December 2020. The outcome of the inspections carried out were issued on 15 December 2020.	15 December 2020
– A GLP inspection at a CRO in Germany between 3 to 6 November 2020. The outcome of the inspection carried out was issued on 6 November 2020.	6 November 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Comirnaty on	21 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human to human transmission. In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel Coronavirus (2019-nCoV) was the underlying cause. In early January 2020, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public, and the virus was categorized in the Betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 infections and the resulting disease COVID-19 have spread globally, affecting a growing number of countries. On 11 March 2020 the WHO characterized the COVID-19 outbreak as a pandemic. As of 01 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

2.1.2. Epidemiology and risk factors

Every individual is at risk of infection as there is no pre-existing immunity to the SARS-CoV-2. Following infection some but not all individuals develop protective immunity in terms of neutralising antibody responses and cell mediated immunity. However, it is currently unknown to what extent and for how long this protection lasts.

According to WHO 80% of infected individuals recover without need for hospital care, while 15% develop more severe disease and 5% need intensive care.

Increasing age and underlying medical conditions are considered risk factors for developing severe disease.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development. It has been shown that antibodies against the Spike protein neutralise the virus and prevent infection.

2.1.4. Clinical presentation and diagnosis

The presentation of COVID-19 is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic subjects, progression of disease may lead to acute respiratory distress syndrome requiring ventilation and subsequent multi-organ failure and death.

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

The US Centres for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrheal
- Vomiting
- Fatigue
- Headache
- Nasal congestion or runny nose
- Nausea

All ages may present with the disease, but notably case fatality rates (CFR) are elevated in persons >60 years of age. For example, in Italy the CFR was 0.3% in adults <40 years of age but 12.8% in adults 70 to 79 years of age and 20.2% in patients ≥80 years of age. Comorbidities are also associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease. Healthcare workers are overrepresented among COVID-19 patients due to occupational exposure to infected patients.

In most situations, a molecular test is used to detect SARS-CoV-2 and confirm infection. The reverse transcription polymerase chain reaction (RT-PCR) test methods targeting SARS-CoV-2 viral RNA are the gold standard in vitro methods for diagnosing suspected cases of COVID-19. Samples to be tested are collected from the nose and/or throat with a swab. Molecular methods used to confirm an active infection are usually performed within a few days of exposure and around the time that symptoms may begin.

2.1.5. Management

The management of COVID-19 has developed during 2020, and now includes antiviral therapy (e.g. remdesivir), antibodies administered from convalescent plasma and hyperimmune immunoglobulins, anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants. These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals who have COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for a prophylactic vaccine during the ongoing pandemic, both for protection of particularly vulnerable groups as well as mitigating the effects of the pandemic at a population level, e.g. to maintain a functioning health care system, and to avoid the social and economic consequences of the stringent measures needed to diminish virus spread. There is currently no approved vaccine in EU for prevention of COVID-19.

About the product

BNT162b is a mRNA vaccine for prevention of COVID-19. The vaccine is made of a mRNA encoding for the full-length SARS-CoV-2 spike glycoprotein (S) encapsulated in lipid nanoparticles (LNPs). The sequence of the S protein was chosen based on the sequence for the "SARS-CoV-2 isolate Wuhan-Hu-1", which was available when the program was initiated: GenBank: MN908947.3 (complete genome) and GenBank: QHD43416.1 (spike surface glycoprotein).

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2. The RNA contains common structural elements optimized for mediating high RNA stability and translational efficiency (see section 2.2). The LNPs protect the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (IM) delivery.

The mRNA is translated into the SARS-CoV-2 S protein in the host cell cytosol. The S protein is then expressed on the cell surface where it induces an adaptive immune response. The S protein is identified as a target for neutralising antibodies against the virus and is therefore considered a relevant vaccine component.

The vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) in two 30 µg doses of the diluted vaccine solution given 21 days apart.

Intended indication: *'Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older'.*

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive:

According to the Applicant, there is a positive benefit-risk balance for Comirnaty in the active immunisation to prevent COVID-19 disease caused by SARS-CoV-2, in individuals 16 years of age and older. This is based on evidence from the pivotal study C4591001 (also referred to as BNT162-02), a Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding Study investigating the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in healthy individuals.

The Applicant stated that the available data to date indicate that its vaccine was 95 percent effective and had no serious side effects, showing that the vaccine prevented mild and severe forms of COVID-19.

- It is likely that the applicant will be able to provide comprehensive data.

The Applicant intends to continue the ongoing pivotal Phase 3 study with participants as originally allocated for as long as possible, to obtain long-term data and to ensure sufficient follow-up to support a standard marketing authorisation. In case of availability of any COVID-19 vaccine, the sponsor will appeal to participants to remain in the ongoing study as originally randomized for as long as possible, ideally until a COVID-19 vaccine has full regulatory approval. In all cases, it is intended to follow participants up to the original planned 24 months post-vaccination, regardless of any participants opting to crossover from placebo to active vaccination. The safety and effectiveness of COMIRNATY in individuals <16 years of age have not been established for this application. Four studies in paediatric subjects are planned as laid down in the paediatric investigation plan. A study in pregnant women is also planned in the EU. A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of Comirnaty (Study C4591010) will be conducted in the EU using primary data collection that monitors a cohort of vaccinees and evaluates risk of AESIs. The Applicant will also conduct, non-interventional studies (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 in a real-world setting. These studies will allow to determine the effectiveness of vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups.

- Unmet medical needs will be addressed

According to the Applicant, as there is no approved other vaccine in the EU or successful COVID-19 therapy available in the EU, unmet medical need is existing and is likely to be addressed by this vaccine in view of the high level of protection observed in the pivotal clinical trial.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

According to the Applicant, Efficacy of COMIRNATY to prevent COVID-19 was demonstrated at the final analysis. The observed VE in each subgroup as defined by age, including elderly ≥ 65 years old, sex, race/ethnicity, country, obese subjects, and subjects at risk due to comorbidities, was overall consistent with the effectiveness of BNT162b2 to protect vaccinees against the disease. The benefit of immediate availability of Comirnaty through conditional marketing authorisation is based on the fact that there is no approved vaccine or successful COVID-19 therapy available in the European Union. An effective vaccine can impact the pandemic at this critical time and a COVID-19 vaccination program implemented soon can likely prevent further pandemic waves and thus substantially reduce mortality due to disease.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for dispersion for injection containing 225 µg/ 0.45 mL (prior to dilution) of BNT162b2 (5'capped mRNA encoding full length SARS-CoV-2 Spike protein) as active substance (AS).

Other ingredients are: ALC-0315 (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), 1,2-

Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose and water for injections.

The product is available in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Pack size: 195 vials.

The multidose (5 dose) vial is stored frozen and must be thawed prior to dilution. After thawing, the vaccine should be diluted and used immediately.

After dilution with 1.8 mL sodium chloride (0.9%) solution (not supplied), one dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

2.2.2. Active Substance

General Information

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimised sequence encoding the spike antigen of SARS-CoV-2. The vaccine is based on the spike glycoprotein (S) of SARS-CoV-2. The sequence was chosen based on the sequence for the "Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1". The protein sequence contains two proline mutation, which ensures an antigenically optimal pre-fusion confirmation (P2 S). The RNA does not contain any uridines; instead of uridine the modified N1-methylpseudouridine is used in RNA synthesis. The applicant will provide clarification on the mechanism of action for BNT162b2.

Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured and controlled by either Wyeth BioPharma Division, Andover, United States or by BioNTech Manufacturing GmbH, Mainz, Germany, and Rentschler Biopharma SE, Laupheim, Germany.

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release. These issues were classified as a Major Objection (MO). After further information was obtained from the sites and inspectors, the MO was considered resolved.

EU GMP certificates for the manufacturing and testing sites were subsequently obtained. In conclusion, appropriate manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing sites.

Description of manufacturing process and process controls

Information on the manufacturing process and process controls for both the Andover and the BNT Mainz & Rentschler manufacturing sites were provided.

The manufacturing process of BNT162b2 active substance involves five major steps. The RNA is synthesised from linear DNA via an in vitro transcription (IVT) step. The IVT step is followed by a number of purification and filtration steps. Lastly, the RNA undergoes a final filtration before being dispensed and stored frozen.

Flow diagrams were provided, presenting the process steps, process inputs and the process controls for each step. The purpose of each step in the manufacturing process is sufficiently described. The ranges of hold times and process parameters and routine in-process controls are listed with corresponding acceptance criteria, for each step. It is noted that not all process parameters are listed, but that the lists include all critical and several non-critical process parameters. It is agreed that the key process parameters are described in the dossier. The applicant has agreed to upgrade these parameters to critical process parameters (CPPs) and to include acceptable ranges for these CPPs. Updated information has been submitted during the procedure which comprised modifications of the acceptable ranges of several process parameters and the addition of some controls. The strategy is found acceptable, and the Applicant will provide information on acceptable ranges for some parameters.

The active substance is stored between -15°C and -25°C. Transportation using an insulated shipper is qualified and shipping time to finished product manufacturing sites are defined. Shipping validation of the intermediate has been agreed as recommendation.

The batch numbering system is sufficiently described.

Control of materials

An adequate overview of the raw materials and solutions used in the active substance manufacturing process is provided.

Representative certificates of analysis have been provided. The submitted information supports the appropriate quality of raw materials. It is recommended that the applicant should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials **(REC1)** and should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases **(REC2).** The description of synthesis of 5'cap and its related impurities were requested during the procedure. Appropriate information was given. The applicant should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021 **(REC3)**.

The BNT162b2 active substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA from transformed *Escherichia coli* cells.

The linear DNA template is not part of the final product but defines the sequence of the mRNA product and therefore it is fundamental to ensure the adequate control of the active substance. Changes to the manufacturing process of the linear DNA template (e.g. change to plasmid host cell) may result in a different impurity profile in the active substance. Additional details on the manufacturing process and the control strategy for this starting material, initially only shortly described, have been provided and the dossier will be updated accordingly.

The cell banks involved in the plasmid manufacturing process are described. Master cell bank (MCB) and working cell bank (WCB) qualification tests are listed. Relevant specifications are set and data from the current MCB and WCB are provided. The plasmid MCBs and WCBs are enrolled in a cell bank stability program. The strategy is considered adequate, noting that the dossier will be updated as appropriate. A protocol for establishment of future WCBs is provided.

Following fermentation, the cells are harvested and chemically lysed to recover the plasmid DNA. After this lysis step, the circular plasmid DNA is purified. The circular plasmid DNA is filtered and stored frozen. The strategy for establishing the initial shelf-life is endorsed and data provided support the proposed shelf life. A list of the raw materials as well as other materials used in the manufacture of the

linear DNA template is provided. All materials used are animal origin free and sourced from approved suppliers.

Specifications for the circular plasmid DNA as well as for the DNA linear template are provided. Process- and product-related impurities including host cell genomic DNA, RNA, proteins, endotoxins, bioburden and plasmid isoforms, for the plasmid DNA, are routinely quantified. The reference material is described. Implementation of any changes in the manufacture of the linear DNA template should be applied for in a variation application.

Control of critical steps and intermediates

Process parameters and tests that are used to control the process and active substance quality are provided. The list of CPPs was provided with corresponding updated acceptable ranges.

A summary of the quality attributes with the rationale for the criticality assignment is provided. The rationale for classification into CQA or QA is presented for each attribute and appears reasonable.

The in-process test methods are defined and described in the dossier.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The BNT162b2 active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial process validation/ process performance qualification batches at all sites. All acceptance criteria for the critical operational parameters and acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

In comparability studies, a decrease in RNA integrity was observed for the initial Process 2 batches compared to Process 1 batches. This is further discussed in the subsequent section on manufacturing process development. After adjustment of process parameters for CTP and ATP volumes, RNA integrity level is more consistent and verify that the volume adjustments made for ATP and CTP volumes consistently provide reproducible results with RNA integrity levels more similar to levels achieved in Process 1 batches. Since the target volumes for ATP and CTP have been increased, the proven acceptable ranges (PARs) ranges need to be adjusted and the dossier updated accordingly **(REC8)**. The robustness of the DNase digestion step is not considered comprehensively demonstrated although there is routine control of residual DNA impurities at the active substance level. It has been confirmed that studies to enhance the robustness of this step are ongoing and these should be reported **(REC7)**. The finalised indirect filter qualification assessment, according to the applicant, already available and should be provided for evaluation **(REC6)**.

Relevant hold times and transport times have been defined and were validated by appropriate studies.

The shipping qualification strategy is described in detail and considers both thermal and mechanical aspects of shipping. The shipping procedures and configuration for transport of frozen AS to the

finished product manufacturing sites were validated to maintain product temperature in the acceptable range for a defined duration.

A transport verification study is planned and results will be available in Q1/2021. The recommendation to provide shipping performance qualification data has been agreed **(REC6)**.

Manufacturing process development

Process development changes were adequately summarised. Two active substance processes have been used during the development history; Process 1 (clinical trial material) and Process 2 (commercial process). Details about process differences, justification for making changes, and results from a comparability study are provided. The major changes between active substance process versions were described in the dossier.

Batch analysis results showing comparability between non-clinical and clinical batches are provided. Additional characterization of product-related species and their relation to final product specifications will be provided as a specific obligation.

Electropherograms were presented demonstrating similarities in the peak pattern of RNA species, but some differences between Process 1 and 2 were also noted. It can therefore not be concluded that identical species are obtained by the processes. It is likely that the fragmented species will not result in expressed proteins, due to their expected poor stability and poor translational efficiency (see below). However, the lack of experimental data on the truncated RNA and expressed proteins does not permit a definitive conclusion and needs further characterisation. Therefore, additional characterisation data remain to be provided as a specific obligation **(SO1)**.

Regarding the 5' cap end of the AS, reversed phase high performance liquid chromatography-UV and mass spectrometry (LC- UV/MS) characterisation confirmed that the 5'-capped and uncapped structures are the same but that there is a slight shift towards higher 5'-capping levels in Process 2. The reported quality attribute 'capped-intact RNA' is intended to reflect the proportion of the RNA molecules in the active substance that are a fully intact molecule and have the 5'-cap. It is noted that the capped-intact RNA is not measured, but only calculated from the results of 5'-cap and %RNA integrity tests. Therefore, this argument alone cannot fully confirm the comparability of Process 2 versus Process 1, and further characterisation data and justification of specifications were requested.

According to the Applicant, the majority of fragments are expected to be comprised of truncated transcripts including the 5' region but lacking the 3' region and poly(A)tail. However, the results indicating a substantial proportion of shorter/truncated mRNA with both cap and poly(A)tail are not in agreement with this statement. Therefore, the Applicant was asked to discuss and justify the obtained results and explain the apparent discrepancy. Additional characterisation data using an orthogonal method with enriched samples for fragmented species was provided. Preliminary characterization data on isolated fragmented species suggests they predominantly include the 5'-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction. The characterisation data are requested to be completed with analysis of the main peak from ion pairing RP-HPLC and analysis of other samples from Process 1 and optimised Process 2 **(SO1).** The Applicant will continue to evaluate any potential overestimation of poly(A) tail and should characterise fragments for any future AS process changes **(SO1)**.

Furthermore, the poly(A)tail of the 3' end was characterised by LC-UV/MS. While the results were demonstrated to be comparable between Process 1 and Process 2 batches, significant differences were identified. As expected, poly(A) tail heterogeneity was observed both for Process 1 and Process 2 batches. Thus, slight differences in the poly(A)tail pattern were observed when comparing Process 1

and Process 2 AS batches. The Applicant explains that the redistribution is probably due to the use of a linearised DNA plasmid template in Process 2 instead of a PCR-derived DNA template in Process 1. For both processes, the poly(A)tail is anticipated to be sufficiently long to guarantee stability of the RNA and function in translation. This explanation is considered reasonable by the CHMP.

The overall primary sequence of BNT162b2 active substance was demonstrated to be comparable by LC/MS/MS -oligonucleotide mapping. Circular dichroism (CD) spectroscopy confirmed that the higher-order structure of Process 1 and Process 2 AS batches were comparable.

To demonstrate functionality, the protein size after in-vitro expression of BNT162b2 active substance was determined. The expressed protein sizes were demonstrated to be comparable between Process 1 and Process 2 batches. However, further clarification is requested and include correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **(SO1)**.

A second comparability study was presented to assess comparability across the Process 2 manufacturing facilities, batches each from the Andover and BioNTech sites were included in the study. In addition, Process 2 batches, planned for clinical supply and for emergency supply in the US market and representative batches from Process 1 were included in the comparison.

In conclusion, the Process 2 batches manufactured at the Andover and BioNTech sites were demonstrated to be comparable with respect to identity as monitored by agarose gels and 5'Cap structure characterised by LC-UV and subsequent MS analysis. Furthermore, the primary sequence and the secondary structure was demonstrated to be comparable for all Process 1 and Process 2 batches included in the study. Poly(A) tail length and distribution was investigated by RP-HPLC and MS analysis. All process 2 batches were found comparable, while the Process 1 batches showed a somewhat different poly(A) tail pattern.

The expressed protein size after in-vitro expression of BNT162b2 active substance was determined and the results demonstrate comparability between batches. However, the identity of the bands identified by WB are not sufficiently justified and further clarification is requested **(SO1)**.

Overall, the submitted data confirm consistent and comparable quality of Process 2 batches manufactured at the Andover and BioNTech sites.

Process characterisation studies using scale-down models of individual unit operations, were performed.

It should be noted that future changes to any of the process parameters, regardless of the classification of CPP or non-CPP, should be applied for as variation to the terms of the MA.

Initially, addition volumes for ATP and CTP were identified as non-CPPs as both were supplied in theoretical excess. Following additional manufacturing campaigns and additional small-scale studies it was shown that these volumes could be limiting, and the ranges were widened at the higher end. It is noted that after the adjustment of these volumes, the percentage of RNA integrity has increased to levels more consistent with Process 1 batches. Nevertheless, since the target volumes for ATP and CTP have been increased to avoid that these nucleotides are rate-limiting in order to increase the percentage of RNA integrity, the PAR ranges need to be adjusted and the dossier updated accordingly **(REC8)**.

The acceptable ranges for CPPs will be updated in the dossier.

A safety risk assessment for potential process-related impurities included in the active substance process relative to patient safety was performed. The sources of the impurities are sufficiently addressed.

The safety risk assessment strategy involves comparison of the theoretical worst-case concentration of impurities, assuming no removal, to calculated safety concern thresholds.

The worst-case levels of residual raw materials and reagents from the BNT162b2 active substance manufacturing process were calculated to be significantly below the pre-determined safety limits. This is found acceptable.

Characterisation

Analytical characterisation was performed on BNT162b2 active substance manufactured at commercial scale. This is found acceptable.

The physico-chemical characterisation involved primary structure, 5' cap structure, poly(A)tail and higher order structure evaluation. Primary structure was confirmed by oligonucleotide mapping and the orthogonal method, RNA sequencing using Next Generation Sequencing (NGS) technology. The results confirm the RNA sequence. The 5'-cap and 3' poly A tail were confirmed by two separate LC-UV/MS-methods. It was demonstrated that the predominant form of the 5' terminus is the full-length nucleotide sequence with the 5'-Cap. The higher order structure of BNT162b2 mRNA active substance was characterised in solution using biophysical techniques.

Overall, state-of-the-art methods were applied for physico-chemical characterisation and the results confirmed the expected sequence and quality attributes. It is recommended that the applicant should comprehensively describe the capability of a specific analytical method to detect lower amounts of product related impurity in the presence of the correct form in the active substance. **(REC9)**.

An uncertainty in the characterisation section is that no biological characterisation is presented. In response to questions during the procedure, the applicant has committed to update dossier with the strategy for potency determination and to address relevant functional assays including the in vitro expression (potency) results and results from the analysis of expressed protein size for active substance lot 20Y513C101. It is recommended that the applicant should discuss the results and the assay suitability for a certain method used for biological characterization of protein expression for the active substance **(REC10)**.

As described above, the expressed protein size results are currently not sufficiently confirmed and a specific obligation is laid down in the terms of the MA requiring their adequate characterisation **(SO1).**

Process-related and product-related impurities as well as potential contaminants are described. A number of batches were evaluated for impurities, i.e. clinical, initial emergency supply and PPQ batches from both manufacturing sites.

The sole product-related impurity addressed is double-stranded RNA, derived from the in-vitro transcription reaction. Results from the active substance batches demonstrate that the level of double stranded RNA is low, acceptable and consistent.

In addition to double stranded RNA, there are truncated RNA, also referred to as fragmented species. Truncated RNA is reflected in the AS specification in terms of RNA integrity. However, the characterisation of BNT162b2 AS is currently not found to be complete in relation to a specific parameter. This is especially important considering that the current AS and finished product acceptance criteria allow for a proportion of fragmented species. The Applicant should provide additional data to further characterise the truncated and modified mRNA species present in the finished product. Relevant protein/peptide characterization data for predominant species should be provided **(SO1)**.

Residual DNA template is a process-related impurity derived from the linearised DNA template added to the in-vitro transcription reaction. Residual DNA template is measured as defined in the active substance specification. The levels are controlled by a specification limit which is considered suitably low.

The potential contaminants described in this section are endotoxin and bioburden. Acceptable results are shown for the Proteinase K pool, UF retentate pre recovery, UF-product pool and the active substance, for all batches investigated.

Specification

The active substance specifications contain tests for appearance (clarity, coloration (Ph. Eur.)), pH (Ph. Eur.), content (RNA Concentration) (UV Spectroscopy), Identity of Encoded RNA Sequence (RT-PCR), RNA Integrity (Capillary Gel Electrophoresis), 5'- Cap (RP-HPLC), Poly(A) Tail (ddPCR), Residual DNA Template (qPCR), dsRNA (Immunoblot), Bacterial Endotoxin (Ph. Eur.) and Bioburden (Ph. Eur.).

The proposed specification for active substance is considered acceptable for authorisation with respect to the attributes chosen for routine release testing. During the procedure the specification limits for a number of attributes were tightened in response to questions.

The length of the poly(A) tails in BNT162b2 active substance is important for RNA stability and translational efficiency and even though comparable results have been reported to date, the poly(A) tail length should be included to the active substance release testing **(SO2)**.

The rationale used to establish the acceptance criteria is described in detail and based on a limited data set representative of BNT162b2 active substance manufactured at the intended commercial scale and process. From the available data, mRNA integrity, dsRNA and Poly(A) tail acceptance criteria are considered in relation with batches used in clinical studies and with the demonstrated manufacturing capability and need to be re-assessed and revised as appropriate as further data becomes available **(SO2).**

Potency testing is not included in the control of active substance but instead is performed at the level of finished product release testing. Considering the nature of this product, the approach is endorsed by the CHMP.

Analytical methods

All analytical methods used for testing of the active substance are sufficiently described in the dossier. The following tests are performed in accordance with Ph Eur chapters; clarity (Ph Eur 2.2.1), colour (Ph Eur 2.2.2), pH (Ph Eur 2.2.3), bacterial endotoxins (Ph Eur 2.6.14) and bioburden (Ph Eur 2.6.12).

All non-compendial analytical methods are sufficiently described. These analytical methods were suitably validated against the parameters presented in ICH Q2(R1).

The technical procedure for the quantification of the poly(A) tail is considered, in general, sufficiently described but the suitability of this method for the intended purpose remains to be confirmed **(SO2)**.

Batch analysis

Batch results are presented for active substance batches used for nonclinical toxicology, clinical trials, process performance qualification (PPQ), emergency supply and stability.

In general, the results obtained using the commercial process (Process 2) demonstrate batch to batch consistency with a few exceptions.

Reference materials

The current reference standard is referred to as the Clinical Reference Material (CRM). A stability protocol is provided. The Applicant has agreed to provide additional information such as protocol on preparation and qualification on the future reference material, as requested **(REC12)**.

In future, a two-tiered system for future commercial reference material will be implemented. A primary reference material (PRM) and an initial working reference material (WRM) will be established for the active substance reference material.

Container closure

The information regarding container closure system is acceptable. Compliance with Ph. Eur. has been verified.

Stability

Based on the limited stability data presented a shelf-life at -20 ± 5°C can be approved for the active substance when stored in the commercial container closure system. The stability program is designed to follow ICH guidelines. The test methods used are stability indicating. Data from the sites Andover, Mainz, Rentschler are included.

It is noted that the Applicant states that testing is currently in progress on the clinical batches and the dossier will be updated with data for these batches, as well as any new data available for the primary process validation batches. Thermal cycling studies have been initiated and a minimum of one process validation batch will be subjected to photostability studies at a future date.

Based on the stability data presented a shelf-life at -20 ± 5°C can be approved for the active substance when stored in the commercial container closure system.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The BNT162b2 finished product (FP) is supplied as a preservative-free, 5 dose multidose concentrate to be diluted prior to intramuscular injection. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

Each vial, containing 0.45 mL of the finished product at pH 6.9 - 7.9 is designed to deliver a total of 5 doses after dilution by addition of 1.8 mL of sterile 0.9% sodium chloride solution to a total volume of 2.25 mL. Each dose contains 30 µg of RNA in 0.3 mL.

The overfill in the vial is required to ensure that the full five doses can be removed from the multi-dose vial after dilution and correctly administered, taking account of potential loss of product during these dilution and administration steps. The justification for the overfill is sufficiently discussed and considered to be acceptable. The applicant development data and finished product testing confirm that 5 doses can be consistently extracted from the vial and delivered after dilution.

The finished product is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap.

The full list of excipients is listed above in section 2.2.1; ALC-0315 and ALC-0159 (functional lipids), DSPC and cholesterol (structural lipids), potassium chloride, potassium dihydrogen phosphate, sodium

chloride and disodium phosphate dihydrate (buffer components), sucrose (cryoprotectant) and water for injections.

All excipients except the functional lipids ALC-0315 and ALC-0159 and the structural lipid DSPC comply with Ph. Eur. The functional lipid excipients ALC-0315 and ALC-0159, are classified as novel excipients. Both structural lipids DSPC and cholesterol are used in several already approved finished products. A justification was provided for why DSPC is not considered to be a novel excipient. DSPC is used as part of the LNP for the EU approved finished product Onpattro which is administered intravenously in a much higher dose than the intramuscular dose for this product. Additionally; DOPC, a structurally related lipid, is present in finished products approved in the EU for intramuscular administration. It was therefore concluded that the level of information provided for DSPC, is in line with the requirements for a known excipient are sufficient and appropriately justified.

The vial, stopper and seal components are compliant with the appropriate Ph. Eur. monographs for primary containers and closures.

Formulation development

The section on formulation development describes and justifies the chosen formulation and is sufficiently comprehensive.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described. The LNPs consists of four lipids, each has a functional or structural purpose. The formed RNA-containing LNPs are solid particles. Furthermore, the accumulated batch-data to date show consistent manufacture of lipid nanoparticles both with respect to size and polydispersity.

Lipid-related impurities have been identified in the finished product and have been characterized. An investigation has been initiated and is ongoing to assess and review potential root causes. The outcome of the investigation shall be provided (SO2).

Visual particulate matter has occasionally been observed in finished product batches. Characterization data have been presented and the control strategy has been discussed. The data demonstrates that the particles are comprised of components of the finished product formulation. A 100% visual inspection is performed during manufacturing and the automatic inspection system is updated to improve the inspection. Routine release or routine stability data indicate that the propensity of particles to form following storage is low. If particles are observed in the diluted vaccine the vial should be discarded.

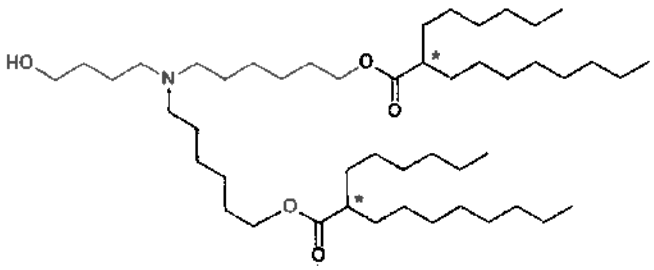
Novel excipients

Two novel excipients are included in the finished product, the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. Limited information regarding the novel excipients are provided.

ALC-0315 (cationic lipid)

The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine and two ester moieties, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate).

Figure 1 ALC-0315 structure



Asterisks (*) indicate chiral centers.

A brief description of the chemical synthesis is provided. The suppliers are defined in the dossier. A similar manufacturing process is used for ALC-0315 in clinical and commercial finished product batches.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. (**SO4**)

The proposed specification is considered acceptable based on the available data. However, additional information regarding specifications that should be provided **(SO4)**.

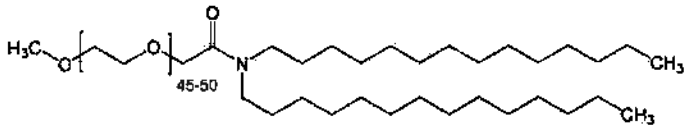
Stability data from one supplier indicate that ALC-0315 is stable when stored at the recommended storage conditions. Additionally, the excipient is stable at room temperature suitable for use in further manufacturing steps. Stability data from one supplier is considered representative for lipid from another supplier.

Lipid related impurities have been observed in some recently manufactured finished product batches, correlated with ALC-0315 lipid batches. The quality of ALC-0315 excipient is considered acceptable based on the available data on condition that specific impurities in the finished product will be further evaluated **(SO2)**.

ALC-0159 (PEGylated lipid)

The ALC-0159 novel excipient is a PEGylated lipid, 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide.

Figure 2 ALC-0159 structure



A brief description of the chemical synthesis is provided.

The suppliers are defined in the dossier. The same supplier was used during development for clinical phase 1, 2 and 3 studies. The same synthetic route was used for ALC-0159 throughout development of the finished product.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant is requested to provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **(SO5)**

The proposed specification is considered acceptable based on available data. However, in order to improve impurity control strategy and to ensure batch to batch consistency of the finished product, there are additional information regarding specifications that should be provided **(SO5)**.

Stability data indicate that ALC-0159 is stable when stored at the recommended storage conditions.

Manufacturing process development

The development history of the finished product is sufficiently described. The process has been transferred to commercial facilities for manufacture of later clinical materials, emergency supply and commercial supply. A table on finished product lot genealogy and usage has been provided.

The applicant states that comparability is demonstrated in a stepwise approach through a combination of release testing and extended characterization methods. It is agreed that comparability was sufficiently demonstrated with only small differences noted.

During the present regulatory procedure, release testing results of a number of recently manufactured GMP-batches was presented. The release data for the GMP-batches are compared to the clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification and that comparability has been sufficiently demonstrated subject to the specific obligations further described, for the attributes tested and given the pandemic situation. In addition, the comparison will be further extended with additional characterization testing on future batches of finished product. The applicant has confirmed that testing will be performed according to the agreed finished product comparability testing protocol and the results will be submitted in the frame of a specific obligation (**SO3**).

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented and is agreed. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program at the commercial facility has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data (**SO3**).

The development of the manufacturing process is extensively described, and critical process parameters are defined. Process characterisation studies using scale-down models of individual unit operations, were performed.

Overall control strategy was presented but some parameters and ranges may be updated after PPQ and additional characterization studies completed. As for assessment of overall control strategy, a complete set of data and information is needed, this document will be assessed when finalised. A time-plan for the provision of the final data set has been agreed with the applicant **(SO3)**.

The analytical testing strategy of finished product has changed throughout the development and these changes have been described. Bridging studies have been performed for analytical tests that have been changed or replaced (subvisible particles, identity of encoded RNA sequence and RNA integrity). This is found acceptable.

Container closure system

The development of the container closure system is sufficiently presented. The primary packaging is composed of glass vial and rubber stopper and are compliant with the compendial requirements of Ph. Eur.

Controlled extraction studies have been performed on the bromobutyl rubber stopper. The applicant will provide the updated results from the leachables study for assessment. (**REC13**)

Microbiological attributes

Container closure integrity testing has been performed to demonstrate that the 2 mL container closure presentation is integral.

In order to improve the control strategy, the MAH should provide validation results of alternative sterility test i.e. rapid sterility test for assessment before implementation (**REC14**).

Compatibility

The studies described have been performed to assess physicochemical stability of the FP after dilution with 0.9% sodium chloride solution in the original glass vial as well with commonly used commercially available administration components and using worst-case conditions for dosage and administration in the clinical setting. The thawed hold time (in-use period) of undiluted finished product has been defined as 5 days at 2-8 °C and 2 hours at up to 30 °C.

Results presented support physicochemical stability of FP diluted in 0.9% sodium chloride solution for up to 24 hours at ambient or refrigerated temperatures (2-30°C) following an in-use thawed hold time of up to 5 days at 2-8 °C and 2 hours at 30 °C.

Compatibility with dosing components (syringes and needles) has been established for up to 6 hours. Furthermore, a microbiological in-use hold time study has been performed by a challenge test including five compendial micro-organisms. No significant growth (>0.5log10 from the start-point) was observed for any of the microorganisms within 12 hours of inoculation with storage at 20-25°C of diluted FP in 0.9% sodium chloride solution. Therefore, based on the results from the microbiological in-use hold time study, the proposed in-use period for up to 6 hours at ambient temperatures is agreed, as reflected in the product information. Furthermore, it is also stated by the applicant that the in-use period is in alignment with the WHO policy on the use of opened multi-dose vaccine vials (WHO Policy Statement: Multi-dose vial policy (MDVP) – handling of multi-dose vaccine vials after opening, rev 2014).

The compatibility of finished product is acceptably demonstrated by the dilution and administration simulation studies performed.

Manufacture of the product and process controls

The finished product is batch released by Pfizer Manufacturing Belgium NV, Puurs, Belgium or BioNTech Manufacturing GmbH, Mainz, Germany. The GMP status of the manufacturing and testing sites of the finished product have been confirmed.

The finished product manufacturing process includes the following main steps: active substance thawing and dilution, LNP formation and stabilisation, buffer exchange, concentration and filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, visual inspection, labelling, freezing and storage. Critical manufacturing steps are discussed, and relevant in-process controls are applied.

Dossier should be updated to provide more details on increase batch size including range number of AS bag and batches used, configuration of filters filter surfaces used and process controls (**REC14**). The absence of a test for residuals is considered acceptable.

Shipping validation

This section gives a summary of the qualification of the shipping process for transport of BNT162b2 finished product by passive thermal shipping containers for air and road shipments at temperature conditions of -90 to -60 °C from the finished product manufacturing and packaging site to dosing sites in the EU.

Short periods of time outside of the intended routine shipping condition of -90 to -60 °C during transport and at distribution sites have been defined.

The shipping temperature range of -90 to -60 °C is based on available stability data.

One thaw and refreeze cycle is allowed during transportation. Time during transportation out of the intended storage and shipping temperature range (-90 to -60 °C) without thaw is allowed for specified times and conditions for multiple transfers and redistribution during shipping with subsequent refreezing to -90 to -60 °C between transfers. The temperature excursion allowances are supported by data.

The selected shipping methods include shipping containers designed to maintain product temperature through a combination of insulation and dry ice. The applicant has prior experience with these passive thermal conveyances and has demonstrated that they maintain the -90 to -60 °C temperature range during product shipments, including minor shipping delays and short exposures to extreme temperatures occasionally observed during shipping and handling.

All shipments are continuously monitored using temperature data loggers.

The overall qualification strategy considered both thermal and mechanical aspects of shipping in passive thermal conveyance, supported by operational qualification and performance qualification testing. A summary of the shipping qualification strategy has been provided.

For the passive thermal conveyance, the qualification is focused on the ability of the passive system to maintain the required temperatures with specified phase change materials or dry ice when exposed to ambient temperature profiles for worst-case season. These studies are carried out in laboratory chambers to simulate the summer as worst-case ambient profiles.

A simulated distribution study demonstrated finished product and package integrity after exposure to simulated distribution hazard conditions, following the durations outlined in the worst-case extended transport lanes.

Results of thermal qualification have met specified acceptance criteria and support shipments of BNT162b2 finished product using the passive thermal conveyance shipping containers either directly or

via qualified distribution centres. Passive thermal conveyance performance qualification and the simulated shipping study finished product impact testing have been performed to complete shipping qualification assessing both thermal and mechanical aspects of shipping.

Process parameters for storage and shipping are found acceptable.

Media fills

Media fills have been performed for the filling line to validate the aseptic filling process and were run in accordance to guidelines. Results have been provided from three consecutive simulation studies and gave satisfactory results without any contaminated units. Results for the media fill cover the maximum process time for the manufacturing of finished product and simulate worst-case manufacturing conditions. The media fill validation demonstrated that aseptic conditions are maintained during the filling process. For the filling line, the maximum time will be established upon completion of media fill qualification studies. This is found acceptable.

Verification of in-process test methods

Data on verification of in-process test methods was pending at the time of the present regulatory procedure and should be provided during Q2 2021 (**REC15**).

Hold times

Hold times have been established. It is noted that any change of this section needs to be submitted to the Agency via a variation application.

Process validation plan

A FP process validation plan has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

It is described in the dossier that commercial scale PPQ-batches will be manufactured during Dec 2020 to Jan 2021 and the applicant has provided a process validation plan. In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation data, by March 2021. (**SO3**)

Filter validation

Acceptable information has been provided during the procedure for filter validation on the filters used for sterile filtration, describing the material, pore size and surface area. All study results met the predetermined acceptance criteria and the studies for microbial retention, membrane compatibility, extractable substances and integrity test determination have shown that the filters are appropriate for sterile filtration of the finished product. In addition, the applicant has clarified that the filter used for bioburden reduction is identical to the filters used for sterile filtration.

The MAH should provide the results for assessment from the filter validation as soon as they are available (**REC23**).

Control of excipients

ALC-0315 and ALC-0159 are novel excipients, not previously used in an approved finished product within EU. Additional information is provided separately in Section A.3 of the dossier.

DSPC is a non-compendial excipient sufficiently controlled by an in-house specification.

Cholesterol is sufficiently controlled according to the Ph. Eur. monograph with additional tests for residual solvents and microbial contamination.

The other excipients (sucrose, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injection) are controlled according to respective Ph. Eur. monograph.

The processing aids ethanol and citrate buffer are controlled according to Ph. Eur. standards and for HEPES and EDTA, reference is made to the active substance.

Product specification

The release and stability testing specifications for BNT162b2 finished product include tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), ALC-0315 content (HPLC-CAD), ALC-0159 content (HPLC-CAD), DSPC content (HPLC-CAD), Cholesterol content (HPLC-CAD), extractable volume (Ph. Eur.), Lipid identities (HPLC-CAD), Identity of encoded RNA sequence (RT-PCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion). For all quality attributes tested on stability except for RNA integrity, the acceptance criteria for release and stability testing throughout shelf life are the same.

The specifications document for finished product in section 3.2.P.5.1 of the dossier includes a comprehensive panel of relevant tests along with corresponding acceptance criteria.

With the exception of osmolality, volume of injections in containers, HPLC-CAD (lipid identities) and RT-PCR (identity of encoded RNA sequence), which are performed only at FP release, all other analytical procedures are conducted at release and stability studies for finished product. It is stated by the applicant that the acceptance criteria used for stability during shelf-life will be the same as the acceptance criteria used for lot release.

Several questions in relation to the acceptance criteria in the FP specifications were raised during the procedure (i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity). The acceptance criteria were tightened.

For potency, RNA integrity, RNA encapsulation, lipid content and polydispersity index, the acceptance criteria will be re-assessed during Q2 2021 in order to ensure a consistent product quality by providing additional information to enhance the control strategy. This is found acceptable subject to a specific obligation. (**SO2**)

The vial contains an overfill in order to ensure that the full required volume (5 doses) can be delivered following dilution and administration in line with the product information. The finished product specification includes a test to confirm the extractable volume from the vial provides 5 doses. During the procedure the applicant proposed to update the product information and instructions for use to indicate that up to 6 doses can be delivered from the vial. This proposed change to the product information was not considered acceptable as no supporting data were provided to demonstrate that 6 doses can be consistently extracted. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses (**REC21**).

A risk evaluation regarding the risk of N-nitrosamines impurities was provided concluding that there is no risk of the presence of nitrosamines in the finished product taking into account the active

substance, the finished product formulation and primary packaging. The risk assessment is considered acceptable.

It is recommended that a risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D **(REC17)**.

A question was raised during the procedure since no information and discussion was provided in the dossier on lipid-related impurities originating from the degradation of the LNP. It is argued by the applicant that with respect to potential lipid-related impurities originating from the degradation of LNPs, no degradation of the LNP FP has been observed in the stability studies at the recommended storage temperature (-70 to -90 °C) for the LNP as shown by specifications for size and polydispersity, RNA encapsulation, RNA and lipid content and RNA integrity quality attributes. This is acknowledged. In addition, further evaluation of lipid-related impurities in the finished product should be performed and the results submitted and discussed in the frame of a specific obligation (**SO2**).

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

The dossier includes release testing results of four recently manufactured GMP-batches. These finished product GMP batches were manufactured at the commercial FP manufacturing site. The release data for these GMP-batches are compared to min-max ranges of the small-scale clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification. Therefore, it can be concluded that comparability has been sufficiently demonstrated for the attributes tested given the pandemic situation and considering that further data is to be provided in the frame of a specific obligation. In addition, the comparison will be further extended with additional characterization testing on future PPQ-batches of finished product. The applicant has confirmed that testing will be performed according to the finished product comparability testing protocol. and the results will be provided in the frame of specific obligation **(SO3)**.

Reference materials

The finished product reference materials is the same as for active substance.

Stability of the product

A shelf-life of 6 months for the finished product is proposed when stored at the recommended storage condition of -90°C to -60°C.

The applicant has provided stability results up to 6 months at -80 to -60°C of one clinical batch and up to 6 months of a non-clinical batch of finished product. Two weeks data are also provided for two emergency supply under recommended storage conditions. In addition, there are newly initiated stability studies on the recently manufactured GMP-batches as well as plans to initiate stability studies on the future PPQ-batches.

Stability data have also been provided at accelerated (-40°C to +5°C) and stressed (+25°C to +30°C) storage conditions.

The stability studies are performed in accordance with ICH Q5C (Quality of biotechnological products: Stability testing of biotechnological/biological products) and the same or representative container-

closure system are used in these stability studies as will be used for commercial batches. The test methods used are stability indicating.

Overall, the presented stability data indicate no signs of degradation, significant trends or changes in terms of quality at the recommended storage condition (-90 to -60°C).

The applicant has provided updated reports from the ongoing stability studies and the presented data are considered sufficient and in support of the shelf-life claim since comparability has been sufficiently demonstrated between commercial scale GMP batches and the small-scale clinical batches.

In addition, the initial in-use period for the thawed, undiluted vial is 5 days at 2-8°C followed by storage at up to 30°C for not more than 2 hours. This is found acceptable.

Chemical and physical in-use stability has also been demonstrated for 6 hours at 2°C to 30°C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection.

It is described that the future PPQ-lots will be enrolled in the stability program and the stability protocol has been defined in the dossier. This is acceptable; however, the applicant should commit to provide the 6 months stability data for the PPQ-batches for assessment as soon as they are available. (**REC20**). Notwithstanding requests for further stability updates, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

It has been clarified by the applicant that results on photostability testing studies will be provided for assessment (**REC19**).

It is recommended that the applicant should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70°C to -20°C. In addition, the applicant should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8°C as well as the possibilities to extend the claims for transport conditions at 2-8°C **(REC22).**

A shelf-life of 6 months for the finished product at -90 to -60°C is accepted.

Adventitious agents

Adventitious agents' safety evaluation has been provided for the AS manufacturing sites and for the finished product manufacturing site.

Reagents used in active substance manufacturing and in the establishment of the MCB and WCB are the only materials of animal origin used in the manufacture of BNT162b2. The applicant has identified contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents as the main theoretical risk associated with these ingredients and it is deemed of minimal risk.

Additional clarifications were requested and provided for a number of other materials.

Sufficient details on the aseptic validation filling and media fills have been provided. Furthermore, adequate testing for bioburden and endotoxin is performed at different stages of the manufacturing process. Therefore, no additional concerns are raised.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release, the comparability between clinical and commercial material and the absence of validation data on finished product manufactured at the commercial site. These issues were classified as Major Objections (MOs).

After further information was obtained from the sites and inspectors, questions regarding the manufacturing were addressed and manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing and testing sites.

Some of the proposed sites for batch control testing are currently located in the USA. The following time-limited derogation has been introduced as a condition to the MA:

'In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by the 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application'.

Additional data have been submitted by the applicant during the procedure in response to the other MOs and other questions raised.

Having considered the emergency situation and the quality documentation provided, the CHMP imposed some specific obligations (SOs) with clearly defined due dates (refer to Conclusions for details). In addition, the CHMP adopted some Recommendations (RECs) to be addressed by the Applicant.

In addition, it should be ensured that, in accordance with Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and controls (including the specifications) shall be designed to ensure product consistency and a product quality of at least shown to be safe and efficacious in clinical trials and shall introduce any subsequent changes to their manufacturing process and controls as needed.

Active substance

Overall, the information provided is satisfactory. However, certain information is still pending due to the very short time frame of product development and will either be updated in the dossier imminently or further addressed in specific obligations and other post-approval measures.

Information on the manufacturing process and process controls for the manufacturing sites Andover and BNT Mainz & Rentschler have been provided and are considered satisfactory.

Two active substance processes have been used during the development; Process 1 and 2. The major changes between AS Process 1 and 2 are: Increased process scale, DNA template changed from a PCR template to linearised plasmid DNA, magnetic bead purification replaced with proteinase K digestion and UFDF steps. Based on the differences observed between batches manufactured by active substance Process 1 and 2 for the CQA mRNA integrity and lack of characterisation data, a MO was raised regarding comparability, characterisation and clinical qualification of the one proposed acceptance criteria. Biological characterisation of the active substance was limited, and additional data and discussion were requested to address functionality. Additional characterisation data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay **(SO1).**

Truncated RNA species are regarded as product-related impurities and can be expected due to the principle of the in-vitro transcription reaction (i.e. directional polymerase activity) and (theoretical) hydrolysis during manufacturing. Analysis of RNase treated samples showed that all species detected

by the capillary gel electrophoresis (CGE)-based method are composed of RNA. Manufacturing consistency with respect to fragmented species has been sufficiently demonstrated.

There were some differences in truncated RNA species level, however further analyses revealed a comparable overall fragmentation profile among Process 1 and Process 2 active substance batches. Additionally, oligonucleotide mapping data demonstrated no significant differences observed between Process 1 and Process 2 active substance batches.

The company does not expect truncated transcripts formulated in the finished product to pose a safety or efficacy concern, as in their view no protein expression is expected from truncated transcripts. Further, clinical trials with process 1 material have not revealed major safety concerns to date. Truncated BNT162b2 RNA species lacking either the 5′ cap or the poly(A) tail are expected to be rapidly targeted for degradation in the cytoplasm or would show a decrease or loss of translation efficiency. Preliminary characterization data on isolated fragment species suggest that fragment species predominantly include the 5′-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction.

However, as the overall characterisation of the truncated species is still limited, additional analysis of truncated species, additional translated protein characterisation, additional characterisation of lipid-related impurities and potential lipid-RNA species should be provided to support that they are not impacting clinical performance in terms of safety and/or efficacy. The current specification allows for a certain level of truncated mRNA species to be present however data from recent batches have shown levels of truncated species below that level. No related safety issues have been identified in the clinical studies thus far in subjects who received vaccine containing up to a certain level of truncated species. Therefore, the current specification is considered acceptable subject to the submission of additional data in the frame of a specific obligation (**SO1**).

Based on available data, the proposed specification for active substance is acceptable with respect to the attributes chosen for routine release testing. However, the length of the poly(A) tails in BNT162b2 active substance is critical for RNA stability and translational efficiency and therefore should be introduced in active substance release testing in the frame of a specific obligation (**SO2**). Moreover, the active substance specification acceptance limits should be re-assessed and revised as appropriate, as further data become available from ongoing clinical trials and in line with manufacturing process capability (**SO2**).

It is noted that the Applicant states that testing is currently in progress on the clinical batches and data for these batches, as well as any new data available for the primary process validation batches, will be provided. Based on the limited stability data presented, a shelf-life is approved for the active substance.

Finished product

The finished product is a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, intended for 5 doses. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described including studies that were performed with available active substance, representative of the mRNA platform and included in the finished product.

The development of the manufacturing process is extensively described, and critical process parameters are defined.

The manufacturing process includes lipid nanoparticle fabrication and bulk finished product formulation followed by fill and finish, and the process has been acceptably described.

Comparability between the commercial finished product and the clinical finished product has been sufficiently demonstrated for the attributes tested and will be subject to a specific obligation.

Limited data on the finished product batches manufactured at the commercial facility (entire manufacturing process at the commercial site Pfizer, Puurs, at commercial scale, active substance from process 2) were presented. A process validation plan for PPQ lots has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

Further data was requested in order to conclude on the consistency of finished product manufacturing, to assure comparability between the commercial product with the product used in clinical trials, and to support the claimed finished product shelf-life and storage conditions. A process validation plan for PPQ lots has been provided. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program, also comprising the commercial facility at Puurs, Belgium, has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data **(SO3).**

The specifications for finished product include a comprehensive panel of relevant tests along with corresponding acceptance criteria. Several issues in relation to the acceptance criteria in the finished product specifications were raised, i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity. Whilst FP specifications were subsequently amended and overall found to be acceptable, the acceptance limits should be re-assessed, and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability **(SO2)**.

Two novel excipients are included in the LNP. Complete information is not provided for both the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. In order to assure comprehensive control throughout the lifecycle of the finished product and to ensure batch to batch consistency, further information needs to be submitted regarding the synthetic process and control strategy in line with specific obligations **(SO4, SO5).**

Lipid-related impurities have been observed in some recently manufactured finished product batches. For the batches with lipid-related impurities the existing quality control parameters including RNA integrity remain unchanged.

Considering the above and the emergency situation, the characterisation of the active substance and finished product is considered acceptable, and the proposed specifications for RNA Integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. These data are requested to be provided as specific obligations to the applied conditional marketing authorisation **(SO1, SO2)**.

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine from Process 1. The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities. The suitability of the analytical methods used for control of potency and poly(A) tail have not been fully demonstrated.

Data demonstrate the presence of significant amounts of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are poorly characterised, and the limited data provided for protein expression do not fully address the uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein.

The control strategy for active substance and finished product is important to guarantee acceptable quality and ensure batch to batch consistency of the finished product. Regarding the proposed control strategy, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Based on the above, the following uncertainties are considered to be of importance for the benefit-risk assessment:

- Truncated and modified RNA are present as impurities. Considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell there is a possibility that aberrant proteins will be expressed with possibilities for unwanted immunological events. The risk of this occurring is considered low based on the following observations and considerations:
    - Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
    - The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA.
    - The level of any individual aberrant mRNA species would in any way be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The amount of the protein would be expected to be too low to elicit an immune response. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the aberrant protein would be non-significant.
- Lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be sufficiently consistent and acceptable subject to the specific obligations abovementioned.

In general, physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in an acceptable way. While the characterisation data still

need to be completed, the results of tests carried out indicate consistency of product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product is expected to have a satisfactory clinical performance.

The submitted information indicate that currently manufactured product batches are of a quality that is appropriate and sufficiently comparable to that of clinical development batches. However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product a number of issues are expected to be addressed though fulfilment of specific obligations, within defined time frames.

The CHMP has identified the following specific obligations to address the identified quality development issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed below.

In addition, and in accordance with Article 16 of regulation (EC) No 726/2004, the MAH shall inform the Agency of any information which might influence the quality of the medicinal product concerned, such as any necessary tightening of the finished product specifications earlier than July 2021. This is also related to the general obligation to vary the terms of the marketing authorisation to take into account the technical and scientific progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

In the context of the conditional marketing authorisation, the applicant should fulfil the following specific obligations (SOs):

- SO1: In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data. **Due date: July 2021. Interim reports: March 2021.**
- SO2: In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications. **Due date: July 2021. Interim reports: March 2021.**
- SO3: In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data. **Due date: March 2021.**
- SO4: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. **Due date: July 2021, Interim reports: January 2021, April 2021.**
- SO5: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **Due date: July 2021, Interim reports: January 2021, April 2021.**

As regards SO1, the following data are requested in order to complete the information on the active substance and finished product characterisation.

a) Additional data is to be provided to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should further address the potential for translation into

truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterization data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated. **Due date: July 2021. Interim reports: March 2021, and on a monthly basis.**

b) The analysis of the main peak of the RNA integrity test representing the full-length RNA, should be also undertaken addressing 5'cap levels and presence of the poly (A) tail. **Due date: July 2021. Interim report: March 2021**

c) Additional data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **Due date: July 2021. Interim report: March 2021**

As regards SO2, the following data are requested to be provided in order to ensure a comprehensive control strategy, including active substance and finished product specifications:

a) The active substance and finished product specifications acceptance limits, should be re-assessed and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials. **Due date: July 2021, Interim reports March 2021, and on a monthly basis.**

b) Poly(A) tail length is considered a critical attribute, which should be controlled on each batch, even though comparable results were obtained until now. An active substance specification to control poly(A) length should be introduced. A suitable method should be developed and appropriate acceptance criteria should be set. **Due date: July 2021, Interim reports: March 2021**

c) The poly(A) tail percentage is considered a critical attribute, but uncertainties remain on the suitability of the method. Additional data should be provided to support the suitability of the method used for %poly(A) tail or an alternative suitable assay should be developed and introduced. The %poly(A) tail should be characterised following any future active substance process changes. **Due date: July 2021, Interim reports: March 2021**

d) Since mRNA integrity and polydispersity are CQAs for the efficacy of the medicinal product, the finished product acceptance criteria for these parameters should be revised as further data becomes available from ongoing clinical trials and in line with manufacturing process capability. **Due date: July 2021, Interim reports: March 2021.**

e) Additional data should be provided to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly. **Due date: July 2021, Interim reports: March 2021**

f) Lipid-related impurities should be further evaluated. An appropriate control strategy should be introduced, suitably justified and provided for assessment during Q2 2021. **Due date: July**

2021, Interim reports (LMS content in commercial FP batches, investigation results): March 2021, and on a monthly basis.

As regards SO3, the following data are requested to be provided in order to ensure batch to batch consistency and to complete the information on process validation of the finished product manufacturing process.

a) Full commercial scale finished product PPQ-batches will be manufactured at the commercial facility Pfizer Puurs, Belgium. The applicant should provide the summary report on the completed commercial scale process validation activities. **Due date: March 2021.**

b) The applicant should perform testing of future process validation-batches of finished product according to the extended comparability testing protocol and the results should be provided for assessment. **Due date: March 2021.**

As regards SO4, the data are requested to be provided regarding the synthetic process and control strategy for the excipient ALC-0315 in order to improve the impurity control strategy, assure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product.

a) A detailed description of the chemical synthesis of ALC-0315 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**

b) Differences in the manufacturing process between two suppliers should be described and possible impact on impurity profile should be discussed **by July 2021. Interim report: January 2021**

c) Information and justification of quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. **Due date: July 2021, Interim report: January 2021**

d) Information and justification on critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**

e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**

f) The specification limit for total impurities should be re-evaluated as more batch data becomes available and revised, as appropriate. **Due date: July 2021**

g) The specification limit for assay should be tightened based on the provided batch data to improve the quality control strategy of the finished product. **Due date: July 2021**

h) Detailed method validation reports for assay, impurities, and residual solvents for ALC-0315 should be provided. **Due date: July 2021**

i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

As regards SO5, the following data is requested to be provided regarding the synthetic process and control strategy for ALC-0159 in order to improve impurity control strategy, assure comprehensive control and batch-to-batch consistency throughout the lifecycle of the active product.

a) A detailed description of the chemical synthesis of ALC-0159 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**

b) Information and quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. Relevant acceptance criteria for molecular weight and polydispersity should be included in the specification for the starting material carboxy-MPEG. **Due date: July 2021, Interim report: January 2021**

c) Information and justification of critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**

d) The specification limit for assay should be tightened based on batch data in order to provide a more stringent quality control of the finished product. **Due date: July 2021, Interim report: April 2021**

e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**

f) The specification limit for total impurities should be re-evaluated as more batch data are available and revised, as appropriate. **Due date: July 2021**

g) Acceptance criteria for tetrahydrofuran should be added to the specification for ALC-0159, unless otherwise justified, as it is included as a solvent in step 2 of the synthesis. **Due date: January 2021**

h) Detailed method validation reports for assay, impurities and residual solvents for ALC-0159 should be provided. **Due date: July 2021, Interim report: April 2021**

i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

2.2.6. Recommendations for future quality development

In the context of the obligation of the Marketing Authorisation Holder (MAH) to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Active substance

1. The MAH should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials.
2. The MAH should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases.
3. The MAH should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021.
4. The MAH should reassess the specification for the linear DNA template purity and impurities. The Applicant has already agreed to supply these by Q2 2021.
5. The MAH should perform and document a gap analysis to identify any supplemental qualification needed to align the methods used for the DNA template control with ICH requirements. The gaps identified should be addressed either prior to transferring the methods to relevant sites or during the transfer activities.
6. The MAH should provide active substance process validation data regarding the finalised

indirect filter qualification assessment and the shipping validation between sites.

7. The MAH should provide the results of the studies performed to enhance the robustness of the DNase digestion step.
8. The MAH should tighten the low limits of the proven acceptable ranges for the target volumes for ATP and CTP, to the levels needed to ensure a sufficiently high mRNA integrity in the active substance manufacturing process.
9. The MAH should comprehensively describe the capability of the next generation sequencing technology platform to detect lower amounts of RNA species of alternative sequence in the presence of the correct, more abundant RNA for the active substance.
10. The MAH should discuss the results and the assay suitability for the cell-based flow cytometry and the western blot method used for biological characterization of protein expression for the active substance.
11. The MAH should provide a summary of the validation/verification status of the immunoblot analytical procedure used to detect double stranded RNA (dsRNA) in BNT162b2 active substance.
12. In order to improve the control strategy, the MAH should provide the protocol on preparation and qualification of future primary and working reference standards for the active substance.

Finished Product

13. The updated results from the finished product leachables studies should be provided for assessment.
14. In order to ensure batch to batch consistency of the finished product the MAH should expand the description of the manufacturing process with more details. (1) When the batch size is twice the original one, the range number of active substance bags and active substance batches to be thawed, and the number of mixers should be stated. (2) The MAH should confirm the configuration of filters used in finished product manufacture. (3) The surface area of the sterile filter should be adapted to the batch size, unless otherwise justified; (4) process control for RNA content prior to dilution is important, particularly if several runs of TFF are performed in parallel with batch sizes
15. Data on verification of in-process test methods should be provided for assessment during Q1 2021.
16. In order to improve the control strategy, the MAH should provide results of the validation plan phase 2 of the rapid sterility test for assessment before implementation.
17. A risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D and Ph. Eur. monograph Pharmaceutical Preparations (2619). A summary of this risk assessment should be submitted. The risk assessment should cover all relevant elements and sources in accordance with the guideline. The summary must enable a quantitative comparison of observed or predicted levels with the PDE's given in the guideline. It should contain what is necessary to evaluate the appropriateness and completeness of the risk assessment, including any assumptions, calculations etc. made. The control strategy for elemental impurities should be justified based on the risk assessment.
18. The MAH should provide the protocol on preparation and qualification of future primary and working reference materials for finished product testing.
19. In order to provide further information regarding the stability of finished product, Results from photostability testing and temperature cycling studies of the finished product should be provided for assessment in Q1 2021.
20. The applicant should provide the 6 months stability data for the finished product process performance qualification batches for assessment as soon as they are available.
21. This applicant proposed change to the product information to indicate that up to 6 doses can

be delivered from the vial was not considered acceptable as no supporting data was provided. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses.

22. The MAH should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70 °C to -20 °C. In addition, the MAH should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8 °C as well as the possibilities to extend the claims for transport conditions at 2-8 °C.
23. The MAH should provide the results for assessment from the filter validation as soon as they are available.

2.3. Non-clinical aspects

GLP inspections

The pivotal toxicological studies are stated to be GLP compliant by the Applicant. There were some issues identified during the assessment with repeat-dose toxicity study #38166 regarding the documentation which have led to a study audit GLP inspection conducted by the local German GLP Compliance Monitoring Authority at the facility where the study was performed, in November 2020. All the answers to the issues were acknowledged by the CHMP. The Applicant gave also comments on these issues. In light of all the elements provided, the issues identified were considered resolved.

With regard to repeat-dose toxicity study #20GR142 the only major concern identified was resolved with the answers from the Applicant that were considered satisfactory by the CHMP.

2.3.1. Pharmacology

The pharmacology dossier is based on initial studies of the functionality of the BNT162b2 (V9) RNA-based product and the encoded SARS-CoV-2 P2 S protein as well as on supporting studies of SARS-CoV-2 P2 S protein structure. This is followed by characterisation of the humoral and cellular immune response in mouse and nonhuman primate upon immunization with BNT162b2 (V9) and ends up with a SARS-CoV-2 challenge study of BNT162b2 (V9) immunized nonhuman primates.

No secondary pharmacodynamic, safety pharmacology or pharmacodynamic drug interaction studies have been conducted with BNT162b2 due to the nature of the RNA-based vaccine product, which is according to applicable guidelines (WHO guideline on nonclinical evaluation of vaccines, WHO Technical Report Series, No. 927, 2005).

Mechanism of action

SARS-CoV-2 infects the body by the use of the Spike protein (S) to attach to specific cell surface receptors, of which the angiotensin converting enzyme 2 (ACE2) may constitute a major part, as recently suggested. In addition to the initial attachment to a host cell, the S protein is also responsible for viral envelope fusion with the host cell membrane resulting in genome release. Due to its indispensable role, the S protein is a major target of virus neutralizing antibodies and has become a key antigen for vaccine development. By immunisation with the modified RNA (modRNA) product BNT162b2, encoding for the S protein, the intention is to trigger a strong and relatively long-lasting production of high affinity virus neutralizing antibodies, which can act through blocking the S-protein and it's receptor-binding domain (RBD) interaction with host cell receptors but also by opsonisation mediated virus clearance. In addition, the immunisation with BNT162b2 is also intended to elicit a concomitant T cell response of the Th1 type, supporting the B cells responsible for the production of S-specific antibodies and cytotoxic T cells that kill virus infected cells.

The S protein is a trimeric class I fusion protein that exists in a metastable prefusion conformation before engaging with a target cell. BNT162b2 encodes a P2 mutant (P2 S) variant of S where two consecutive proline mutations have been introduced in order to lock the RBD in the prefusion conformation. In addition, BNT162b2 is nucleoside-modified by a substitution of 1-methyl-pseudouridine for uridine and thus its inherent adjuvant activity mediated by binding to innate immune sensors such as toll-like receptors (TLRs) 7 and 8, is dampened, but not abrogated. Furthermore, the structural elements of the vector backbones of the BNT162b2 are optimised for prolonged and strong translation of the antigen-encoding RNA.

The potency of the RNA vaccine is further optimised by encapsulation of the RNA into lipid nano particles (LNPs), which protects the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (i.m.) delivery. The functional and ionizable lipid, ALC-0315, is identified as the primary driver of delivery as it allows the LNPs to have a neutral charge in a physiological environment to facilitate internalization; the endosomal environment exhibits a positive charge and therefore triggers the translocation of RNA into the cytosol (Midoux & Pichon, 2015; Hassett et al, 2019; Patel et al, 2019); ALC-0159 is included in the formulation to provide a steric barrier to: 1) facilitate the control of particle size and homogeneity during manufacturing and product storage, and 2) regulate the association of plasma and proteins with the LNP surface. The composition of the LNPs may also affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity.

Administration of LNP-formulated RNA vaccines IM results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Primary pharmacodynamic studies

Primary pharmacodynamic studies in vitro

To confirm the functionality of the BNT162b2 (V9) RNA-based product, protein expression, transfection frequency from BNT162b2 and cell surface expression of the SARS-CoV-2 P2 S protein antigen was assessed. BNT162b2 (V9) transfection of HEK293T cells indicated SARS-CoV-2 P2 S was correctly expressed on the cell surface, as indicated by flow cytometry staining of non-permeabilized cells with an anti-S1 monoclonal antibody. In addition, the cellular localisation of expressed S1 protein was investigated. The S protein co-localized with an ER marker, as detected by immunofluorescence experiments in HEK293T cells expressing BNT162b2-RNA, suggesting the S protein is processed within the ER.

In a set of supportive studies, it was investigated whether BNT162b2 RNA encodes for an amino acid sequence that authentically express the ACE2 binding site (RBD). Recombinant P2 S was expressed from DNA encoding for the same amino acid sequence as BNT162b2 RNA encodes for. Flow cytometry staining with spike protein (S) binding agents, as human ACE2 and monoclonal antibodies known to bind to authentic S-protein all indicated an authentically presented P2 S protein and ACE2 binding site. Low nanomolar affinity of P2 S binding to ACE2 PD and B38 mAb was demonstrated with the use of biolayer Interferometry.

To further structurally characterize the P2 spike protein, a cryo-electron microscopy (cryoEM) investigation of purified P2 S, expressed from DNA, was conducted. The cryoEM revealed, according to

the Applicant, a particle population closely resembling the prefusion conformation of SARS-CoV-2 spike protein. By fitting a previously published atomic model on to a processed and refined cryoEM dataset, a rebuilt model was obtained showing good agreement with reported structures of prefusion full-length wild type S and its ectodomain with P2 mutations. In the prefusion state the RBD undergo hinge-like conformational movements and can either be in an "up" position (open for receptor binding) or in a "down" position (closed for receptor binding). Three-dimensional classification of the dataset showed a class of particles that was in the conformation one RBD 'up' and two RBD 'down". This partly open conformation represented 20.4% of the trimeric molecules. The remainder were in the all RBD 'down' conformation. Although potent neutralizing epitopes have been described when the RBD is in the "heads down" closed conformation, the "heads up" receptor accessible conformation exposes a potentially greater breadth of neutralizing antibody targets. It is concluded that antibodies to both the up and down conformations will potentially be formed upon immunisation with the P2 S encoding BNT162b2.

Primary pharmacodynamic studies in vivo

The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates. The choice and relevance of the mouse for pharmacological animal model studies was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Non-human primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. The selection of rats as the toxicology test species is consistent with the World Health Organization (WHO) guidance documents on nonclinical evaluation of vaccines (WHO, 2005). The documents recommend conducting vaccine toxicity studies in a species which mounts an immune response to the vaccine. The Wistar Han (WH) rat developed an antigen-specific immune response following BNT162b2 vaccination.

Balb/c, females were immunized IM on day 0 with 0.2, 1 or 5 µg RNA/animal of BNT162b2 (V9), or with buffer alone (n=8). Blood samples were collected on Days 7, 14, 21 and 28 after immunization. The IgG antibody response to SARS-CoV-2- RBD or S1 was analysed by ELISA. Immunization with BNT162b2 induced IgGs that bound to S1 and RBD, as detected by ELISA, and on day 28 after immunization showed a binding affinity of KD 12 nM or 0.99 nM (geometric mean) respectively, as detected by surface plasmon resonance.

To further characterise the antibody response to BNT162b2 and its potential capacity to reduce SARS-CoV-2 infections, a pseudo virus type neutralization assay (pVNT) was used as a surrogate of virus neutralization since studies with authentic SARS-CoV-2 requires a BSL3 containment. The pVNT was based on a recombinant replication-deficient vesicular stomatitis virus (VSV) vector that had been pseudotyped with SARS-CoV-2 S protein according to published protocols. A dose-dependent increases in SARS-CoV-2-S VSV pseudovirus neutralizing antibodies were observed in sera from BNT162b2-immunized mice. On day 14, the difference of the group treated with 5 µg RNA compared to the buffer control was statistically significant ($p = 0.0010$). On days 21 and 28, the differences of the groups treated with 1 µg and 5 µg BNT162b2 compared to the buffer control were statistically significant. The relevance of the pseudovirus assay for authentic SARS-CoV-2 was not discussed. For technical reasons, it was not possible to determine a ratio of neutralizing to non-neutralizing antibodies.

Immunisation of mice with BNT162b2 also induced IFN-γ secreting cells of both the CD4+ and CD8+ T-cell subsets. This was shown by ELISPOT after *ex vivo* re-stimulation of splenocytes with an S-protein overlapping peptide pool Day 28 after immunization. Cytokine profiling was also carried out by Multiplex analysis of cytokine release from the Day 28 Splenocytes. High levels of the Th1 cytokines IFNγ and IL-2 but minute amounts of the Th2 cytokines IL-4, IL-5 and IL-13 were detected after re-stimulation with S but not RBD overlapping peptide mix. The much higher immune cellular responses

elicited against the S1 protein compared to the RBD domain could be explained by the presence of significantly more T cell epitopes in the larger full-length S peptide mix (in addition, S1 covers the RBD domain). It should be emphasized that cellular immune reactivity is much more important against S1 than against the RBD domain, where neutralizing antibodies are more important to the latter. In addition, an elevated secretion of TNFα, GM-CSF, IL-1β, IL-12p70 and IL-18 was recorded after re-stimulation. In order to characterize the immunophenotype of B-and T-cells appearing in lymph nodes from mice immunized with BNT162b2 (V9), B- and T-cell subsets in draining lymph node cells were quantified by flow cytometry 12 days after immunization. Higher numbers of B cells were observed in the samples from mice that received BNT162b2 compared to controls. That included plasma cells, class switched IgG1- and IgG2a-positive B cells, and germinal centre B cells. T-cell counts were elevated, particularly numbers of T follicular helper (Tfh) cells, including subsets with ICOS upregulation, which play an essential role in the formation of germinal centres (Hutloff 2015).

In the nonhuman primate (rhesus macaques) studies, BNT162b2 (V9) was shown to be immunogenic after intramuscular administration. The serum concentrations of both S1-binding and the SARS-CoV-2 neutralizing antibody titres were at least an order of magnitude higher after BNT162b2 immunization of rhesus macaques than for the panel of SARS-CoV-2 convalescent human sera. In this study, total antibody response is measured using a luminex assay and results expressed on U/ml and for the neutralization assay results are expressed in VNT 50.

Antigen specific S-reactive T-cell response after BNT162b2 immunization of the macaques was measured by ELISPOT and ICS. While S-specific T cells were low to undetectable in naïve animals, strong IFNγ but minimal IL-4 ELISpot responses were detected after the second 30 or 100 µg dose of the BNT162b2. Intra cellular staining (ICS) confirmed that BNT162b2 immunization elicited strong S-specific IFNγ producing T cell responses, including a higher frequency of CD4+ T cells that produced IFNγ, IL-2, or TNF-alpha but a lower frequency of CD4+ cells that produce IL-4. An S-specific IFNγ producing CD8+ T cell response was also recorded.

A challenge study in rhesus macaques was conducted as nonclinical proof of concept (PoC). Rhesus macaques share a 100% homology with the human ACE2 sequence that interacts with the RBD of the S protein. BNT162b2 (V9) immunized macaques were challenged with SARS-CoV-2 intra nasally and intratracheally 55 days after the second immunization with BNT162b2. Rhesus macaques were immunized on days 0 and 21, in order to align with the clinical vaccination regimen. Some other COVID-19 vaccine candidates have different prime-boost intervals, such as 4 weeks for both ChAdOx1 (Graham et al., 2020) and mRNA-1273 (Corbett et al., 2020). At the time of challenge, SARS-CoV-2 neutralising titres ranged from 260 to 1,004 in the BNT162b2 (V9)-immunized animals. Neutralising titres were undetectable in animals from the control-immunized and sentinel groups. The presence of SARS-CoV-2 RNA was monitored by nasal and oropharyngeal (OP) swabs and bronchoalveolar lavage (BAL). Viral RNA was detected in BAL fluid from 2 of the 3 control-immunized macaques on Day 3 after challenge and from 1 of 3, on Day 6. At no time point sampled was viral RNA detected in BAL fluid from the BNT162b2 (V9)-immunized and SARS-CoV-2 challenged macaques. The difference in viral RNA detection in BAL fluid between BNT162b2-immunized and control-immunized rhesus macaques after challenge is statistically significant (p=0.0014). From control-immunized macaques, viral RNA was detected in nasal swabs obtained on Days 1, 3, and 6 after SARS-CoV-2 challenge; from BNT162b2 (V9)-immunized macaques, viral RNA was detected only in nasal swabs obtained on Day 1 after challenge and not in swabs obtained on Day 3 or subsequently. The pattern of viral RNA detection from OP swabs was similar to that for nasal swabs. No signs of viral RNA detected vaccine-elicited disease enhancement were observed. The viral RNA levels between control-immunized and BNT162b2-immunized animals after challenge were compared by a non-parametric analysis (Friedman's test), and the p-values are 0.0014 for BAL fluid, 0.2622 for nasal swabs, and 0.0007 for OP swabs.

Despite the presence of viral RNA in BAL fluid from challenged control animals, none of the challenged animals, immunized or control, showed clinical signs of illness (weight change, body temperature change, blood oxygen saturation and heart rate). The Applicant concluded, the absence of clinical signs in any of the challenged animals, immunised or control, despite the presence of viral RNA in BAL fluid from challenged control animals, indicates that the 2-4 year old male rhesus monkey challenge model appears to be an infection model, but not a clinical disease model. However, a further investigation by lung radiograph and computerized tomography (CT) was conducted. Radiographic evidence of pulmonary abnormality was observed in challenged controls but not in unchallenged sentinels nor in challenged BNT162b2-immunized animals except for a CT-score signal in 1 of 6 pre infection and 2 out of six at Day 10/EOP in BNT162b immunised animals. The CT score signal was at the same level as the control at Day 10/EOP. No radiographic evidence of vaccine-elicited enhanced disease was observed.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted with BNT162b2, which is acceptable to the CHMP.

Safety pharmacology studies

No safety pharmacology studies were conducted with BNT162b2. The Applicant refers to that they are not considered necessary according to the WHO guideline (WHO, 2005). In addition, no findings on vital organ functions have been recorded in the repeat dose toxicology studies. Thus, the absence of safety pharmacology studies is endorsed by the CHMP.

Pharmacodynamic drug interactions studies

No pharmacodynamics drug interaction studies were conducted with BNT162b2. This is agreeable to the CHMP.

2.3.2. Pharmacokinetics

The applicant has determined the pharmacokinetics of the two novel LNP excipients ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) in plasma and liver as well as their elimination and metabolism in rats. Furthermore, the Applicant has studied the biodistribution of the two novel lipids (in rats) and the biodistribution of a LNP-formulated surrogate luciferase RNA in mice (IV), as well as the biodistribution of a [^{3}H]-Labelled Lipid Nanoparticle-mRNA Formulation in rats (IM).

No traditional pharmacokinetic or biodistribution studies have been performed with the vaccine candidate BNT162b2.

In study PF-07302048_06Jul20_072424, the applicant has used a qualified LC-MS/MS method to support quantitation of the two novel LNP excipients. The bioanalysis methods appear to be adequately characterized and validated for use in the GLP studies.

PK studies with the two novel LNP-excipients ALC-0315 and ALC-0159:

Wistar Han rats were IV bolus injected with LNP formulated luciferase-encoding RNA at 1 mg/kg and ALC-0315 and ALC-0159 concentrations at 15,3 mg/kg and 1,96 mg/kg respectively. ALC-0315 and ALC-0159 levels in plasma, liver, urine and faeces were analysed by LC-MS/MS at different time-points up to 2-weeks.

ALC-0315 and ALC-0159 were rapidly cleared from plasma during the first 24 hours with an initial t½ of 1.62 and 1.72 h, respectively. 24 hours post-dosing, less than 1% of the maximum plasma concentrations remained. A slower clearance rate was observed after 24 hours with ALC-0315 and ALC-0159 terminal elimination t½ of 139 and 72.7 h, respectively.

Following plasma clearance, the liver appears to be to major organ to which ALC-0315 and ALC-0159 distribute. The applicant has estimated the percent of dose distributed to the liver to be ~60% for ALC-0315 and ~20% for ALC-0159. The observed liver distribution is consistent with the observations from the biodistribution study and the repeat-dose toxicology, both using IM administration.

For ALC-0315 (aminolipid), the maximum detected concentration in the liver (294 µg/g liver) was reached 3 hours after IV injection. ALC-0315 was eliminated slowly from the liver and after 2-weeks the concentration of ALC-0315 was still ~25% of the maximum concentration indicating that ALC-0315 would be eliminated from rat liver in approximately 6-weeks. For ALC-0159 (PEG-lipid), the maximum detected concentration in the liver (15.2 µg/g liver) was reached 30 minutes following IV injection. ALC-0159, was eliminated from the liver faster than ALC-0315 and after 2-weeks the concentration of ALC-0159 was only ~0,04% of the maximum detected concentration. The applicant was asked to discuss the long half-life of ALC-0315 and its effect, discussion on the comparison with patisiran, as well as the impact on the boosts and post treatment contraception duration. The applicant considered that there were no non-clinical safety issues based on the repeat dose toxicity studies at doses (on a mg/kg basis) much greater than administered to humans; this was acceptable to the CHMP.

Both patisaran lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives. According to the applicant, it is difficult to further contextualize the pharmacokinetic data and therefore to understand the safety of these molecules, beyond consideration of dose. There is a large dose differential between the human BNT162b2 dose and the dose used in the toxicity studies (300-1000x) which provides an acceptable safety margin.

Moreover, according to the Applicant given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. Finally, the applicant is of the opinion that these results support no requirements for contraception. The CHMP found this position agreeable.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159.

Biodistribution of a LNP-formulated luciferase surrogate reporter:

To determine the biodistribution of the LNP-formulated modRNA, the applicant did study distribution of the modRNA in two different non-GLP studies, in mice and rats, determined the biodistribution of a surrogate luciferase modRNA formulated with a LNP with identical lipid composition used in BNT162b2 (mouse study) or the biodistribution of a [3H]-Labelled Lipid Nanoparticle-mRNA Formulation (rat study).

The mouse study used three female BALB-c mice per group and luciferase protein expression was determined by *in vivo* bioluminescence readouts using an *In Vivo* Imaging System (IVIS) following injection of the luciferase substrate luciferine. The readouts were performed at 6h, 24h, 48h, 72h, 6d and 9d post IM injection (intended clinical route) in the right and left hind leg with each 1 µg (total of 2µg) of LNP-formulated luciferase RNA.

In vivo luciferase expression was detected at different timepoints at the injection sites and in the liver region indicating drainage to the liver. As expected with an mRNA product, the luciferase expression was transient and decreased over time. Luciferase signals at the injection sites, most likely reflecting distribution to the lymph nodes draining the injection sites, peaked 6h post injection with signals of

approximately 10 000 times of buffer control animals. The signal decreased slowly during the first 72 hours and after 6 and 9 days the signals were further weakened to approximately levels of 18 and 7 times the signals obtained from animals injected with buffer control.

The signals from the liver region peaked 6h post injection and decreased to background levels 48h after injection. The liver expression is also supportive of the data from the rat PK study and the findings in the rat repeat-dose toxicological study showing reversible liver vacuolation and increased γGGT levels.

The biodistribution was also studied in rats using radiolabeled LNP and luciferase modRNA (study 185350). The radiolabeling data, measuring distribution to blood, plasma and selected tissues, of IM injection of a single dose of 50 µg mRNA over a 48-hour period is considered more sensitive than the bioluminescence method and indicate a broader biodistribution pattern than was observed with bioluminescence. Over 48 hours, distribution from the injection site to most tissues occurred, with the majority of tissues exhibiting low levels of radioactivity.

Radioactivity was detected in most tissues from the first time point (0.25 h) and results support that injections site and the liver are the major sites of distribution. The greatest mean concentration was found remaining in the injection site at each time point in both sexes. Low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, distribution was mainly observed to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of radiolabeled LNP+modRNA outside the injection site was greatest in the liver (up to 21.5%) and was much less in spleen (≤1.1%), adrenal glands (≤0.1%) and ovaries (≤0.1%). The mean concentrations and tissue distribution pattern were broadly similar between the sexes. No evidence of vaccine-related macroscopic or microscopic findings were found in the ovaries in the repeat-dose toxicity studies (Study 38166 and Study 20GR142) and no effects on fertility were identified in the DART study.

Immunogenicity of a LNP formulated luciferase modRNA:

Activation of the innate immune system following IM injection of a LNP-formulated luciferase reporter RNA into mice was assessed in a Luminex-based multiplex assay were serum samples (day -1 (pre), 6 h and day 9) were tested for levels of the following chemokines and cytokines: MCP-1, MIP-1β, TNF-α, IFN-α, IFN- γ, IL-2, Il-6, IL-10, IL1-β, IP-10. The applicant tested 3 different LNPs, all formulated together with luciferase RNA. The results suggest that the LNP formulation used in BNT162b2 (LNP8) slightly increased levels of MCP-1, IL-6, and IP-10 at 6h post immunisation. All chemokine/cytokine levels dropped to background levels at day 9.

In addition to innate immune activation, LNP formulated luciferase modRNA was able to induce IFN-γ T-cell responses (when challenged with MHC I-specific luciferase peptide pools) measured in splenocytes isolated from the mice at day 9.The LNP formulated luciferase modRNA did not induce the formation of luciferase-specific IgGs as measured by ELISA.

In an additional hPBMC study (R-20-0357), overall, low levels of pro-inflammatory cytokines (TNF, IL-6, IFNγ, IL-1β) and low or medium levels of chemokines (IP-10, MIP-1β, MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. IP-10, MIP-1b, MCP-1 were seen to be increased among donors, because of transfection of antigen presenting cells after infection.

Metabolism of the two novel LNP-excipients ALC-0315 and ALC-0159:

Metabolism studies were conducted to evaluate the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid). No metabolic studies were performed with the modRNA or the other two lipids of the LNP. Overall, it seems as both ALC-0159 and ALC-0315 are metabolised by hydrolytic

metabolism of the amide or ester functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

The metabolism of the novel excipients, ALC-0159 and ALC-0315, were examined *in vitro* using blood, liver S9 fractions and hepatocytes, all from mouse, rat, monkey and human. The *in vivo* metabolism was examined in rat plasma, urine, faeces, and liver from a rat pharmacokinetics study where a luciferase-encoding modRNA formulated in an LNP was used.

Metabolism of ALC-0315 appears to occur via two sequential ester hydrolysis reactions, first yielding the monoester metabolite followed by the doubly de-esterified metabolite. The monoester metabolite was observed *in vitro* in rat blood, monkey S9 fraction, and *in vivo* in rat plasma and rat liver. The doubly de-esterified metabolite was observed *in vitro* in mouse and rat blood; monkey liver S9 fraction; and *in vivo* in rat plasma, urine, faeces and liver. Subsequent metabolism of the doubly de-esterified metabolite resulted in a glucuronide metabolite which was observed in urine only from the rat pharmacokinetics study. Additionally, 6-hexyldecanoic acid, the acid product of both hydrolysis reactions of ALC-0315, was identified *in vitro* in mouse and rat blood; mouse, rat, monkey and human hepatocytes; mouse, rat and human liver S9 fractions; and *in vivo* in rat plasma.

ALC-0315 was stable over 120 min (>93% remaining) in liver microsomes and S9 fractions and over 240 min (>93% remaining) in hepatocytes in all species and test systems.

The primary route of metabolism for ALC-0159 appears to involve amide bond hydrolysis yielding *N,N*-ditetradecylamine. This metabolite was identified in mouse and rat blood as well as hepatocytes and liver S9 from mouse, rat, monkey and human.

ALC-0159 was stable over 120 min (>82% remaining) in liver microsomes and S9 fractions and over 240 min (>87% remaining) in hepatocytes in all species and test systems.

Excretion of the two novel LNP-excipients ALC-0315 and ALC-0159:

Excretion of the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) was studied in the rat PK study. No excretion studies were performed with the modRNA or the other two lipids of the LNP which is considered acceptable by the CHMP.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159. Since almost no unchanged ALC-3015 was detected in urine or faeces, metabolism may play a bigger role in the elimination of ALC-0315 than ALC-0159.

2.3.3. Toxicology

The toxicological dossier for BNT162b2 is based on a total of three pivotal toxicological experimental studies; two repeat-dose toxicity rat studies and one DART fertility-EFD rat study. The test substance in the repeat-dose toxicity studies is BNT162b2 (100 µg of variant 8 in one study (study 38166) and 30 µg of the clinically relevant variant 9 in the second study (study 20GR142)), which consists of a modified RNA in a lipid nanoparticle (LNP) formulation. The differences between the variants are due to codon optimization. The LNP contains four excipients whereof two are considered novel (ALC-0315 and ALC-0159).

Repeat dose toxicity

The two general/repeat-dose toxicity studies involved IM exposure of Han Wistar rats to BNT162b2 for a total of 17 days (three weekly administrations) followed by three weeks of recovery. Overall, the

study designs only included a single experimental group each with a variant of BNT162b2 (V8 or V9 variant), with no dose-response assessment or specific experimental groups for the LNP alone or its novel excipients. No test substance-linked mortality or clinical signs were observed (except a slight increase [<1C] in body temperature). No ophthalmological and auditory effects were found. The animal model of choice, the rat, has not been assessed in the pharmacological dossier but a limited absorption/distribution study has been conducted in pharmacokinetics dossier. Immunogenicity was assessed in the toxicology studies.

Body weight and food intake: Exposure generated a slight reduction of absolute BW statistically significant at D9 (-6.8% to -11.3%; BNT162b2 V8) alternatively a weak body weight increase reduction [BNT162b2 v9]. No changes in food intake were observed.

Gross pathology and organ weights: At 100ug BNT162b2 V8 and 30ug BNT162b2 V9, the tissue at the injection site was thickened/enlarged with oedema and erythema at the end of exposure in a reversible manner. The spleen was enlarged (reversible) with up to 60% for both vaccine variants and doses. There was also an enlargement of the draining and inguinal lymph nodes at 100ug (BNT162b2 V8). Overall, there were signs of a significant immune response which is likely linked to the test substance. There was a trend of slightly enlarged liver in females at 100ug (BNT162b2 V8) but not at 30ug (BNT162b2 V9).

Histopathology: At 100ug BNT162b2 V8, there were observations of various inflammatory signs at the injection site (e.g. fibrosis, myofiber degeneration, oedema, subcutis inflammation and epidermis hyperplasia). Also, there was inflammation of the perineural tissue of the sciatic nerve and surrounding bone in most rats at d17. The bone marrow demonstrated increased cellularity and the lymph nodes showed plasmacytosis, inflammation and increased cellularity. The spleen demonstrated increased haematopoiesis in half the animals at d17. The liver showed hepatocellular periportal vacuolation at d17 (fully reversed during recovery) which may be related to hepatic clearance of ALC0315. Histopathology assessment of 30ug BNT162b2 V9 generated similar results as 100ug BNT162b2 V8 although not on as extensive level (possibly due to a lesser dose). Minimal to moderate inflammation and oedema was observed at the injection site (usually resolved after ~3d). There was minimal to moderate increased plasma cell cellularity in the lymph nodes and germinal center cellularity plus hematopoietic cell cellularity in the spleen at d17 (reversible at end of recovery). There was minimal increase cellularity in the bone marrow. Reversible vacuolisation in the liver was also observed.

The Applicant explained that peri-portal liver vacuolization was observed in both pivotal studies but are not related to any microscopic evidence of liver/biliary injury in animals (cellular hypertrophy, inflammation) nor any clinical data from Phase 1 study. Vacuoles are considered by the Applicant to be a result of ALC-0315 accumulation in liver and not PEG.

A novel finding at 30ug was minimal extra-capsular inflammation in the joints at d17.

Moreover, increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells does not provide additional information. The CHMP found this agreeable.

Immunogenicity: Treatment of rats with 100 ug BNT162b2 V8 generated SARS-CoV-2 neutralizing titers (based on a vesicular stomatitis virus (VSV)-based pseudovirus neutralization assay) and IgG antibodies against the S1 fragment and the RBD (based on ELISA) in serum samples. Treatment of

rats with 30 ug BNT162b2 V9 generated SARS-CoV-2 neutralizing antibodies (not a pseudovirus neutralization assay).

Haematology: At 30ug BNT162b2 V9 and 100ug BNT162b2 V8, there was a moderate to strong reduction of reticulocytes (48-74%, not specified for V9) coupled to lowered red cell mass parameters (RBC, HGB, and HCT). There was a moderate to strong increase (>100%) in large unclassified cells [LUC], neutrophils, eosinophils, basophils and fibrinogen that may be related to the inflammatory/immune response. The changes were reversible. No effects on coagulation were observed for V8 whereas a slight increase in fibrinogen was observed with V8 and V9.

Clinical pathology: A very strong but reversible increase (>100%) in pro-inflammatory acute phase proteins in the blood (A1AGP, A2M) was seen with both 30ug BNT162b2 V9 and 100ug BNT162b2 V8. Also, indicative of pro-inflammation, a slight to moderate reduced albumin/globulin ratio was seen for both variants. V8 (100ug) exposure generated increased levels of γGT (>200%) and increased γGT enzyme activity and increased AST levels (+ ~19%). V9 (30ug) exposure led to slight to moderate increases in AST and ALP levels (+20-100%), possible indicative of liver effects but no changes in γGT levels. There were no changes in cytokine levels (IFNγ, TNFalpha, Il-1b, Il6, Il-10) after 100ug V8 exposure (not measured for V9). For 100ug V8, there were no changes measured in urine whereas there was a slight-moderate reduction in pH for 30ug V9.

Genotoxicity

No genotoxicity studies have been provided. This is acceptable as the components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide molety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

Reproduction Toxicity

In the DART study, the test substances used were BNT162b1, BNT162b2 and BNT162b3, which were given to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day). The test substances were administered intramuscularly (IM) to F0 female Wistar rats 21 and 14 days before the start of mating (M-21 and M-14, respectively) and then on Gestation Day (GD) 9 and GD20, for a total of 4 doses. A subgroup was terminated at GD21 and another (litter) group was terminated at PND21. SARS-CoV-2 neutralizing antibody titers were found in the majority of females just prior to mating (M-14), in most females and foetuses at the end of gestation (GD21), and in most offspring at the end of lactation (PND21). There was transient reduced body weight gain and food consumption after each dose. No effects on the estrous cycle or fertility index were observed. There was an increase (~2x) of pre-implantation loss (9.77%, compared to control 4.09%) although this was within historical control data range (5.1%-11.5%). Among foetuses (from a total of n=21 dams/litters), there was a very low incidence of gastroschisis, mouth/jaw malformations, right sided aortic arch, and cervical vertebrae abnormalities, although these findings were within historical control data. Regarding skeletal findings, the exposed group had comparable to control group levels of presacral vertebral arches supernumerary lumbar ribs, supernumerary lumbar short ribs, caudal vertebrae number < 5). There were no signs of adverse effects on the postnatal

pups (terminated at PND21). It is noted that there is currently no available data on the placental transfer of BNT162b2. This information is reflected in section 5.3 of the SmPC.

Local Tolerance

No dedicated local tolerance studies have been conducted; however the assessment of local tolerance was performed in repeat-dose toxicity studies. At 100ug BNT162b2 V8, there was mostly slight to moderate oedemas but in some cases severe oedema. The severity increased with the 2nd and 3rd injections. The data for 30ug BNT162b2 V9 exposure indicated less severe but similar effects.

2.3.4. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100 Corr 2), due to their nature vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this Application for Marketing Authorisation, which is considered acceptable.

2.3.5. Discussion on non-clinical aspects

Pharmacology

The proposed medicinal product is composed of a modRNA formulated with functional and structural lipids forming lipid nano particles (LNPs), the latter having the purpose to protect the modRNA from degradation and enable transfection of the modRNA into host cells after IM injection. The composition of the LNPs is likely to affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity (see also toxicology below).

The general immune activating mode of action of LNP-formulated RNA vaccines have been described in the literature. The administration of LNP-formulated RNA results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Whether other cells than professional APCs may transiently express the vaccine derived spike protein and therefore from a theoretical point of view, as compared to SARS-CoV-2 infected cells, also could potentially be targets for previously primed spike protein reactive cytotoxic T cells, if present, is not known. However, no overt signs of such adverse pharmacological responses have been recorded in the repeat dose toxicity study or in the clinical trials. In the clinical trial, a second dose was administered to patients who had been immunologically primed by the first dose. Moreover, in the clinical trials it appeared around 270 patients that was shown to have been seropositive for SARS-COV-2 before vaccination. In these cases, the expression of the spike protein on host cells occurred in the presence of a primed immune response to the spike protein but no overt adverse pharmacological response has been observed. The low amount of vaccine product in a single dose may limit the distribution of modRNA/LNP mainly to the injection site and to migrating APCs. Due to the transient expression of the modRNA, no persistent expression is expected.

Regarding the structural and biophysical characterization of the modRNA, a schematic description shows that 5 different sequences are included in the BNT162b2, of which two being coding sequences.

Concerning the protein expression obtained from the V8 and V9 variants, specific immune responses (total IgG binding Ab + neutralizing Ab) were obtained at significant levels against the Spike S protein in animals with both variants (in mice and rats), indicating the efficiency of the *in vivo* expression of Spike S protein. An additional study was provided (R-20-0360) further demonstrating *in vitro* protein expression. Transfection efficiency, expression rate and cellular viability were analysed in HEK293T cells, upon transfection with different constructs (saRNA, uRNA, modRNA V8 and V9). HEK293T cells were efficiently transfected by both modRNA V8 and modRNA V9 with higher transfection rate for V9, but quite similar the expression rate by V8 and V9.

Although some of the structural and biophysical characterization of P2 S as a vaccine antigen has been provided, it was investigated in supportive studies based on P2S expressed from DNA and not the product modRNA. While it is not considered to be of critical importance for the assessment in this procedure, it still provides a scientific understanding supporting the nonclinical key studies of humoral and cellular immune response, including SARS-CoV-2 neutralizing antibodies, as well as SARS-CoV-2 challenge nonclinical PoC.

In-vivo pharmacodynamics: The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates and was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Nonhuman primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. This is accepted but a more in-depth discussion on the suitability of these pharmacological animal models have not been provided (e.g. susceptibility for SARS-CoV-2 infection and similarity to COVID 19 disease; potential bias for Th1- or Th2-skewed responses has been well characterized for certain mice strains). Only single immunisation was conducted in mice, as compared to the clinical 2-dose regimen, which was adequate since only characterization of the immune response, but no challenge study was carried out in mice. Also, no or limited attention to the induction of long-term memory responses nor immunogenicity and protection in aged animals has been paid. That being said, the induction of virus neutralizing antibodies in both mice (VSV-SARS-CoV-2 S) and primates (SARS-CoV-2) indicated that BNT162b2 immunization has the potential to induce neutralizing antibodies also in humans. Thus, vaccination with modRNA is expected to induce robust neutralising antibodies and a concomitant T cell response to achieve protective immunity.

In mice, the immune response was assessed by single immunization only. Taking the phenotyping of B and T cells in aggregate, the data indicates a concurrent induction of SARS-CoV-2 S-specific neutralizing antibody titers and a Th1-driven T-cell response by immunization with BNT162b2 (this was also seen in nonhuman primates).

Concerning the nonhuman primate (rhesus macaques) studies, the applicant considers the human convalescent serum panel as an assessable benchmark to judge the quality of the immune response to the vaccine; this is accepted by the CHMP.

Concerning the characterization of the T cell responses, the Applicant suggests the S-specific IFNγ producing T cell responses, including a high frequency of CD4+ T cells that produced IFNγ, IL-2, or TNF-α but a low frequency of CD4+ cells that produce IL-4, indicates a Th1-biased response occurred after the BNT162b2 (V9) immunization. This reasoning appears acceptable to the CHMP. The role of such a Th1 biased response was put in the context of antigen-specific T-cell responses playing an important role in generation of antigen-specific antibody response as well as in elimination of infected cells to mediate protection against disease.

When immunised macaques were challenged with SARS-CoV-2, a clear and statistically significant effect was observed on reduced presence of viral RNA in bronchoalveolar lavage (BAL) and oropharyngeal (OP) swabs. A clear effect was also recorded by blinded X ray scoring of the lungs. A

protective effect is also evident in the CT score Day 3 after challenge, however at Day 10/EOP, there was a CT signal in 2 out of six BNT162b immunized monkeys at the same level as observed in the control group. That signal is of unclear significance since also in 1 out of 6 pre infection BNT162b immunized animals a similar CT-score signal was observed. During this time period the SARS-CoV-2 neutralizing GMT in the BNT162b2-immunised rhesus macaques continued to decrease but remained above the GMT of a human convalescent serum panel.

In conclusion of the preclinical pharmacology, the presented data, including immunogenicity, triggering of neutralizing antibodies and Th1 response and reduced presence of viral RNA in challenged animals as well as radiological lung parameters, provide support for the vaccination approach. Due to species differences in the immune system between animal model species and humans, the conclusion whether this candidate vaccine will be sufficiently effective in humans needs to be established in clinical studies.

Pharmacokinetic

Pharmacokinetic (regarding the two novel LNP excipients): The two novel lipid excipients play different roles in the formulation and have different pharmacokinetics. It is worth to notice that the lipid displaying a persistent kinetic over time in liver is ALC-0315.

ALC-0159 is comprised of a polyethylene glycol (PEG) headgroup (~2000 M.Wt.) attached to hydrophobic carbon chains (ie, the lipid anchor). ALC-0159 is present in BNT162 at a low mol% (<2 mol%), and therefore dose, relative to the other lipids. PEGylated lipid can exchange out of the LNP after administration, thus allowing the desired binding of endogenous proteins (eg, Apolipoprotein E) and removing the steric barrier that would otherwise restrict interactions of the LNP with target cells and proteins.

ALC-0315 is an ionizable aminolipid in BNT162b2 and is the most important lipid component for efficient self-assembly and encapsulation of the mRNA within the LNP, and for providing successful delivery of mRNA into target cells.

The PEG-lipid (ALC-0159) is designed to largely exchange out of the LNP after administration and before uptake into target cells, whereas the aminolipid (ALC-0315) is critical to the efficient intracellular delivery of the mRNA through endosomal uptake and release and must remain with the LNP.

ALC-0159 is much more hydrophilic, in large part due to the presence of the PEG molecule which is known to be a strongly hydrophilic molecule (Ma et al, 1990). Due to the more hydrophilic and essential neutral nature of this molecule, ALC-0159 has a much lower affinity for tissues and relative to ALC-0315 there will be freer compound available for redistribution from tissue to plasma; thus, elimination will be more rapid.

The Applicant pointed out that during the course of the 2-week pharmacokinetic study, liver concentrations of ALC-0315 fell 4-fold from their maximum value indicating that 75% of the material delivered to the liver was eliminated over this two-week period.

ALC-0315 has no known biology. In the absence of this 'biological relevance' the applicant used an estimation of >95% elimination of ALC-0315 to represent the essential elimination from the body. The elimination half-life of ALC-0315 in the liver following IV administration in the rat is approximately 6-8 days. These data indicate that 95% elimination of ALC-0315 will occur approx. 30-40 days following final administration in the rat.

Based on the understanding of the process involved in the terminal half-life, redistribution from tissues into which the lipid nanoparticle is delivered, a similar half-life and time to 95% elimination in human is expected (Mahmood et al, 2010). Examination of the scaling of the comparable lipids (PEG2000-C-DMG, DLin-MC3-DMA) in patisiran indicates that the half-life of these lipids appears to scale with a value approaching the typically used exponent for half-life (0.25). If this is the case for ALC-0315 we may

expect a half-life approximating 20-30 days in human for ALC-0315 and 4-5 months for 95% elimination of the lipid (Mahmood et al, 2010).

Both lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives.

Given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. This is noted by the CHMP.

Biodistribution: Several literature reports indicate that LNP-formulated RNAs can distribute rather non-specifically to several organs such as spleen, heart, kidney, lung and brain.

In line with this, results from the newly transmitted study 185350, indicate a broader biodistribution pattern with low and measurable radioactivity in the ovaries and testes. Given the current absence of toxicity in the DART data, the absence of toxicological findings in gonads in the repeat-dose studies and that the radioactivity in the gonads were low (below 0,1% of total dose), the current data does not indicate it to be a safety concern. The relative high dose used in the rats (500x margin to human dose based on weight) also supports a low risk from distribution to the gonads in humans.

RNA stability and kinetics are not expected to be the same for all RNAs and are influenced by the nucleosides of the RNA and although expression of the full-length spike (S) protein is expected to follow similar kinetics of that of the luciferase with a transient expression fading over time, it cannot be excluded that differences in stability/persistence of the signal could differ between the luciferase protein and the spike (S) protein.

In an additional hPBMC study (R-20-0357), low levels of pro-inflammatory cytokines (TNF, IL-6, IFNγ, IL-1β) and low or medium levels of chemokines (IP-10, MIP-1β, MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. The Applicant underlines that no specific general trend in cytokine secretion can be observed, given variability among donors and based on the low numbers of donors in the experiment.

Toxicology

Although no extensive pharmacological assessment has been conducted in rat (only in mouse and non-human primate), the rat was used as a toxicological animal model in the repeat-dose toxicity studies. The positive neutralization assay results in the repeat-dose toxicity studies demonstrate that V8 and V9 generate an immune response in this species (i.e. SARS-CoV-2 antibodies), partially supporting the use of the rat as an animal model. Other SARS-CoV-2 immune responses in rat remain unclear. The immune responses, especially at the injection sites (e.g. oedema, erythema), seem to increase with each injection in the studies (n=3). There was a marked increase in acute phase proteins, fibrinogen and reduced albumin-globulin ratio (but no increase in cytokines with V8, unclear for V9). There was also a general increase in immune cells (LUC, neutrophils, eosinophils, basophils) and a decrease in red blood cell parameters (reticulocytes, RGB, HGB, HCT). The spleen was enlarged at both 30ug V9 and 100ug V9 and the draining and inguinal lymph nodes were enlarged mostly at 100ug (V8) but also in a few animals at 30ug (V9).

Systemic complement activation (which sometimes may be induced by liposomal drugs and biologicals and potentially result in hypersensitivity reactions) was not investigated as no signs indicative of such clinical manifestations were detected. An absence of dose-response designs in the studies increases the difficulty to interpret the effects. Overall, the V8 and V9 test substances invoked a strong but mostly reversible immune-linked response in rats after 17d exposure. Increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the

inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The Applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells would not provide additional information. The CHMP agreed with this position.

With regards to the vaccine components, only the whole formulation (modified RNA in LNPs) were used, so there is no toxicological data on the LNP alone or its specific novel excipients. The novel LNP components, these are not considered primarily as adjuvant substances.

No genotoxicity nor carcinogenicity studies have been provided. The components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

As the pharmacokinetic distribution studies in rat demonstrated that a relatively large proportion - second to the levels at the injection site - of the total dose distributes to the liver (up to 18%, and far more than levels seen in spleen [<1.1%], adrenal glands [<0.1%] and ovaries [<0.1%]). While there was no severe pathogenesis in liver, there were some reversible functional hepatic and/or biliary effects with V8 and V9 (enlarged liver, vacuolation, strongly increased γGT levels at >200% and activity, minor-moderate increase in levels of AST and ALP) which may be linked to the LNP. The γGT changes were not observed with 30ug V9, which may be due to variant differences and/or, more likely, a lower dose. The applicant is of the view that the vacuoles are a result of primarily ALC-0315 accumulation in liver. It can be noted that ALC-0159 needs to be lost from the surface of the LNP to facilitate efficient uptake into target cells. At the same time, ALC-0315 is present in the LNP at a high mol% (50 mol%) relative to the other lipids in the BNT162 vaccine, suggesting that this lipid is more likely to be present within the cells (and possibly in the vacuoles).

The assessment of the data available as regards to the DART study shows that there is no clear adverse signs on fertility and early embryogenesis effects. There were no effects on the oestrous cycle in dams but there was an ~2x increase in pre-implantation loss (~9.77% vs 4.1% in controls) but these effects are within historical control data (5.1% to 11.5%) so these findings do not raise any specific concern. It can be noted that the choice of rat as an DART animal model is supported by means of the repeat-dose toxicity rat studies which demonstrates an immune response to the vaccine candidates [V8 and V9] and the publication of Bowman et al (2013; PUBMED ID [PMID] 24391099) that reports that foetal-maternal IgG ratios are relatively low during organogenesis but that these ratios approach 1 by the end of gestation in both rat and human.

2.3.6. Conclusion on the non-clinical aspects

The applicant sufficiently addressed other concerns raised to be granted MA from a non-clinical perspective.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

Some rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher exposure in rats due to body weight differences) developed some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) which is consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible. These findings are described in SmPC section 5.3.

As per guidance, no genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential. This is acceptable to the CHMP.

Finally, the combined fertility and developmental toxicity study showed that SARS-CoV-2 neutralising antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, gestation, or embryo-foetal or offspring development up to weaning. The CHMP noted that no data are available on vaccine placental transfer or excretion in milk.

2.4. Clinical aspects

2.4.1. Introduction

Pfizer and BioNTech have developed a vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a FIH study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study.

Phase 1/2 Study BNT162-01

Study BNT162-01 is the ongoing, FIH, Phase 1 dose level-finding study, in which healthy adults 18 to 55 years of age all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. The protocol was later amended to allow inclusion of older adult participants up to 85 years of age. The available Phase 1 safety and immunogenicity data for adults 18 to 55 years of age are reported in this application. Multiple vaccine candidates are being evaluated in this study. For each vaccine candidate, participants received escalating dose levels (N=12 per dose level) with progression to subsequent dose levels based on recommendation from a Sponsor Safety Review Committee (SRC).

Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 pivotal study for registration. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study planning to enrol ~44,000 participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. In Phase 1, two age groups were studied separately, younger participants (18 to 55 years of age) and older participants (65 to 85 years of age). The study population includes male and female participants deemed healthy as determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with high risk of exposure to SARS-CoV-2 infection due to exposure in the workplace and/or medical conditions that represent risk factors, clinically important prior illness or laboratory abnormalities, serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by polymerase chain reaction (PCR).

GCP

The Applicant claimed that the Clinical trials included in the application were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In addition, to seek further reassurance of the GCP compliance of the studies included in this dossier, in the context of the COVID-19 pandemic, EMA gathered additional information as indicated below from EU and non-EU regulatory authorities, and shared them with the CHMP to be considered in the assessment:

- a full inspection report from GCP inspection by Regierungspräsidium Karlsruhe and Paul-Ehrlich-Institut conducted at one of the investigator sites and at a CRO in Germany for the study BNT 162-01;
- Establishment Inspection Reports from GCP inspection by Food and Drug Administrations (USA Regulatory Authority) of six investigator sites in USA for study C4591001 (BNT 162-02);
- A full inspection Report and the summaries of the outcome from two GCP inspections by the National Administration of Drugs, Foods and Medical Devices (Argentinian Regulatory Authority) conducted at the single site located in Argentina for the study C4591001(BNT 162-02).

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

- Tabular overview of clinical studies

Table 1 Overview of the Clinical Development

Sponsor	Study Number (Status)	Phase Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech	BNT162-01 (ongoing)	Phase 1/2 randomized, open-label, dose-escalation, first-in-human	BNT162b2 (1, 3, 10, 20, 30 µg)	Phase 1: 60	Adults (18-55 years of age)
BioNTech (Pfizer)	C4591001 (ongoing)	Phase 1/2/3 randomized, observer-blind, placebo-control	Phase 1: BNT162b2 (10, 20, 30 µg) Placebo	Phase 1: 90 randomized 4:1 (within each dose/age group)	Phase 1: Adults (18-55 years of age, 65-85 years of age)
			Phase 2: BNT162b2 (30 µg) Placebo	Phase 2: 360 randomized 1:1	Phase 2: Adults (18-55 years of age, 65-85 years of age)
			Phase 3: BNT162b2 (30 µg) Placebo	Phase 3: ~44,000 randomized 1:1 (includes 360 in Phase 2)	Phase 3: Adolescents, Adults (12-15 years of age, 16-55 years of age, >55 years of age)

Note: study information relevant to the scope of data presented in this application are summarized in this table.

Table 2 Overview of the pivotal phase 3 study

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Diagnosis Incl. criteria	Primary Endpoint
C4591001	131 United States 9 Turkey 6 Germany 4 South Africa 2 Brazil 1 Argentina.	randomized, multinational, placebo-controlled, observer-blind,	2 doses of 30 µg given 21 days apart	Primary: To evaluate the efficacy of BNT162b2 against confirmed severe COVID-19 occurring from 7 and 14 days after the 2nd dose in participants with and without evidence of infection before vaccination	Healthy volunteers at risk of COVID-19	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection

2.4.2. Pharmacokinetics

Not applicable.

2.4.3. Pharmacodynamics

Mechanism of action

The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Immunogenicity studies

For vaccines, pharmacodynamics relates to investigation of immunogenicity. The available data were generated from the phase 1/2 study BNT162-01 conducted in Germany, and from the phase 1 and 2 parts of the phase 1/2/3 study C4591001, conducted in the USA (later phases were multinational). Both studies were designed to choose the optimal vaccine candidate and an appropriate dose and schedule for further studies. Among the four prophylactic SARS-CoV-2 RNA vaccines initially tested the following two candidates were selected for further development:

BNT162b1: RNA-lipid nanoparticle (LNP) vaccine containing nucleoside-modified messenger ribonucleic acid (modRNA) that encodes the RBD (receptor-binding domain)

BNT162b2: RNA-LNP vaccine containing modRNA that encodes SARS-CoV-2 full-length, P2 mutant (see section 2.2.2), prefusion spike glycoprotein (P2 S).

Key features of the two studies are summarised in the below table.

Study id	BNT162-01	C4591001
Title	A multi-site, Phase 1/2, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using	A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine

	different dosing regimens in healthy adults	Candidates Against COVID-19 in Healthy Individuals
Design	This is an open-label, multi-site, Phase 1/2, 2-part, dose-escalation study. Part A of the study includes the first in human dose and dose ranging groups in healthy adults (aged 18 to 85yrs).	This is a Phase 1/2/3, randomized, multinational, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals. The study consists of 2 parts: Phase 1 to identify preferred vaccine candidate(s) and dose level(s); and Phase 2/3 as an expanded cohort and efficacy part.
Immunogenicity objectives	To describe the immune response in healthy adults after dose 1 only or after both dose 1 and dose 2 measured by a functional antibody titre	To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses
Study population	Healthy adults aged 18 to 55yrs BNT162b1: N=84 (12/group) BNT162b2: N=60 (12/group) Healthy adults aged 56-85 yrs BNT162b1: N=36 (12/group) BNT162b2: N=36 (12/group)	Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive Phase 1 comprised 15 participants (randomization ratio of 4:1 so that 12 received active vaccine and 3 received placebo) per group; 13 vaccine groups were studied, corresponding to a total of 195 participants (the 100 µg dose was only used in the younger adult cohort)
IMP and dose level	BNT162b1: 1µg, 3µg, 10µg, 20µg, 30µg, 50µg, and 60µg. BNT162b2: 1µg, 3µg, 10µg, 20µg, 30µg	BNT162b1: 10 µg, 20 µg, 30µg, 100 µg BNT162b2: 10µg, 20µg, 30µg Placebo: normal saline
Dosing frequency	Two injections ~21d apart	Two injections ~21d apart
Immunogenicity endpoints	Virus neutralization test (VNT). Antibody binding assay, CMI assays, e.g. ELISpot and intracellular cytokine staining (ICS).	SARS-CoV-2 neutralization assay S1-binding IgG level assay RBD-binding IgG level assay N- binding antibody assay

Endpoints and Assays used to evaluate immunogenicity

In Study BNT162-01, immunogenicity was evaluated in Phase 1 using a SARS-CoV-2 serum neutralization assay to determine neutralizing titres and the fold rise in SARS-CoV-2 serum neutralizing titres. Immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1 (Day 8); and at Day 22 (before Dose 2) and 7 days, 14 days, and 21 days after Dose 2. Only qualified assays were used. In addition, T cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from

whole blood samples of vaccinated Phase 1 participants were evaluated by enzyme-linked immunospot (ELISPOT) and intracellular cytokine staining visualized with fluorescence activated cell sorting (FACS). Blood samples were collected from study participants prior to the first vaccine dose and on Day 29 (7 days) after the second vaccine dose. Assessments included cytokines associated with Th1 responses such as IFNγ and IL-2 and those associated with Th2 responses such as IL-4, to analyse the induction of balanced versus Th1-dominant or Th2-dominant immune responses.

In Study C4591001, immunogenicity was evaluated in Phase 1 and Phase 2 using a SARS-CoV-2 serum neutralization assay to determine titres and a SARS-CoV-2 RBD- or S1-binding IgG direct Luminex immunoassay to determine antibody binding levels. Fold rises were assessed also. Only qualified assays were used. In Phase 1, immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1; and at Day 21 (before Dose 2) and 7 days, 14 days, and 1 month after Dose 2. Data were summarized for each dose level and age group. In Phase 2, immunogenicity was assessed at Day 1 (before Dose 1) and 1 month after Dose 2. Data were summarized for each age strata group and by evidence of prior SARS-CoV-2 infection at baseline per NAAT (PCR) or N-binding IgG assay. To facilitate interpretation of immunogenicity data generated in Study C4591001, a human convalescent serum (HCS) panel was obtained from Sanguine Biosciences (Sherman Oaks, CA), MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY). The 38 sera in the panel were collected from SARS-CoV-2 infected or COVID-19 diagnosed individuals 18 to 83 years of age ≥14 days after PCR-confirmed diagnosis at a time when they were asymptomatic. The serum donors had predominantly had symptomatic infections (35 of 38) including 1 who had been hospitalized. In Phase 3, exploratory immunogenicity assessments are planned at time points up to 24 months, to be reported at a later time.

These are the immunogenicity assays that were used in clinical trials:

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 S1-binding IgG in Human Serum

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 RBD-binding IgG in Human Serum

Roche Elecsys SARS-CoV-2 N Binding Antibody Assay

mNeonGreen SARS-CoV-2 Microneutralization Assay

ELISpot Assay

Intracellular Cytokine Staining (ICS) for BNT162b1 and BNT162b2

The SARS-CoV-2 Wuhan-Hu-1 isolate spike glycoprotein (GenBank accession # QHD43416.1) is the reference sequence for the recombinant S1 and RBD proteins used in the Luminex assays. The SARS-CoV-2 neutralisation assay used a previously described strain of SARS-CoV-2 (USA_WA1/2020).

Study BNT162-01

Immunogenicity - functional antibody responses (secondary objectives)

Functional antibody titre data are available up until Day 43 for younger adults (18 to 55 yrs) dosed with 1, 10, 30, 50, and 60 µg BNT162b1 on Days 1 (all dose levels) and 22 (all dose levels except 60 µg) (n=12 per group). Data are available for the 10 and 30 µg up until Day 50 for younger adults dosed with 1, 10, 20, and 30 µg BNT162b2 on Days 1 and 22 (dose level 1 µg, n=9; dose levels 10, 20, and 30 µg, n=12).

Virus neutralizing antibody GMTs for participants aged 18 to 55 years after dosing with BNT162b1, are shown in Figure 3. On Day 22, at 21 d after the first dose, virus neutralizing antibody GMTs had increased in a dose-dependent manner for all dose groups. At 7 d after the second dose (Day 29), neutralizing GMTs showed a strong, dose level dependent booster response. In the 60 µg dose group,

which was only dosed once, neutralizing GMTs remained at a lower level, indicating that a booster dose is necessary to increase functional antibody titres.

On Day 43 (21 d after the second dose of BNT162b1), neutralizing GMTs decreased (with exception of the 1 µg dose level). Day 43 virus neutralizing GMTs were 0.7-fold (1 µg) to 3.6-fold (50 µg) those of a COVID-19 HCS panel.

The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs at least 14 d after confirmed diagnosis and at a time when the individuals were asymptomatic.

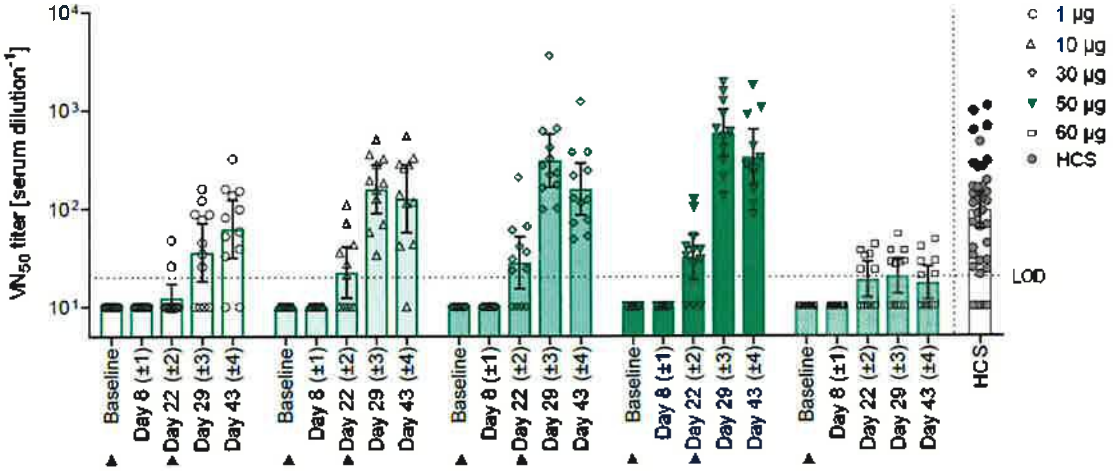


Figure 3: BNT162b1 – Functional 50% SARS-CoV-2 neutralizing antibody titers (VN50) – IMM

VN_{50} titers with 95% confidence intervals are shown for younger participants (aged 18 to 55 years) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the LOD. IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum

For virus neutralizing antibody GMTs for participants aged 18 to 55 yrs after dosing with BNT162b2, see Figure 4. Participants dosed with BNT162b2 showed a strong IMP-induced antibody response. Virus neutralizing GMTs were detected at 21 d after Dose 1 (Day 22) and had increased substantially in younger participants (aged 18 to 55 yrs) immunized with ≥3 µg BNT162b2, and older participants (aged 56 to 85 yrs) immunized with 20 µg BNT162b2 by 7 d after Dose 2 (Day 29). Day 29 virus neutralizing GMTs were comparable between the younger and older adult in the 20 µg dose level cohorts. The lowest tested dose of 1 µg BNT162b2 elicited only a minimal neutralizing response in participants aged 18 to 55 yrs.

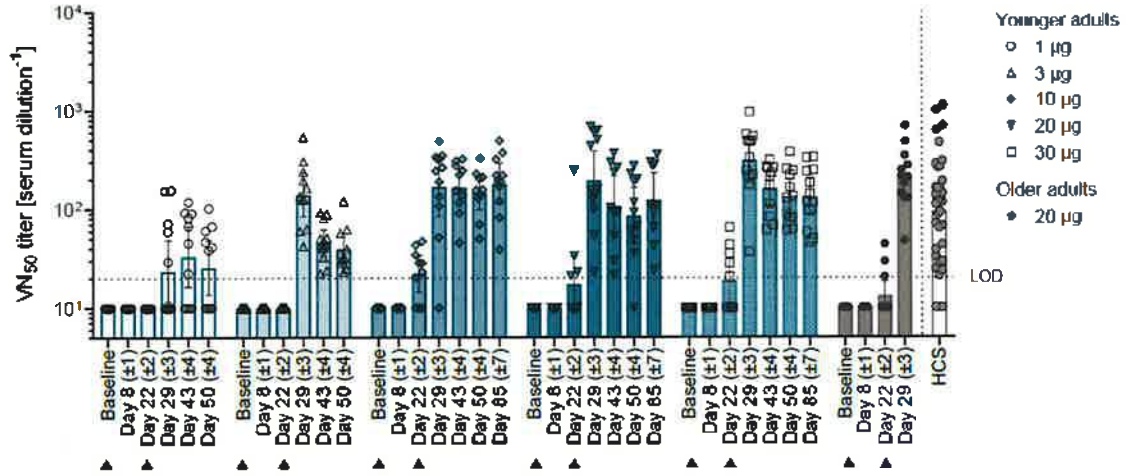
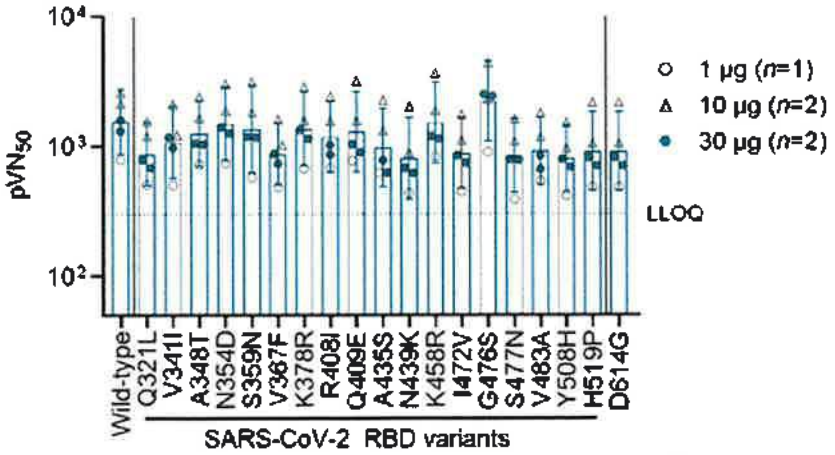


Figure 4: BNT162b2 – Functional 50% SARS-CoV-2 neutralizing antibody titres (VN50) – IMM
VN50 titres with 95% confidence intervals are shown for younger adults (aged 18 to 55 years) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and older adults (aged 56 to 85 yrs) immunized with 20 µg BNT162b2. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the LOD.
IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum.

Neutralisation of different spike protein mutants

Different pseudoviruses including RBD sequence variants have been tested in a pseudovirus neutralization assay with sera from BNT162b1-and BNT162b2-immunized participants in the BNT162-01 study. Efficient neutralization of spike protein mutants was observed with sera from BNT162b1- and BNT162b2-immunized participants demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies.



BNT162b2-induced virus neutralization titers with pseudovirus 50% neutralization titers (pVNT50) across a pseudovirus panel with 19 SARS-CoV-2 spike protein variants including 18 RBD mutants and the dominant spike protein variant D614G. LLOQ = Lower level of quantification (at 300). Data shown as group (total n=5) GMT with 95% CI.

Cell mediated immunity (CMI)

CMI were measured in terms of IFNγ- producing CD4+ and CD8+ T cells by ELISpot. Both vaccine candidates elicited clear responses (baseline vs post-dose 2). Further characterisation was determined using intracellular cytokine staining for Th1 cytokines (IFNγ, IL-2) and Th2 cytokines (IL-4). Both vaccine candidates stimulated predominantly Th1 responses, both in CD4 and CD8 T cells.

Study C4591001

Methods

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations. Phase 1 and Phase 2 data were reported as the following, for SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-binding and RBD-binding IgG concentrations:

- geometric mean titers/concentrations (GMTs/GMCs)
- geometric mean-fold rise (GMFR)
- geometric mean ratio (GMR) (for Phase 1 only)
- proportions of participants with ≥4-fold rise (for Phase 1 only)
- antibody titers/levels at defined thresholds (for Phase 2 only)

For immunogenicity results of SARS-CoV-2 serum neutralizing titers and S1- or RBD-binding IgG concentrations, GMTs or GMCs were computed with associated 95% CIs.

The GMFR was calculated by exponentiating the mean of the difference of logarithm transformed assay results: (later time point) – (earlier time point) with two-sided CIs. The GMR was calculated as the mean of the difference of logarithm transformed assay results: (SARS-CoV-2 serum neutralizing titers) – (SARS-CoV-2 anti-S binding antibody) for each participant, then exponentiating the mean, with two-sided CIs.

Results

The study set out to evaluate 2 SARS-CoV-2 RNA vaccine candidates, as a 2-dose (separated by 21 days) schedule, at different dose levels (BNT162b1: 10, 20, 30, and 100 µg, BNT162b2: 10, 20, and 30 µg) and in different age groups (18 55 y; 65-85 y), to select a vaccine and dose level for further testing in Phase 2/3. Cut-off date: 24-Aug-2020 (1 month post-dose 2 = D52).

Immunogenicity results are available for both adult age groups up to 1 month post-Dose 2 for the BNT162b1 and BNT162b2 vaccine candidates at the 10-µg, 20-µg, and 30-µg dose levels, and up to 7 weeks after Dose 1 of BNT162b1 at the 100-µg dose level (younger age group only).

Results for the 7 days after Dose 1 time point are only analysed and presented in the younger age group (18 to 55 years of age) for 10 µg and 30 µg BNT162b1.

Immunogenicity results SARS-CoV-2 Neutralizing Titres

BNT162b1

In the younger age group, SARS-CoV-2 50% neutralizing GMTs modestly increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b1 (Figure 5).

Generally similar trends were observed in the older age group, with higher GMTs observed in the 20-µg and 30-µg dose groups of BNT162b1 compared to the 10-µg dose group (Figure 6). In the older age

group, the SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.

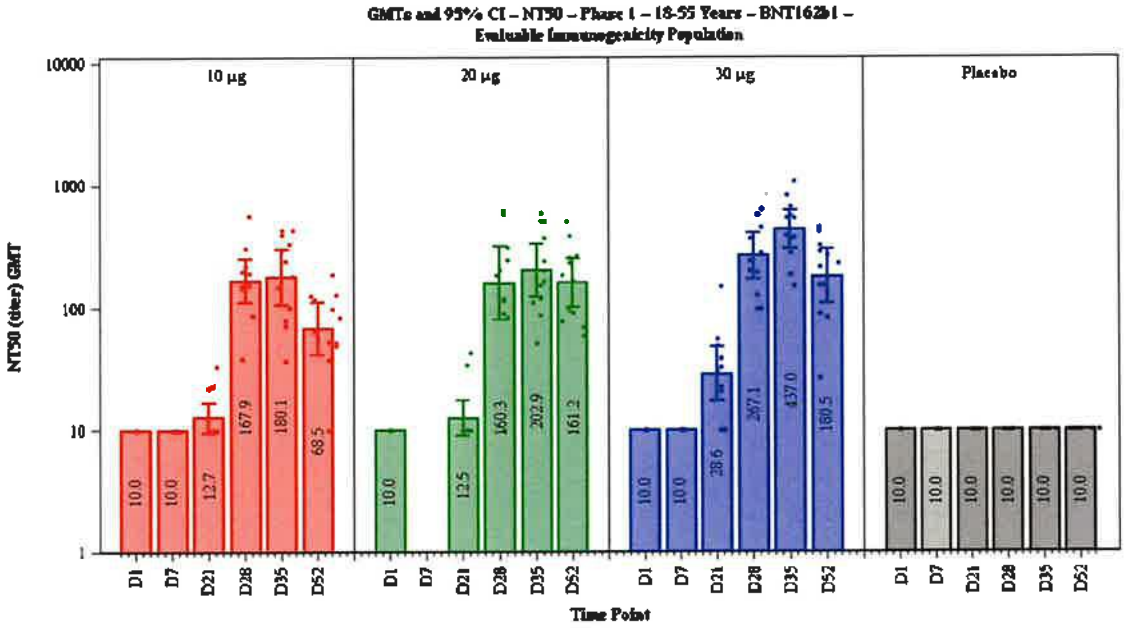


Figure 5. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

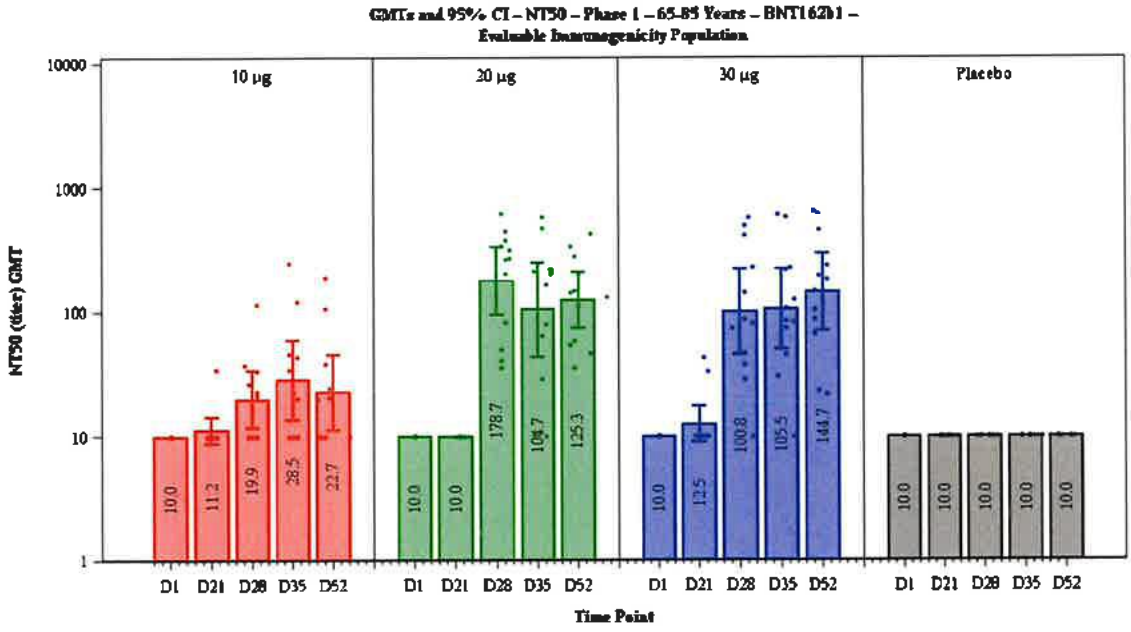
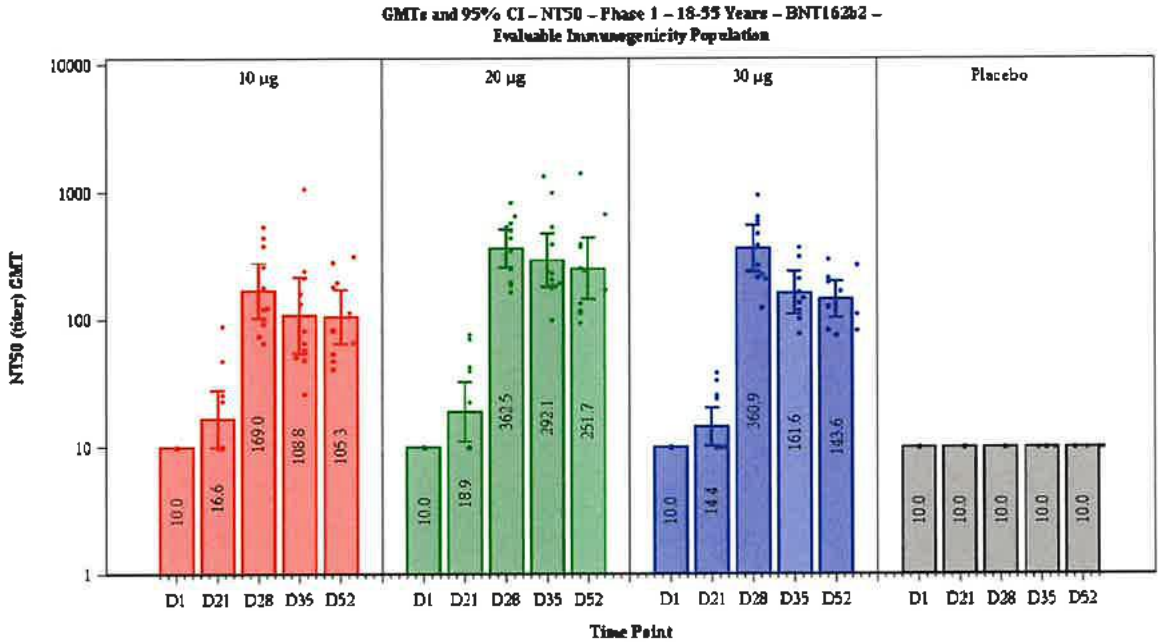


Figure 6. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart– 65-85 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

BNT162b2

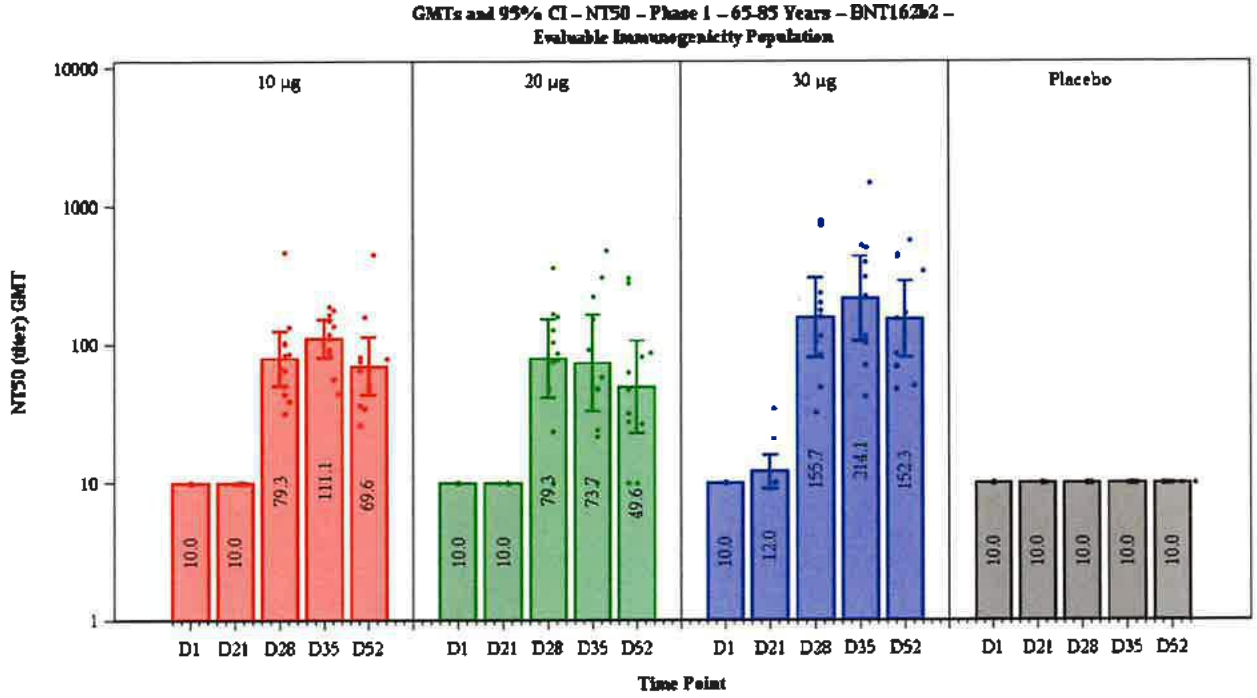
In the younger age group, SARS-CoV-2 50% neutralizing GMTs increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b2 (Figure 7).

Similar trends were generally observed in the older age group, with higher GMTs observed in the 30-µg dose groups compared to the 20-µg and 10-µg dose groups (Figure 8). In the older age group, SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
Note: Dots present individual antibody levels
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: advs Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001_IA_P1_Serology/advs_f002_sars_50_18_b2_p1

Figure 7. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_65_b2_p1

Figure 8. Geometric Mean Titres and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Evaluable Immunogenicity Population

2.4.4. Discussion on clinical pharmacology

The choice and dose of vaccine candidate was based on the results of two clinical phase I studies. Immune responses and safety of the two candidates were studied in both studies. The immune responses in terms of neutralising antibody responses clearly demonstrated that two doses resulted in increased geometric mean titres (GMTs) compared to responses after only the first dose. Thus, in the absence of a serological correlate of protection, these data supported that two doses would be needed in adults. The responses were numerically higher in higher dose groups compared to lower doses but did not substantially differ between 10ug and 30ug. The neutralising antibody responses between the two vaccine candidates are considered similar although no formal comparison was made. The responses to the vaccines were higher compared to a pool of human convalescent sera in study BNT162-001. In both studies subjects 55 years of age and older were included as well as younger adults. The responses in elderly were lower compared to younger adults, but the difference is likely of no clinical relevance, also considering the delayed peak.

For BNT162b1 and BNT162b2, the S1- and RBD-binding IgG kinetics were comparable to the kinetics of neutralizing antibodies, with lower IgG concentrations in older age group than in younger age group.

Further evaluation of antibody persistence is ongoing. Neutralizing antibody titres will be followed until the end of 162 days post-dose 2 for study BNT162-01 and up to 2-years for study C459001. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation).

Immune responses induced by the vaccine against emerging circulating strains of SARS-CoV-2 will be also be investigated. Effectiveness studies included in the RMP will be important to understand the performance of the vaccine in case of e.g. mutating variants.

Efficient neutralization of spike protein mutants including RBD sequence variants was observed with sera from vaccine-immunized study BNT162-01 participants, demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies. This may be important to consider when facing emerging variants with mutations in the spike proteins, e.g. the UK variant, as the vaccine might still be able to confer sufficient cross-neutralisation.

Further characterisation of immune responses was included in study BNT162-001. Cellular immune responses were demonstrated in terms of IFNγ-producing CD4 and CD8 T cells. In addition, a clear Th1-polarised response, i.e. IFNγ/IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED. For the 30 µg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults, whereas for the 30 µg dose cohort vaccinated with BNT162b1, RBD-specific IL-2 producing CD4+ and CD8+ T cells were reduced in older adults.

2.4.5. Conclusions on clinical pharmacology

The immune response data overall support the choice of vaccine candidate, BNT162b2, and the choice of a 2-dose schedule of 30 µg. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation), including data on persistence of immune responses.

2.5. Clinical efficacy

2.5.1. Dose response study

See section 2.4.3.

2.5.2. Main study

Title of study

Study C4951001: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Methods

Study Participants

Main Inclusion criteria:

- Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3) at randomization.
- Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks

before enrolment, could be included. Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfil the criteria specified in the protocol.

- Phase 2/3 only: Participants who, in the judgment of the investigator, were at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).
- Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent

Exclusion criteria:

- Other medical or psychiatric condition including recent or active suicidal ideation/behaviour or laboratory abnormality that increased the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention.
- Receipt of medications intended to prevent COVID-19.
- Previous clinical or microbiological diagnosis of COVID-19.
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding.
- Previous vaccination with any coronavirus vaccine.
- Individuals who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids were administered short term (<14 days) for treatment of an acute illness, participants should not have been enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.
- Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation
- Previous participation in other studies involving study intervention containing lipid nanoparticles.

Treatments

The vaccine candidate selected for Phase 2/3 evaluation was BNT162b2 at a dose of 30 µg. In phase 2/3 the participants were randomized 1:1 to receive vaccine or placebo, normal saline (0.9% sodium chloride solution for injection). The injection was intramuscular for both vaccine and the placebo.

Available safety, efficacy and immunogenicity data pertain to vaccine made according with the manufacturing process employed for clinical trial batches.

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply (commercial process) will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. Data are expected in February 2021. See the Quality section regarding comparability of clinical lots and commercial lots.

Objectives

The outcomes of the primary efficacy objectives were included in the Clinical Study Report submitted in this application. Results of the secondary objectives are expected during 2021.

Primary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination

Primary safety objectives

- To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)
- To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3
- To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3

Secondary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination

- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination.

Secondary immunogenicity objectives

- To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age (data not included in this report)

Exploratory objectives

- To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination
- To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study
- To describe the serological responses to the BNT vaccine candidate in cases of:
  - Confirmed COVID-19
  - Confirmed severe COVID-19
  - SARS-CoV-2 infection without confirmed COVID-19
- To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease
- To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by two different manufacturing processes (see under Treatment).

Outcomes/endpoints

Immunogenicity

See pharmacodynamics section for description of immunological methods used in phase 1 and 2 of this study. The same methods are used also in phase 3, but results are not yet available.

Primary Efficacy Endpoints

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Secondary Efficacy Endpoints

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2.

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

COVID-19 Case Definitions

Participants who developed any potential COVID-19 symptoms were to contact the site immediately and, if confirmed, to participate in an in-person or telehealth visit as soon as possible (within 3 days of symptom onset and at the latest 4 days after symptom resolution). At the visit (or prior to the visit, if a self-swab was used), investigators were to collect clinical information and results from local standard-of-care tests sufficient to confirm a COVID-19 diagnosis. Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a validated reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA) to detect SARS-CoV-2. If the evaluation was conducted by telehealth, the participant was to self-collect a nasal swab and ship for assessment at the central laboratory. A local nucleic acid amplification test (NAAT) result was only acceptable if it met protocol specified criteria and if a central laboratory result was not available.

Two definitions of SARS-CoV-2 related cases, and SARS-CoV-2 related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

Confirmed COVID-19 (defined for FDA guidance): presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhoea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC:

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2<300mm Hg);

- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

In addition, evidence of prior infection was determined by virological testing via NAAT on mid-turbinate swab and serological testing for IgG to the SARS-CoV-2 N-antigen. A serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result.

In addition, prior infection with SARS-CoV-2 was assessed also at Dose 2 (NAAT) and is being evaluated for up to 24 months. The purpose is to assess persistence of efficacy, explore efficacy against asymptomatic SARS-CoV-2 infections, and ensure safety in both seronegative and seropositive participants.

Sample size

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

Randomisation and Blinding (masking)

Allocation of participants to vaccine groups were performed through the use of an IRT system (IWR). Participants were randomised 1:1 to active vaccine or placebo.

The trial included participants ≥12 years of age, stratified as follows: 12 to 15, 16 to 55 years or >56 years. It was intended that a minimum of 40% of participants were to be enrolled in the >56-year stratum.

The study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments.

Exceptions to blinding for e.g. DMC activities were described and found acceptable.

Efficacy Analysis Methods

During Phase 2/3, interim analyses were pre-specified in the protocol to be conducted after accrual of at least 62, 92, and 120 evaluable COVID-19 cases, where overwhelming efficacy could be declared if the primary endpoint was met with a posterior probability that the true VE is >30% (i.e., Pr[VE >30%|data] >99.5% at an interim analysis or >98.6% at the final analysis). The success threshold for each interim analysis was calibrated to protect overall type I error at 2.5%. Futility was also assessed, and the study could be stopped for lack of benefit if the predicted probability of demonstrating vaccine efficacy at the final analysis was <5% at any of the first 2 planned interim analyses. Efficacy and futility boundaries were applied in a nonbinding way. The calculation of posterior probability and the credible interval were adjusted for surveillance time. For subgroup analyses of the primary efficacy endpoint, a 2-sided 95% confidence interval (CI) was calculated. VE is defined as 100% × (1 − IRR), where illness rate ratio (IRR) is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. VE is demonstrated if there is convincing evidence (i.e., posterior probability greater than 99.5% at an interim analysis or greater than 98.6% at the final analysis) that the true VE of BNT162b2 is >30% using a beta-binomial model, where VE represents efficacy for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior SARS-CoV-2 infection before and during the vaccination regimen. Participants with positive or unknown NAAT results at any illness visit prior to 7 days after Dose 2 were not included in the evaluation for VE. Cases were counted from 7 days after Dose 2.

The interim analysis was performed for the first primary efficacy endpoint only. Other efficacy data analysed for the interim analysis were summarized with descriptive summary statistics, including COVID-19 case counts in the BNT162b2 and placebo groups on the basis of:

- evidence of prior SARS-CoV-2 infection at baseline per NAAT or N-antigen binding assay
- subgroup status (i.e., age, sex, race, ethnicity baseline SARS-CoV-2 status)
- COVID-19 cases meeting protocol criteria as severe after the first and second doses.

Overwhelming efficacy success criteria were met at the first interim analysis, so further formal interim analyses would not be conducted. The final analysis of all protocol specified primary and secondary efficacy endpoints was pre-specified in the protocol to be conducted after accrual of the final number of COVID-19 cases (at least 164 cases). Subgroup analyses of VE were performed for the primary endpoints and secondary endpoint of severe COVID-19 cases. Additional post hoc analyses of subgroups defined by comorbidity risk assessment were performed. Secondary efficacy was analysed in the same manner as primary efficacy (Section 2.5.4.1.2.2), using the cases definitions for severe COVID-19 and CDC criteria for COVID-19

Statistical methods

The estimands to evaluate the efficacy objectives were based on evaluable populations for efficacy. These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE was also analysed by all-available efficacy population.

The evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized, with Dose 2 received within the predefined window (19-42 days after Dose 1),and had no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2. This was the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy populations, including all randomized participants who completed 1 and 2 vaccination doses respectively, were also performed.

The two primary endpoints were tested hierarchically. Key secondary efficacy endpoints were evaluated sequentially in a prespecified order after the primary endpoints were met. Missing data were not imputed for the primary or secondary analyses. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with MNAR assumption.

VE was estimated as follows: 100 × (1 − IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose.

A Bayesian approach was used for the primary and secondary endpoints. A beta prior, beta (0.700102, 1), was used for θ = (1-VE)/(2-VE). The prior was centred at θ = 0.4118 (VE=30%). The 95% interval for θ is (0.005, 0.964) and the corresponding prior 95% interval for VE is (-26.2, 0.995). The Bayesian approach was not used for the point estimate for VE. At final analysis, efficacy was to be declared if the posterior probability of VE greater than or equal to 30% ("p") > 98.60%.

During Phase 2/3, 4 interim analyses (IAs) were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. The final analysis was to be performed when 164 cases were observed. However, only one interim analysis was performed, at 94 cases. The final analysis was performed with 170 cases. At the time of the IAs, futility and VE with respect to the first primary endpoint were planned to be assessed. The IA that was performed was successful, as was the final analysis, and results were consistent with the IA.

The success threshold for each interim analysis was to be calibrated to protect overall type I error at 2.5%. The risk of falsely concluding the VE to be above 30% (the type I error rate) with the proposed Bayesian model and over the interim analyses and final analysis under assumption of 30% vaccine efficacy is 0.021 (one sided). Hence the type I error rate for the primary endpoint is controlled. Although only one interim analysis was performed, the overall Type I error (overall probability of success when true VE=30%) was controlled at 0.025 with the originally proposed success/futility boundaries.

Although Bayesian analysis are not usually accepted as confirmatory evidence in pivotal trials, the magnitude of the effect in this study, makes this concern redundant. Hence, the conclusions of the inference are considered robust.

Results

Disposition of All Randomised Subjects – ~38000 Subjects for Phase 2/3 Analysis

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=18904) n[b] (%)	Placebo (N[a]=18892) n[b] (%)	Total (N[a]=37796) n[b] (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Not vaccinated	46 (0.2)	43 (0.2)	89 (0.2)
Vaccinated			
Dose 1	18858 (99.8)	18849 (99.8)	37707 (99.8)
Dose 2	18555 (98.2)	18533 (98.1)	37088 (98.1)
Completed 1-month post-Dose 2 visit (vaccination period)	16902 (89.4)	16804 (88.9)	33706 (89.2)
Discontinued from vaccination period but continue in the study	121 (0.6)	111 (0.6)	232 (0.6)
Discontinued after Dose 1 and before Dose 2	121 (0.6)	107 (0.6)	228 (0.6)

Discontinued after Dose 2 and before 1-month post–Dose 2 visit	0	4 (0.0)	4 (0.0)
Reason for discontinuation from vaccination period			
No longer meets eligibility criteria	48 (0.3)	81 (0.4)	129 (0.3)
Withdrawal by subject	45 (0.2)	9 (0.0)	54 (0.1)
Adverse event	20 (0.1)	12 (0.1)	32 (0.1)
Pregnancy	4 (0.0)	4 (0.0)	8 (0.0)
Physician decision	2 (0.0)	1 (0.0)	3 (0.0)
Lost to follow-up	0	2 (0.0)	2 (0.0)
Medication error without associated adverse event	0	1 (0.0)	1 (0.0)
Other	2 (0.0)	1 (0.0)	3 (0.0)
Withdrawn from the study	180 (1.0)	259 (1.4)	439 (1.2)
Withdrawn after Dose 1 and before Dose 2	132 (0.7)	164 (0.9)	296 (0.8)
Withdrawn after Dose 2 and before 1-month post–Dose 2 visit	44 (0.2)	84 (0.4)	128 (0.3)
Withdrawn after 1-month post–Dose 2 visit	4 (0.0)	11 (0.1)	15 (0.0)
Reason for withdrawal from the study			
Withdrawal by subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to follow-up	80 (0.4)	86 (0.5)	166 (0.4)
Adverse event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	3 (0.0)	5 (0.0)
Physician decision	1 (0.0)	2 (0.0)	3 (0.0)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Medication error without associated adverse event	1 (0.0)	0	1 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)
Other	3 (0.0)	3 (0.0)	6 (0.0)

Note : 1 subject was randomised but did not sign informed consent and is not included in any analysis population
Note: because of a dosing error, 2 subjects received an additional dose of BNT162b2 (30µg) and one dose of placebo
Note: HIV-positive subjects are included in this summary but not included in the analysis of the overall study objectives.
a. N=number of randomised subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations
b. n=number of subjects with the specific characteristics

Recruitment

This study is ongoing, and participants are continuing to be enrolled and evaluated in Phase 3.

Subject First Visit: 29 April 2020

Data Cut-off dates:

- 24 August 2020 (Phase 1 safety and immunogenicity data through 1 month after Dose 2)
- 02 September 2020 (Phase 2 safety data 7 days after Dose 2 only)
- 06 October 2020 (Phase 2/3 safety data 1 month after Dose 2 for the first 6610 participants, and available safety data for all 36,855 participants)
- 04 November 2020 (Phase 2/3 first interim analysis for efficacy at 94 cases)

As a result, 44,822 subjects have been enrolled and 43,386 subjects have been randomised at 153 centres, in 6 countries worldwide, including: United States (131 centres, 33,068 subjects), Argentina (1 site, 5,776 subjects), Brazil (2 sites, 2,900 subjects), Turkey (9 sites, 342 subjects), South Africa (4 sites, 800 subjects) and Germany (6 sites, 500 subjects).

Conduct of the study

This study has gone through extensive changes or amendments. The amendments of the phase 1 of the study are deemed acceptable for a dose-finding design. Protocol amendments concerning the phase 3 of the study are overall adequately motivated and acceptable, since they are not expected to affect the conclusions on efficacy. Main Amendments have allowed to include adolescents from 12 to 15 years in the study and added corresponding objectives. Furthermore, secondary efficacy endpoints to include COVID-19 cases that occurred from 14 days after the second dose were added. The SAP was amended twice in line with protocol amendments.

Baseline data

Overall, demographic characteristics were well balanced between study groups.

Demographics (population for the primary efficacy endpoint)[a]

	Comirnaty (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥12 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
75 through 85 years	799 (4.4)	807 (4.4)
>85 years	5 (0.0)	5 (0.0)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomised participants who receive all vaccination(s) as randomised within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.

c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥ 30 kg/m²)
   - Diabetes (Type 1, Type 2 or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

Baseline comorbidities - safety population 38,000 subjects- at final analysis:

Table 3. Baseline Charlson Comorbidities ~ 3800 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
Charlson Comorbidity Index Category	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Subjects w h any Charlson comorb ty	3934 (20.9)	3809 (20.2)	7743 (20.5)
AIDS/HIV	59 (0.3)	62 (0.3)	121 (0.3)
Any M l g v	733 (3.9)	662 (3.5)	1395 (3.7)
Cerebrovascu Disease	195 (1.0)	166 (0.9)	361 (1.0)
Chronic Pulmonary Disease	1478 (7.8)	1453 (7.7)	2931 (7.8)
Congest ve l eart Fai ure	88 (0.5)	83 (0.4)	171 (0.5)
Deme t	7 (0.0)	11 (0.1)	18 (0.0)
D abeles W Chronic Com ication	99 (0.5)	113 (0.6)	212 (0.6)
D abeles Witho Chronic Compl c o	1473 (7.8)	1478 (7.8)	2951 (7.8)
Hem p eg or Paraplegia	13 (0.1)	21 (0.1)	34 (0.1)
Le em	12 (0.1)	10 (0.1)	22 (0.1)
Lymph ma	22 (0.1)	32 (0.2)	54 (0.1)
M etastatic olid umor	4 (0.0)	3 (0.0)	7 (0.0)
Mi d Liver isease	125 (0.7)	89 (0.5)	214 (0.6)
Moderate or Severe Live D sease	1 (0.0)	2 (0.0)	3 (0.0)
Myocardial Infarction	194 (1.0)	188 (1.0)	382 (1.0)
Peptic Ulce Disease	52 (0.3)	71 (0.4)	123 (0.3)
Periphera Vascular Disease	124 (0.7)	117 (0.6)	241 (0.6)
Rena Dise	123 (0.7)	133 (0.7)	256 (0.7)
Rheumati Disease	62 (0.3)	56 (0.3)	118 (0.3)

Note: MedDRA (v23.1) coding dictionary applied.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic. Subjects with multiple occurrences within each category are counted only once. For 'Subjects with any Charlson comorbidity', n = number of subjects reporting at least 1 occurrence of any Charlson comorbidity.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:04) Source Data: admh Table Generation: 17NOV2020 (16:21) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/admh_s002_risk_p3_saf

The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease

not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Numbers analysed

The disposition of the efficacy populations is described in the Table below. There was an imbalance between the two study groups on the number of subjects excluded from the evaluable efficacy population. The two reasons responsible for this imbalance were "Dosing/administration error, subject did not receive correct dose of vaccine" (n=105 in vaccines and n=3 in placebo) and "IP administered that was deemed not suitable for use by Almac" (n=144 in vaccines and n=0 in placebo). There may be several explanations for this imbalance as listed below:

- As the placebo was a fixed volume of saline, with no dilution required, the likelihood of a dosing error in the placebo group was lower compared to vaccine, which did required dilution.
- An isolated dosing/administrative error event in one clinical centre affecting a higher number of participants receiving BNT162b2 (n=52 participants) has contributed to this imbalance.
- Almac was responsible for determining suitability for use of investigational product that was subject to a temperature excursion. Due to the differences in the required storage conditions (ambient for the placebo versus ultracold for the BNT162b2), temperature excursions were not an issue for the placebo but were for BNT162b2.

The protocol design was such that, if a participant experienced any of the specified trigger symptoms that could indicate COVID-19, a potential COVID-19 illness visit should occur, including obtaining a swab for the central laboratory.

Table 4 Efficacy Populations

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Subjects without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Subjects excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			

Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Subjects without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Subjects without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Subjects excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Subjects without evidence of infection prior to 7 days after Dose 2	18242 (83.6)	18379 (84.2)	36621 (83.9)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Subjects without evidence of infection prior to 14 days after Dose 2	18219 (83.5)	18315 (83.9)	36534 (83.7)
Subjects excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Subjects excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects may have been excluded for more than 1 reason.

Outcomes and estimation

Primary Efficacy Endpoints – Final Analysis

The result for the first primary efficacy analysis is shown in Table 5. VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 95.2%, with 8 and 165 cases in the BNT162b2 and placebo group.

Table 5 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 =severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details

For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with or without evidence of prior SARS-CoV-2 infection through 7 days after Dose 2. Cases were counted from 7 days after Dose 2 (Table 6). VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 94.8%, with and 9 and 172 cases in the BNT162b2 and placebo group, respectively.

Table 6 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.9, 97.3)	>0.9999

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

However the seropositive subjects were not many: among 38,000 subjects there were 407 individuals seropositive in the vaccine group and 436 in the placebo group in the age strata 16-55 YOA, and 150 individual seropositive in the vaccine group and 152 in the placebo group in the >55 YOA age strata.

All Confirmed Cases of COVID-19 After Dose 1

An analysis of the cases occurring from dose 1 and until dose 2 or 1 week after dose 2 provides information on onset of protection.

All reports of COVID-19 with onset at any time after Dose 1 are accounted for in Table 7, which provides a summary of cases for all participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group (Table 7). Notably, in the BNT162b2 group, most cases occurred before Dose 2.

Figure 9 displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy (modified intention-to-treat) population. Disease onset appears to track together for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group. From table 7 and figure 9 it is evident that the first dose offers partial protection, while few cases occur after the second dose.

Table 7 Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All- Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
≥10 days after Dose 1 to before Dose 2	6		45		86.7	(68.6, 95.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

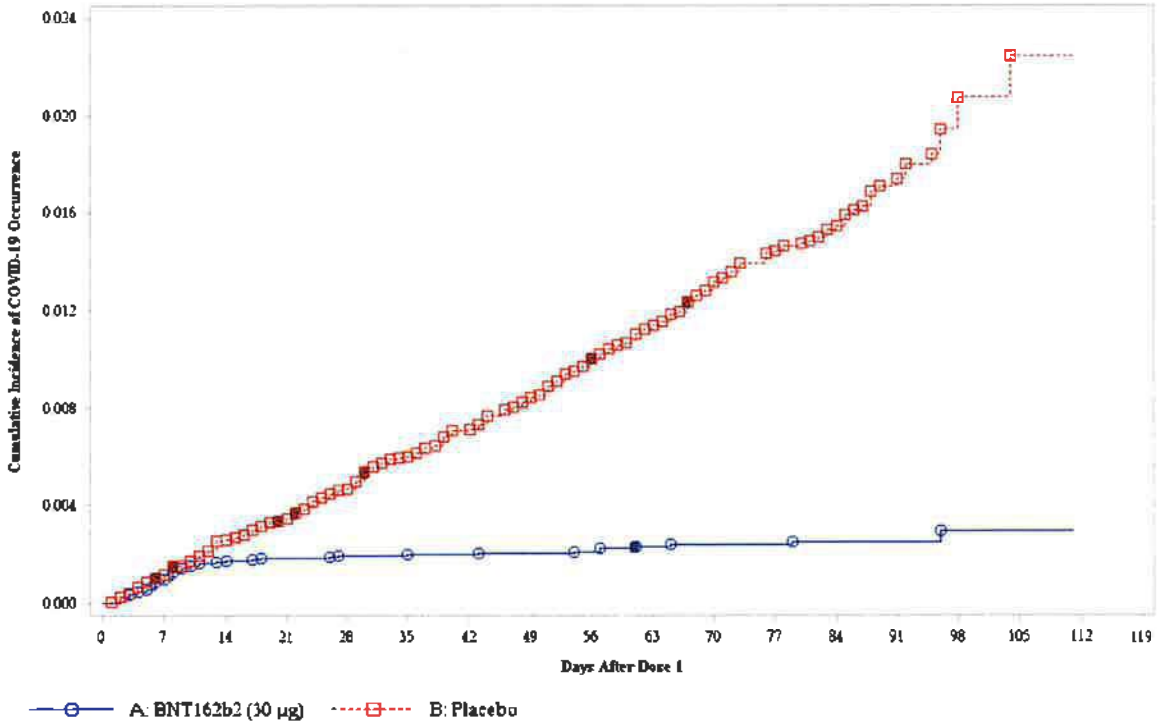


Figure 9. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Immunogenicity results

The immunogenicity part of study C4591001 are presented in this section and aimed to confirm the conclusions on safety and immunogenicity from phase 1. These are the only immunogenicity results from a larger study population available at this stage, and further results from phase 3 are expected post approval. In addition, any data generated in attempts to establish a serological correlate of protection are expected to be reported when available.

The results of the immunogenicity analyses here reported are generated from the Dose 2 evaluable immunogenicity population; baseline positive participants (by N-binding antibody or positive NAAT at Visit 1) were not excluded from these analyses.

SARS-CoV-2 Neutralizing Titres and S1-Binding IgG Concentrations GMTs/GMCs

At 1 month after Dose 2 (Day 52) of BNT162b2, there were substantial increases in SARS-CoV-2 50% neutralizing GMTs (Figure 10) and S1-binding IgG concentrations (GMCs) (Figure 11). GMTs/GMCs were higher in younger participants (18 to 55 years of age) than in older participants (56 to 85 years of age). Similar trends were observed for the SARS-CoV-2 90% neutralizing GMTs (data not shown in this report).

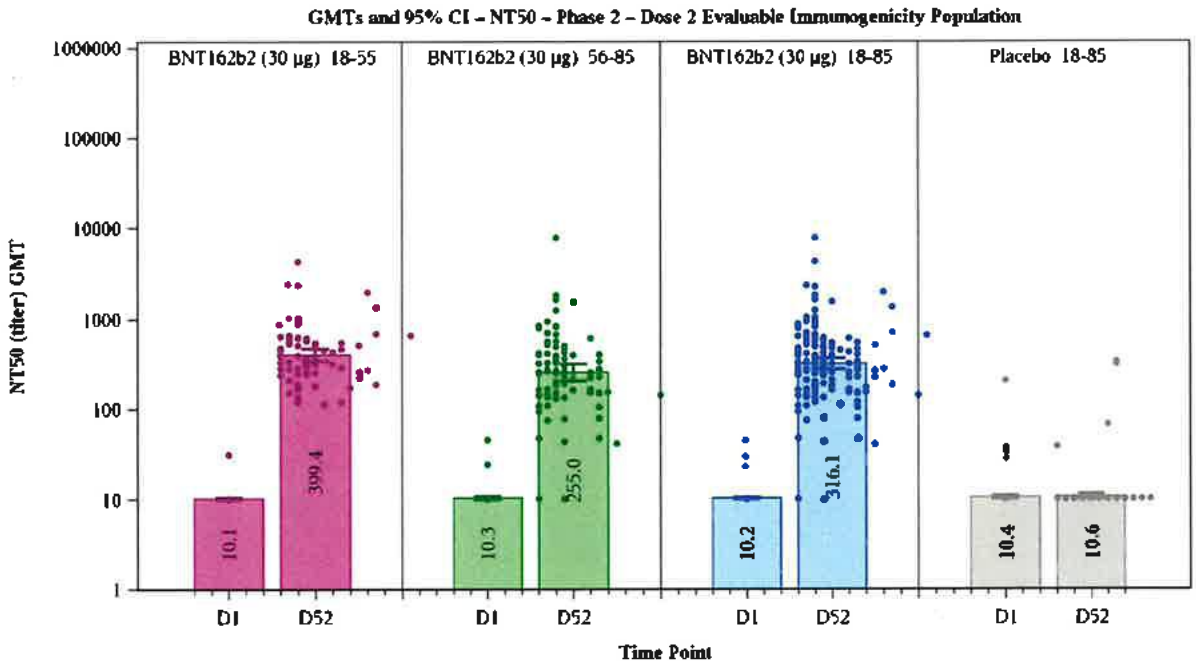


Figure 10. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay – NT50 – Phase 2 – Dose 2 Evaluable Immunogenicity Population

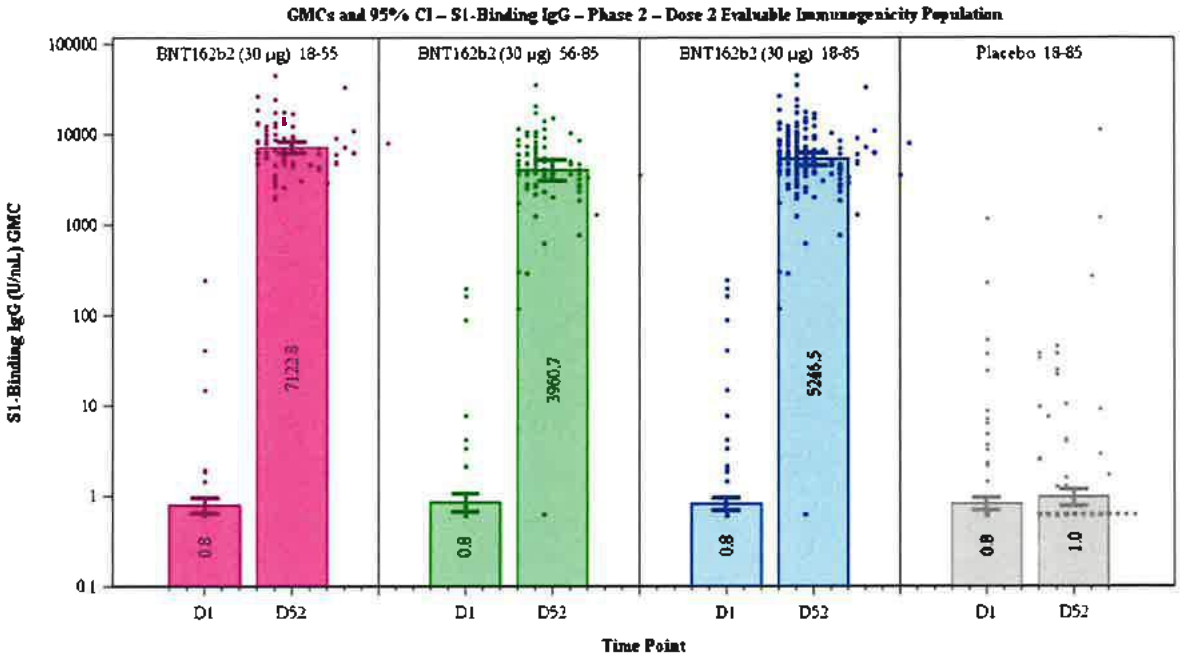


Figure 11. Geometric Mean Concentrations and 95% CI: S1-Binding IgG Level Assay – Phase 2 Dose 2 Evaluable Immunogenicity Population

A few participants in the Dose 2 evaluable immunogenicity population had a positive baseline SARS-CoV-2 status. These SARS-CoV-2 status positive participants were analysed separately from the baseline negative participants. In general, at 1 month after Dose 2 among BNT162b2 recipients, SARS-CoV-2 50% neutralizing GMTs and S1-binding IgG GMCs in participants with a positive baseline SARS-CoV-2 status (n=3) were numerically higher than those observed in participants with a negative baseline SARS-CoV-2 status (n=163).

Ancillary analyses

Vaccine Efficacy by Subgroup

For both primary endpoints, VE was also evaluated for subgroups of participants by age, sex race/ethnicity, and country, without evidence of prior infection (Table 8). Results for additional age groups are shown in Table 9.

Post hoc analyses of efficacy by risk status were performed. For these analyses, at-risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese (defined as BMI ≥30 kg/m2) (table 11). Results for the all-available population were similar; no clinically meaningful differences were observed in VE on the basis of subgroup.

These subgroup analyses are considered of importance. There is no evidence of significantly reduced efficacy in older age groups, i.e. >90% vaccine efficacy even in over 75-year-old subjects, although not statistically significant as there were only few cases in this age stratum. There were no cases in the 16-17-year-old age stratum, but efficacy is not anticipated to be lower in younger age groups compared to the overall study population. Additionally, it is reassuring that other factors, e.g. ethnicity/race, gender did not impact efficacy. Efficacy was not demonstrated in subjects who were

seropositive at baseline, but the subgroup was very small and results are considered inconclusive rather than negative at this stage.

Table 8 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
16 to 55	5	1.234 (9897)	114	1.239 (9955)	95.6	(89.4, 98.6)
>55	3	0.980 (7500)	48	0.983 (7543)	93.7	(80.6, 98.8)
≥65	1	0.508 (3848)	19	0.511 (3880)	94.7	(66.7, 99.9)
Sex						
Male	3	1.124 (8875)	81	1.108 (8762)	96.4	(88.9, 99.3)
Female	5	1.090 (8536)	81	1.114 (8749)	93.7	(84.7, 98.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
All others[f]	1	0.160 (1405)	9	0.155 (1355)	89.3	(22.6, 99.8)
Ethnicity						
Hispanic/Latino	3	0.605 (4764)	53	0.600 (4746)	94.4	(82.7, 98.9)
Non-Hispanic/non-Latino	5	1.596 (12548)	109	1.608 (12661)	95.4	(88.9, 98.5)
Country						
Argentina	1	0.351 (2545)	35	0.346 (2521)	97.2	(83.3, 99.9)
Brazil	1	0.119 (1129)	8	0.117 (1121)	87.7	(8.1, 99.7)
USA	6	1.732 (13359)	119	1.747 (13506)	94.9	(88.6, 98.2)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 9 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.6, 97.6)
Age group (years)						
16 to 55	6	1.309 (10653)	120	1.317 (10738)	95.0	(88.7, 98.2)
>55	3	1.022 (7892)	49	1.028 (7956)	93.8	(80.9, 98.8)
≥65	1	0.530 (4044)	19	0.532 (4067)	94.7	(66.8, 99.9)
Sex						
Male	4	1.183 (9457)	85	1.170 (9342)	95.3	(87.6, 98.8)
Female	5	1.149 (9102)	84	1.176 (9366)	93.9	(85.2, 98.1)
Race						
White	7	1.975 (15294)	153	1.990 (15473)	95.4	(90.3, 98.2)
Black or African American	0	0.187 (1758)	7	0.188 (1758)	100.0	(30.4, 100.0)
All others[f]	2	0.170 (1507)	9	0.167 (1477)	78.2	(-5.4, 97.7)
Ethnicity						
Hispanic/Latino	3	0.637 (5074)	55	0.638 (5090)	94.5	(83.2, 98.9)
Non-Hispanic/non-Latino	6	1.681 (13380)	114	1.693 (13509)	94.7	(88.1, 98.1)
Country						
Argentina	1	0.366 (2664)	36	0.367 (2684)	97.2	(83.5, 99.9)
Brazil	2	0.134 (1274)	8	0.132 (1257)	75.4	(-23.5, 97.5)
USA	6	1.816 (14141)	124	1.830 (14287)	95.1	(89.1, 98.2)
South Africa	0	0.015 (362)	1	0.015 (363)	100.0	(-3818.9, 100.0)
Prior SARS-CoV-2 Status						
Positive at baseline[g]	1	0.056 (526)	1	0.060 (567)	-7.1	(-8309.9, 98.6)
Negative at baseline but positive prior to 7 days after Dose 2[h]	0	0.003 (27)	1	0.004 (34)	100.0	(-6004.9, 100.0)
Negative prior to 7 days after Dose 2[i]	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Unknown	0	0.059 (595)	5	0.060 (596)	100.0	(-9.6, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; VE= vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
g. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
h. Negative N-binding antibody result and negative NAAT result at Visit 1, positive NAAT result at Visit 2 or at unscheduled visit, if any, prior to 7 days after Dose 2.

i. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1 and Visit 2, and negative NAAT result at unscheduled visit, if any, prior to 7 days after Dose 2.

Table 10 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Requested Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
12 to 15	0	0.000 (14)	0	0.000 (13)	NE	(NE, NE)
16 to 17	0	0.002 (52)	0	0.003 (55)	NE	(NE, NE)
18 to 64	7	1.703 (13497)	143	1.708 (13563)	95.1	(89.6, 98.1)
65 to 74	1	0.406 (3074)	14	0.406 (3095)	92.9	(53.1, 99.8)
≥75	0	0.102 (774)	5	0.106 (785)	100.0	(-13.1, 100.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
American Indian or Alaska native	0	0.011 (100)	1	0.010 (96)	100.0	(-3429.0, 100.0)
Asian	1	0.092 (764)	4	0.093 (769)	74.6	(-156.6, 99.5)
Native Hawaiian or other Pacific Islander	0	0.006 (46)	1	0.003 (29)	100.0	(-2266.9, 100.0)
Multiracial	0	0.042 (414)	1	0.036 (359)	100.0	(-3231.3, 100.0)
Not reported	0	0.010 (81)	2	0.012 (102)	100.0	(-563.3, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Table 11 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
At risk[f]						
Yes	4	1.025 (8030)	86	1.025 (8029)	95.3	(87.7, 98.8)
No	4	1.189 (9381)	76	1.197 (9482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7671)	69	0.964 (7701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5878)	74	0.746 (5917)	95.9	(87.6, 99.2)
≥65 and not at risk	0	0.227 (1701)	7	0.233 (1771)	100.0	(29.0, 100.0)
≥65 and at risk	1	0.281 (2147)	12	0.279 (2109)	91.7	(44.2, 99.8)
Obese[g]						
Yes	3	0.763 (6000)	67	0.782 (6103)	95.4	(86.0, 99.1)
No	5	1.451 (11406)	95	1.439 (11404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8811)	83	1.101 (8825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4734)	60	0.609 (4789)	94.9	(84.4, 99.0)
≥65 and not obese	1	0.343 (2582)	12	0.338 (2567)	91.8	(44.5, 99.8)
≥65 and obese	0	0.165 (1265)	7	0.173 (1313)	100.0	(27.1, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least one of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

Vaccine efficacy by different age subgroup is shown below in line with the information included in the SmPC.

Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection and participants with or without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COVID-19 mRNA Vaccine N[a]=18,198 Cases** n1[b] Surveillance time[c] (n2[d])	**Placebo**	**Vaccine efficacy** % (95% CI)[f]
		162 2,222 (17,511)	95.0 (90.0, 97.9)
	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

Vaccine efficacy for Severe COVID-19 cases, Final analysis

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, the estimated VE against severe COVID-19 occurring at least 7 days after Dose 2 was 66.4%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively (Table 12). The posterior probability for the true vaccine efficacy greater than 30% is 74.29%, which did not meet the prespecified success criterion of >98.6% for this endpoint due to the small number of severe cases observed after Dose 2 in the study.

Consequently, statistical testing of subsequent secondary endpoints (i.e., the additional secondary endpoints related to severe disease with pre-specified control of overall type 1 error) ended. However, descriptive summaries for the additional endpoints were provided.

Table 12 Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days AfterDose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial C4591001

Title: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer- Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals		
Study identifier	C4591001	
Design	Phase 1/2/3 randomized, observer-blind, placebo-controlled	
	Follow-up for efficacy	Until nov 14, 2020
	Follow-up for safety	At least 1 month, median 2 months
Hypothesis	Superiority of vaccine vs placebo for vaccine efficacy	
Treatments groups	Active arm	BNT162b2 (30 µg), 2 doses, 21 days apart, randomized 22 000

	Control arm		Saline placebo, 2 doses, 21 days apart, randomized 22 000
Endpoints and definitions	First Primary endpoint	VE-7d-no-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2
	Second Primary endpoint	VE-7d-no/yes-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.
	Secondary Endpoint	VE-14d-no-no/yes-SARS-Cov-2	COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2
	Secondary Endpoint	VE-7d/14d-no-no/yes-SARS-Cov-2-Severe	Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2
Database lock	November 14, 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population	Per protocol, Evaluable Efficacy population		
Effect estimate per comparison VE=100x (1- IRR) IRR= caseN/groupN Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time., Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.	Primary endpoint	VE-7d-no-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=8/18198 Cases in Placebo arm N= 162/18325
		Vaccine Efficacy VE %	95.0
		95% Credible Interval	90.3, 97.6
		Pr (VE >30% |data)	>0.9999
	Co-Primary	VE-7d-no/yes-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=9/18559 Cases in Placebo arm N= 169/18708
		Vaccine Efficacy VE %	94.6
		95% Credible Interval	89.9, 97.3

		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-14d-no- SARS-CoV-2	Cases in Active arm N=8/18175 Cases in Placebo arm N= 139/18261
		Vaccine Efficacy VE %	94.2
		95% Credible Interval	88.7, 97.2
		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-14d-no/yes-SARS-CoV-2	Cases in Active arm N=8/19965 Cases in Placebo arm N= 144/20171
		Vaccine Efficacy VE %	94.4
		95% Credible Interval	89.1, 97.3
		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-7d-no-SARS-CoV-2-Severe	Cases in Active arm N=1/18198 Cases in Placebo arm N= 3/18325
		Vaccine Efficacy VE %	66.4
		95% Credible Interval	-124.8, 96.3
		Pr (VE >30% |data)	0.7429
Notes	Subgroup analyses support the overall results, e.g. elderly and patients with risk factors appear to be protected as well.		

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the selected vaccine BNT162b2 was investigated in one pivotal trial, BNT162-02 study. This is a phase 1/2/3, multicentre, multinational, randomized, placebo-controlled, observer blind, dose finding, vaccine candidate efficacy and safety study in subjects that are healthy or have clinically stable comorbidities. Safety and immunogenicity data generated during the phase 1 portion of this study supported the selection of BNT162b2 at 30 µg, as a prime/boost regimen (separated by 21 days) as the vaccine candidate to proceed into Phase 2/3.

Phase 2/3 was designed to evaluate the efficacy of BNT162b2, and to provide additional safety and immunogenicity data in a larger population. The study design for the pivotal phase 3 study is overall acceptable and in line with applicable guidelines. In the Phase 2/3 portion, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for

up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. It is an observer-blind study, which is considered acceptable as placebo and vaccine differed in appearance. Randomisation and blinding were considered acceptable.

Overall inclusion and exclusion criteria are acceptable and the study population is considered representative of the target population for vaccination, including subjects at higher risk of severe disease, i.e. age above 65 years (>20% with no upper age limit) and relevant underlying diseases (46%, e.g. obesity, chronic pulmonary diseases, diabetes, hypertension, and cardiovascular disease). Immunocompromised subjects and pregnant or breastfeeding women were excluded from the study. Subjects with known stable infection with HIV, HBV, HCV could be enrolled. Further, individuals who had previous clinical or microbiological diagnosis of COVID-19 were excluded, since the natural infection would affect the immunogenicity of the vaccine.

The study mainly recruited in the USA, but other sites worldwide were also included.

The primary endpoint (laboratory confirmed symptomatic COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection up to 7 days after receipt of the second dose, and then in all participants regardless of serostatus) is considered relevant for the purpose of establishing vaccine efficacy.

SARS-CoV-2 genomic RNA has been detected in nasal swab samples using Cepheid Xpert Xpress SARS-CoV-2 PCR assay on the GeneXpert Molecular Diagnostic System. This method detects 2 structural genes of SARS-CoV-2: E and N2. A validation of this method was performed, and in addition the test was issued a EUA by FDA. In order to assess the analytical detection limit, live virus and commercial control (AccuPlexTM SARS-CoV-2) were used. Clinical sensitivity and specificity were evaluated in comparison with results obtained using another FDA authorised real-time RT-PCR method with positive or negative clinical specimens and pre-pandemic samples. Results showed that Cepheid Xpert Xpress PCR assay is a sensitive and specific method for the detection of SARS-CoV-2 RNA in nasal swabs. The positive rate of self-swab is similar to site-swab, 3.7% and 4.7% positive from self-swab and site-swab respectively in the BNT162b2 group.

The third main secondary endpoint evaluated vaccine efficacy against severe cases of the disease (defined as confirmed COVID-19 with the presence of at least one of pre-defined severity criteria), to determine whether the vaccine decreased the incidence of confirmed severe COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection, 7 to 14 days after the second dose. Prevention of severe disease is an important endpoint, but the relative rarity of severe cases would require either a very large study population and/or a very long study duration to be certain to achieve sufficient statistical power. Therefore, it is acceptable as a secondary endpoint.

The immunogenicity secondary and exploratory endpoints are considered acceptable.

This is an event-driven study. This case-driven approach is deemed appropriate as the rate of accumulation of cases was not certain which could allow a rapid assessment of efficacy in case of a high attack rate. With assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. The randomisation procedure is considered appropriate to control confounding factors.

The statistical methods are overall acceptable. The Bayesian approach used is not expected to affect the decisions from the hypothesis testing procedure. For consistency and ease of interpretation, the Clopper Pearson confidence intervals will be included in the SmPC rather than the Bayesian credible intervals. Of the four pre-planned interim analyses only one was performed, and the final analysis was also submitted. These analyses give highly consistent results with VE far from the null hypothesis limit

of 30%. Confidence intervals were not adjusted for multiplicity, which is considered acceptable in this context.

While it could be argued that alpha could be allocated according to a group sequential design, since no failed interim analysis has been performed, the alpha allocated to the interim analysis may be recycled to the final analysis. Hence the final analysis could have been performed at full alpha level and the coverage probability of the "naïve" confidence interval is therefor considered correct.

The interim and final analyses are conducted in an evaluable efficacy population of participants who receive the two doses within the predefined window and excluding subjects with other major protocol deviation, in order to obtain a best-case estimate of vaccine efficacy. However, this approach could result in bias due to exclusion of subjects. For this reason, sensitivity analyses assessing VE based on all laboratory-confirmed cases with symptom onset at any time after the first dose (dose 1 all-available efficacy population) and 7 days after the second dose (dose 2 all-available efficacy population) have been performed without excluding participants with major protocol deviations.

Overall, the study report including the final analysis is considered adequate. This is not the final report for the study, as the study is expected to continue for a total of 24 months.

Baseline data

At the cut-off date of 14 November 2020, the disposition of the 38,000 participants were similar in the BNT162b2 and placebo groups. Overall, 0.2% of participants did not receive study vaccine. A small percentage of participants discontinued study vaccine after Dose 1 and before Dose 2 (0.6%). The reasons for discontinuation were also balanced. The most frequently reported reasons for discontinuation included: no longer meets eligibility criteria (0.3% BNT162b2; 0.4% placebo; the most common reason was previous clinical or microbiological diagnosis of COVID-19), withdrawal by participant, and AEs (0.1% in both treatment groups).

The distribution of demographics and other baseline characteristics was similar between both arms among participants without evidence of infection up to 7 days after dose 2 in the final analysis evaluable efficacy population. Overall, most participants were White (82.8%) and non-Hispanic/non-Latino (72.7%) (26.8% of Hispanic/latino ethnicity), median age was 52.0 years, and approximately 49% were female. There were 42.6% of participants in the older age group (>50 years), 26% of participants over 65 years of age and 0.7% (112 subjects) of participants adolescents (12-17 years). In 75-85 years and >85 years age groups, 837 and 5 participants respectively had been vaccinated with BNT162b2 (Dose 2 all-available efficacy).

Across both treatment groups, 20.5% had any comorbidity (per the Charlson comorbidity index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%) and were reported at similar frequencies in each group. Obese participants made up 35.1% of the safety population. Overall, 120 subjects were HIV-positive and were evenly distributed between treatment groups.

Efficacy data and additional analyses

The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

The first interim analysis for vaccine efficacy (VE) was conducted on 08-Nov-2020 by an IDMC. The data cut-off date was 04-Nov-2020, when a total of 94 confirmed COVID-19 cases were accrued. There were 4 COVID-19 cases in the BNT162b2 group compared to 90 COVID-19 cases reported in the

placebo group. These data gave a vaccine efficacy of 95.5% (95%CI: 88.8%, 97.5%) among participants without evidence of infection up to 7 days after Dose 2, and a >99.99% posterior probability for the true vaccine efficacy greater than 30% conditioning on available data. Participants included in the first interim analysis were also included in the final analysis.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued.

The protective efficacy in subjects without prior evidence of SARS-CoV-2 infection from 7 days after dose 2 was high, 95.0% (95% CI: 90.0; 97.9) in the primary efficacy population (8 cases and 162 cases in the BNT162b2 and placebo groups, respectively). The posterior probability of >99.99% for the true VE greater than 30% met the pre-specified success criterion of >98.6% for this endpoint.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after dose 2 was 94.2%, 95%CI (88.7%, 97.2%) (8 and 139 cases in the BNT162b2 and placebo groups respectively) with a posterior probability (VE≥30%/data) of >99.99%.

Slightly more subjects in the placebo group had symptoms of COVID-19 without being a confirmed case by PCR. This is also reflected in slightly more subjects in the placebo arm with result not available from the swab. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with the available data, assuming a higher than the observed case rate when imputing missing efficacy endpoints from participants in the BNT162b2 group only, to reflect potentially unknowable missing not at random (MNAR) effects that are unfavourable for efficacy results of the study. 500 imputations were performed that were generated using SAS PROC MI Fully Conditional Specification (FCS) method. Each imputation filled in the missing laboratory results based on a logistic regression model at the subject level. VE after imputation was over 80% also with up to 15-fold increase of positivity rate applied to the BNT162b2 group. Hence, there is no concern that this slight imbalance has introduced any significant bias to the results presented below.

The 2-dose schedule is considered justified both based on immune responses and on the actual efficacy results. In dose 1 all-available efficacy (mITT) population, regardless of evidence of infection before or during the vaccination regimen, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group (n=21,314 subjects) compared to 275 cases in the placebo group (n=21,258 subjects). Notably, in the BNT162b2 group, most cases (36/(50)) occurred before Dose 2. The estimated VE against confirmed COVID-19 occurring after dose 1 was 82% (2-sided 95% CI: 75.6 %, 86.9%), with an estimated VE of 52.4% (2-sided 95% CI: 29.5%, 68.4%) against confirmed COVID-19 occurring after dose 1 but before dose 2.

The cumulative incidence curves for the first COVID-19 occurrence after dose 1 (all-available efficacy population) showed that COVID-19 disease onset seems to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, then cumulative curves diverge with more cases accumulating in the placebo group than in the BNT162b2 group. During the follow-up time of approximately 2 months post-dose 2, the BNT162b2 cumulative curve is stable which would not suggest waning protection. A longer follow-up is necessary to investigate the duration of the efficacy of the vaccine in protecting against the disease.

For both primary endpoints, no clinically meaningful differences in VE by subgroup were observed by age group, country, ethnicity, sex, or race in the dose 2 evaluable efficacy population, with VE estimates that ranged from 91.2% to 100.0%. Efficacy was consistent across relevant subgroups.

The results in elderly are of great importance, as increasing age is an identified risk factor for severe disease and death. The results from this study are therefore reassuring suggesting a high protective efficacy in subjects ≥65 years of age (95%, 95% CI: 66.8; 99.9). There was no indication of

decreasing efficacy in subjects ≥75 years although the number of cases was small (0 in the vaccine group and 5 in placebo). In addition, the number of subjects >85YOA is very limited (5 subjects) hence the impact of immunosenescence on vaccine efficacy in these very old individuals remain uncertain.

Among participants without prior evidence of SARS-CoV-2 infection before and during vaccination regimen, VE for participants at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, obese with body mass index (BMI) ≥30 kg/m2, chronic pulmonary disease, diabetes mellitus, hypertension) was 95.3%, as compared with 94.7% for those not at risk. VE for participants ≥65 years of age and at risk was 91.7%, as compared with 100% for those ≥65 years of age and not at risk. VE was similar in obese (95.4%) and non-obese (94.8%) participants. The VE by comorbidity status are as follows: cardiovascular (VE 100.0 (-0.8, 100.0)), Chronic pulmonary disease (93.0 (54.1, 99.8)), diabetes (94.7 (66.8, 99.9)), Hypertension (95.4 (82.6, 99.5)).

Severe disease cases were uncommon in the study: 1 case in the vaccine group and 4 cases in the placebo group (one case in the all evaluable population) after 7 days post second vaccination. None of the severe cases were baseline positive for SARS-CoV-2.

In the evaluable efficacy population, subjects without evidence of prior SARS-CoV-2 infection, the estimated VE against severe COVID-19 occurring at least 7 days after dose 2 was 66.4% (95% CI: -124.8%: 96.3%). The posterior probability for the true VE greater than 30% is 74.29% (7 days) and 74.32% (14 days), which did not meet the pre-specified success criterion for this endpoint, therefore no reliable conclusion can be drawn at this stage. While data on severe COVID-19 are limited, the experience with other vaccines (rotavirus and influenza vaccines with known efficacy against mild disease but better efficacy against severe disease) coupled with the high observed vaccine efficacy observed for BNT162b2 on all COVID-19 cases in populations with any comorbidity gives reassurance that the vaccine is likely to prevent severe disease. However, a precise estimate of its protective effect is presently lacking. The final study report may include additional data to the extent that the study is continued in a randomised fashion with a placebo group.

The second primary endpoint -VE in participants with and without prior evidence of SARS-CoV-2 infection- yielded similar results as the one in the population excluding those without evidence of prior infection. However, analysis is largely driven by events in subjects without evidence of prior infection, and therefore does not provide additional information.

It is not possible to conclude on vaccine efficacy in subjects with prior COVID-19, or signs of infection with SARS-CoV2 because only a small number of subjects were found to be seropositive at baseline (approximately 550 in each vaccine and placebo group), and only 2 cases of disease were reported in this subset (1 in each group). Further data may become available as the trial proceeds, but it is unlikely that the study will be able to deliver conclusive evidence for a number of reasons (e.g. it is very likely that the number of subjects seropositive will remain limited, and that there will be a lower incidence of disease in seropositive placebo recipients compared to seronegative placebo recipients due to existing partial protection). The extent of additional protection in seropositive subjects is presently uncertain. Effectiveness studies may give us some information on this regard.

Genome sequencing of the SARS-CoV-2 strains in the BNT162b2 vaccine and placebo groups has not been performed. However, this work is planned by the Applicant.

The primary analysis of efficacy was conducted when the pre-defined number of 164 COVID-19 cases had occurred. This correspond to about 1.5 months of median follow-up time duration after completion of the full vaccination regimen. Therefore, available efficacy data are limited in term of follow-up duration, and the efficacy of the vaccine over longer-time remains unknown. Data are expected to become available post-authorisation.

Immune responses in terms of neutralising antibodies were measured in the phase 1 and 2 part of the study. Overall, the immune responses measured in the phase 1 and 2 part of the pivotal study are consistent and in line with the phase 1 study BNT162-01 results. As expected, both neutralising antibody levels and S-protein binding antibody levels were higher in the youngest age stratum compared to the older age stratum. Serum titres in vaccinated subjects were numerically higher compared to human convalescent sera, up to 1 month after dose 2. There is presently no established correlate of protection.

Very limited results by baseline serostatus were provided, but updated immunogenicity data is expected to become available.

Cell mediated immune responses were demonstrated in the phase 1 part of the study as well as in the other phase 1/2 study BNT162-01, but in a small cohort of subjects only. A clear Th1-polarised response, i.e. IFNγ/IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED.

In total 14 adolescents aged 12-15 years were included in the vaccine group and 13 in the placebo group, and 52 adolescents aged 16-17 years in the vaccine and 55 in the placebo group. Vaccine efficacy could not be estimated for these subjects as no cases of disease were reported. No immune response data are available. However extrapolation of efficacy is possible from young adults because, from an immune system perspective, adolescents do not differ from young adults, thus there are no reasons to believe that the vaccine will not be as efficacious at least in the age subgroup proposed for the current indication (>16 years).

At cut-off date (14-Nov-2020), 120 subjects HIV positive were vaccinated with BNT162b2. Immunogenicity and efficacy data are not available at this time but will be provided post-authorisation.

Additional efficacy data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.5.4. Conclusions on clinical efficacy

Excellent vaccine efficacy (preventing symptomatic COVID-19) was shown in subjects without evidence of prior SARS-Cov2 infection (VE 95.0% (95% CI: 90.3%, 97.6%), which was consistent across relevant subgroups. It is likely that the vaccine also protects against severe COVID-19, though these events were rare in the study, and statistically certain conclusion cannot be drawn. It is presently not known if the vaccine protects against asymptomatic infection, or its impact on viral transmission. The duration of protection is not known.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- The final clinical study report will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA. This will provide long-term data.

Regarding missing data to confirm efficacy in subpopulations that were not studied or whose data are limited please refer to sections 2.7 and 3.3.

2.6. Clinical safety

The candidate vaccine BNT162b2 at 30 µg given twice 21 days apart was assessed a first-in-human (FIH) study in April 2020 in Germany (BNT162-01) and a Phase 1/2/3 study (C4591001) was initiated shortly afterwards in the United States (US). Hence, the safety data base for BNT162b2 constitutes of two Phase 1 studies (BNT162-01 and C4591001) and one Phase 2/3 study still ongoing (C4591001).

The cut-off for safety data included in this assessment is 14 November 2020.

The two Phase 1 trials (BNT162-01 and C4591001) are described in previous sections. Study C4591001 was initially started as a Phase 1/2 study in the USA and was then amended to expand to a global Phase 3 study.

Phase 2/3 of Study C4591001 included subjects that were stratified into two age groups: 18-55 years and >55-85 years. The Phase 3 part however was subsequently amended (6 Sept 2020 protocol amendment) to include subjects from 16 years of age in the younger age group (and then from 12 years of age) and subjects >85 years of age in the older age group.

AEs were collected during the Phase 2/3 study from the signing of the informed consensus document through and including 1 month after Dose 2 (visit no. 3). In addition, in all follow-up visits where blood samples for immunogenicity data are taken, any AEs and SAEs as appropriate occurring up to 48 hours were recorded after each visit. Immunogenicity follow-up is planned to occur during that period with visits 1-month, 6-months, 12-months and 24-months post the first vaccination. AEs are categorized by frequency, maximum severity, seriousness, and relationship to study intervention using SOC and PT according to MedDRA. SAEs are recorded for up to 6 months after Dose 2 (ongoing at the time of this submission). In addition, any potential COVID-19 illness will lead to extra visits followed by convalescent visits. At the cut-off date 14-Nov-20, the longest follow-up time available was 12-13 weeks after Dose 2 (N=780: N=382 BNT162b2 and N=398 placebo).

Overall the study enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up.

The assessment is based on the following safety data (cut-off date 14 Nov 2020):

- Phase 1: i) Study C4591001 (N=72 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=18); ii) Study BNT162-01 (N=60 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=0).
- Phase 2/3 participants with a follow-up ≥ 2 months after Dose 2 (N=19,037) of either BNT162b2 (N=9531) or placebo (N=9536). This subset constitutes the core safety data set in this assessment.
- All enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up. In this population, the total number of subjects 16-17 years were 283 (N=138 BNT162b; N=145 placebo) and 100 participants were 12 to 15 years of age (N=100; 49 in the BNT162b2 group and 51 in the placebo group).
- Phase 2/3 participants (N=37,706) randomised before 9 October 2020 who received BNT162b2 (N=18,860) or placebo (N=18,846). These subjects had a median follow-up time of 2 months after Dose 2 (at least 1 month after dose 2). Among these, 1,148 subjects had a positive SARS-CoV-2 baseline status (vaccinated N=558; placebo N=590).
- Reactogenicity was evaluated based on a subset of subjects in the Phase 2/3 study, i.e. 8,183 (N=4,093 BNT162b2; N=4,090 placebo), who reported on local reactions, systemic events,

and antipyretic/pain medication usage for 7 days after each dose by using an e-diary. Eight subjects aged 16-17 years were included in this subset (BNT162b2 N=5; placebo N=3).

2.6.1. Patient exposure

Distribution and Exposure were presented for the population with median follow up of 2 months and for the whole population. Of the 37,796 subjects in the group with median follow up of 2 months who were randomized in the study before 9 October 2020, 90 participants (0.2%) were excluded from the safety population (89 did not receive study intervention and 1 did not provide informed consent).

		BNT162b2 N = 18904	**Placebo N = 18892**
		N (%)	**N (%)**
Median follow up 2 months (at least one month after dose 2)	Randomized	18904 (100%)	18892 (100%)
	Vaccinated with Dose 1	18858 (99.8%)	18849 (99.8%)
	Vaccinated with Dose 2	18553 (98.1)	18534 (98.1%)
HIV positive		59	61
Follow up ≥ 2months after dose 2		9531 (50.5%)	9536 (50.6%)
Follow up ≥ 10 to < 12 weeks after dose 2		2853 (15.1%)	2809 (14.9%)
Follow up ≥ 12 to < 14 weeks after dose 2		382 (2.0%)	398 (2.1%)

For Dose 1, three participants randomized to the placebo group received BNT162b2, and two participants randomized to the BNT162b2 group received placebo. For Dose 2, four participants randomized to the placebo group received BNT162b2, and five participants randomized to the BNT162b2 group received placebo.

The majority of participants received Dose 2 between 19 to 23 days after Dose 1 in the BNT162b2 (93.1%) and placebo (92.9%) groups.

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. Note that HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition but did not have safety data available to contribute to the safety analyses at the time of the data cut-off.

In total 1145 individuals of the safety population were SARS-CoV-2 seropositive at baseline.

A high exposure rate of 99.8% to the first dose was reached in both vaccine and control arm and a small number of individuals were withdrawn after the first dose, leading to a high rate of exposure to the second dose in both study arms (98.2% and 98.1%). Reasons for withdrawals (1.0% and 1.4%, respectively) were in most cases withdrawals by the participant, or loss to follow-up.

There were no clinically meaningful differences in the safety population by age group, baseline SARS-CoV-2 status, ethnicity, race, or sex.

Table 14 Safety Population, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis

		Vaccine Group (as Administered)		
		BNT162b2 (30 µg)	Placebo	Total
Baseline SARS-CoV-2 Status		n[a]	n[a]	n[a] (%)
Positive	Randomized[b]			1148
	Vaccinated	557	588	1145 (99.7)
	Safety population	557	588	1145 (99.7)
	HIV-positive	12	8	20 (1.7)
	Excluded from safety population			3 (0.3)
	Reason for exclusion			
	Subject did not receive study vaccine			3 (0.3)
Negative	Randomized[b]			35764
	Vaccinated	17885	17858	35743 (99.9)
	Safety population	17884	17858	35742 (99.9)
	HIV-positive	43	50	93 (0.3)
	Excluded from safety population			22 (0.1)
	Reason for exclusion			
	Subject did not receive study vaccine			21 (0.1)
	Did not provide informed consent			1 (0.0)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. n = Number of subjects with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 18NOV2020 (07:27)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adsl s003 saf pop bs p3

The disposition, exposure and withdrawal profile of the whole study population was comparable to the group that was randomised before 9 October 2020 with median follow up of 2 months.

Among the 37,706 subjects with a median follow-up of 2 months, 50.6% had ≥2 months duration of follow-up after Dose 2 and 91.6% had a duration of follow-up time of ≥1 month after Dose 2. Around 3000 individuals have already a follow of at least 10 weeks after dose 2. Updates, including additional safety data as well as assessment of the differences in safety profile in the longer follow-up compared to the initial safety dataset, if any, shall be provided when more mature data will be available.

Six-months post Dose 2 follow-up data from the first ~6000 subjects are expected by the end of February 2021 and this will allow a relevant discussion on the safety profile versus the initial dataset.

Based on the population with a median follow up of 2 months, demographic characteristics are considered well balanced between vaccine and placebo arm. Most included subjects were white (83%), with a median age of 52 years. A balanced distribution is seen regarding gender (51% male, 49%

female). The younger and older age groups were 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Of note, 35% of individuals were obese in both study arms. Across both treatment groups, 20.7% had any comorbidity.

The number of subjects with any Charlson co-morbidity diagnoses was balanced in both study arms (20%). Most prevalent were the diagnoses diabetes mellitus (7.8%) and COPD (7.8%) followed by subjects showing any type of malignant disease (3.9% in vaccine and 3.5% in placebo group). Other diagnoses were abundant with ≤ 1% in both study arms (population with a median follow up of 2 months). In the population with a follow-up ≥2 months, Charlson co-morbidity diagnoses was similar.

The demographic distribution was somewhat different when comparing seropositive and seronegative individuals, observing a median age of 43 years in seropositive and of 52 years in seronegative individuals. Furthermore, the seropositive group covered a higher proportion of obese individuals (42.2% versus 34.7%). Demographic characteristics in the whole population were comparable to those seen in the population with a median follow up time of 2 months.

2.6.2. Reactogenicity

Reactogenicity was evaluated in a subset of the Phase 2/3 study of 8,183 subjects (BNT162b2 n=4093; placebo n=4090) from both age groups (16 to 55 and >55 years of age) that received BNT162b2 or vaccine according to the proposed dosing regimen. Of note, the number of subjects aged 16-17 years included in this subset was limited (n=8; BNT162b2 n=5; placebo n=3). After each dose, the subjects reported any local reactions, systemic events, including antipyretic/pain medication usage for 7 days, by using an e-diary (cut-off date 14 Nov 20).

Local reactions

The most commonly reported local reaction among the subject that received BNT162b2 was pain at the injection site, which occurred slightly more common among subjects 16-55 years (N=2291 [83.1%] post Dose 1; N=2098 [77.8%] post Dose 2) compared to those >55 years of age (N=1802 [71.1%] post Dose 1; N=1660 [66.1%] post Dose 2). In the placebo group, pain at the injection site after Doses 1 and 2 was reported at a lower frequency (16-55 [14.0% and 11.7%]; >55 [9.3% vs 7.7%]).

There was no difference in frequency of redness and swelling at injection site after the two doses of BNT162b2. Redness occurred in about 5-7% in both age groups (16-55 [4.5% after Dose 1, 5.9% after Dose 2]; >55 [4.7% after Dose 1, 7.2% after Dose 2]). Swelling was reported also in about 5-7% of the subjects in both age groups (16-55 [5.8% after Dose 1, 6.3% after Dose 2]; >55 [6.5% after Dose 1, 7.5% after Dose 2]). In the placebo group, redness and swelling were reported infrequently in both age groups (≤1.2%).

Overall, the majority of local reactions were mild or moderate in severity, no Grade 4 reactions were reported. Severe local reactions (≤0.7%) were reported infrequently in the BNT162b2 group after either dose and was more commonly reported in the younger group. Across age groups, local reactions for the BNT162b2 group after either dose had a median onset between 1-3 days (Day 1 was the day of vaccination), with a median duration of 1-2 days.

No clinically meaningful differences in local reactions were observed by baseline SARS-CoV-2 status subgroups. However, since the baseline SARS-CoV-2 positive subgroup included very few participants (vaccinated n=154; placebo n=164), these results should be interpreted with caution.

Systemic reactions

Table 15 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group 16-55 Years – Reactogenicity Subset for Phase 2/3 Analysis– Safety Population

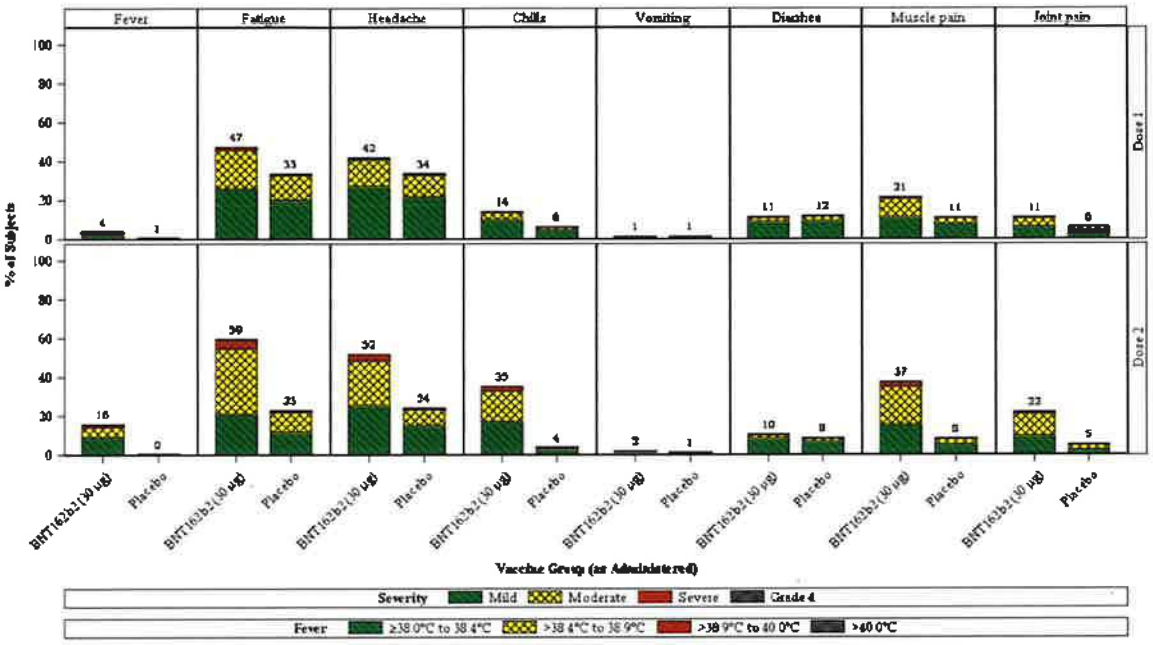
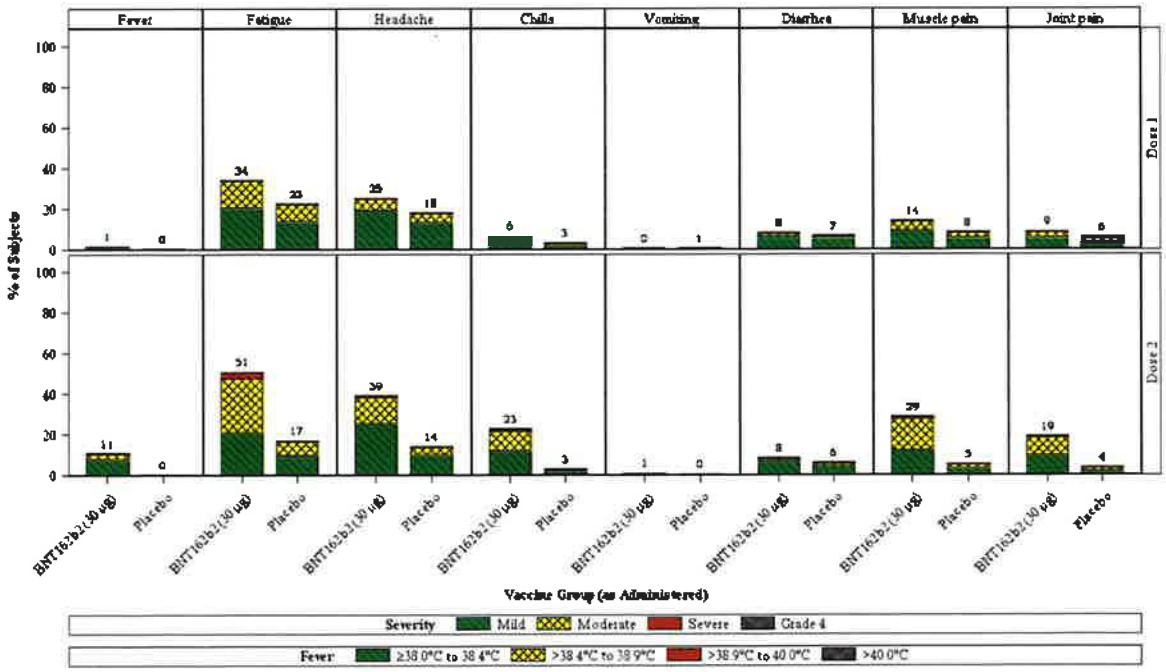


Table 16 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group >55 Years – Reactogenicity Subset for Phase 2/3 Analysis–Safety Population



Systemic events were generally reported more frequently in the BNT162b2 group than in the placebo group, for both age groups and doses. Across age groups, median onset day for all systemic events after either dose of BNT162b2 was 2-3 days, with a median duration of 1 day.

Systemic events were generally increased in frequency and severity in the younger age group compared with the older age group, with frequencies and severity increasing with number of doses (Dose 1 *vs* Dose 2). Vomiting and diarrhoea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhoea reported at similar incidences after each dose. Systemic events in the younger group compared with the older group, with frequencies increasing with number of doses (Dose 1 vs Dose 2), were: fatigue, headache, muscle pain, chills, joint pain and, fever.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.9% vs 37.7%) than in the younger age group (27.8% vs 45.0%). Of note, medication use increased in both age groups after Dose 2 as compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (ranging from 9.8% to 22.0%).

No clinically meaningful differences in systemic reactions were observed by baseline SARS-CoV-2 status subgroups, however as mentioned data in baseline SARS-CoV-2 positive subjects are limited.

Overall, the reported reactogenicity is in line with what can be expected from any vaccine. The local and systemic reactions were transient and of short duration, the majority were mild to moderate at intensity and the reactions were milder among older subjects (>55 years).

2.6.3. Adverse events

In the subset of participants randomised before 9 October 2020 with Median 2 Months of Follow-Up After Dose 2 (N= 37,586; from Dose 1 to 1 month after dose 2) and the subset of participants with at least 2 Months of Follow-Up After Dose 2 (N=19,067; from dose 1 to data cut off 14 November 2020), the numbers of overall participants who reported at least 1 AE and at least 1 related AE were higher in the BNT162b2 group as compared with the placebo group. This trend continued to be seen through the data cut-off date for all enrolled participants (N=43,252; from dose 1 to data cut-off 14 November 2020). Overall, AEs reported from Dose 1 to 7 days after Dose 1 and from Dose 2 to 7 days after Dose 2 were largely attributable to reactogenicity events (see above). This observation provides a reasonable explanation for the greater rates of AEs observed overall in the BNT162b2 group (26.7%) compared with the placebo group (12.2%).

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn because of AEs.

Table 17 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to date cutoff date (14 Nov 2020) – Subjects with 2 months follow-up time after dose 2 for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
Adverse Event	BNT162b2 (30 µg) (N[a]=9531) n[b] (%)	Placebo (N[a]=9536) n[b] (%)	Total (N[a]=19067) n[b] (%)
Any event	2044 (21.4)	11 1 .	3241 (17.0)
Related[c]	1297 (13.6)		1640 (8.6)
Severe	105 (1 1)		174 (0.9)
Life-threatening	10 (0.1)	1	21 (0.1)
Any serious adverse event	57 (0.6)		110 (0.6)
Related[c]	2 (0 0)		2 (0.0)
Severe	32 (0.3)	.	65 (0.3)
Life-threatening	10 (0.1)	.1	21 (0.1)
Any adverse event leading to withdrawal	1 (0 0)	0	1 (0.0)
Related[c]	0	0	0
Severe	0	0	0
Life-threatening	1 (0.0)	0	1 (0.0)
Death	1 (0.0)	0	1 (0 0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16.28)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adae s091 all 2mpd2 p23 saf

Overall, in participants with 2 months follow up after dose 2, 21.4% / 12.6% (vaccine/placebo) and 13.6%/3.6% experienced at least 1 AE and 1 related AE, respectively. It is noted that the frequency of AEs and related AEs is lower compared to individuals with a median follow up of 2 months (27%/12.5% and 20.8%/5.1%).

The frequency of individuals experiencing AEs were slightly higher in the younger compared to older individuals (29.3% and 23.8% vaccine arm; 13.2% and 11.7% placebo arm). SAEs and deaths were however balanced in both study arms in both age groups.

The frequency of immediate AEs after dose 1 was low in participants with median 2 months of follow-up after Dose 2 (0.4%) and the whole population (≤0.5%), belonging mostly to the SOC general disorders and administration site conditions, primarily injection site reactions. No participant reported an immediate allergic reaction to vaccine.

Severe AEs, SAEs, AEs leading to discontinuation, and deaths were reported by ≤1.1%, 0.6%, 0.0%, and 0.0%, i.e. low and equally distributed in both study arms. No differences vs. the whole population were seen according to age groups.

The rate of AEs and related AEs was slightly higher in the SARS-CoV-2 negative group compared to SARS-CoV-2-positive individuals. Stratification according to serostatus in the safety group median follow up 2 months reveals overall very low numbers of severe AEs, SAEs and deaths.

Table 18 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to 1 Month after Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subject for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Positive

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=545) n[b] (%)	Placebo (N[a]=580) n[b] (%)
	120 (22.0)	57 (9.8)
	90 (16.5)	26 (4.5)
	8 (1.5)	2 (0.3)
	2 (0.4)	0
	4 (0.7)	1 (0.2)
	0	0
	2 (0.4)	1 (0.2)
	2 (0.4)	0
1	2 (0.4)	1 (0.2)
	0	0
	0	0
	1 (0.2)	0
	1 (0.2)	0

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adae s091 pd2 bs p3 saf

Table 19 Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Negative

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=17841)	Placebo (N[a]=17808)
Adverse Event	n[b] (%)	n[b] (%)
Any event	4837 (27.1)	2253 (12.7)
Related[c]	3742 (21.0)	911 (5.1)
Severe	205 (1.1)	105 (0.6)
Life-threatening	16 (0.1)	20 (0.1)
Any serious adverse event	97 (0.5)	80 (0.4)
Related[c]	3 (0.0)	0
Severe	54 (0.3)	47 (0.3)
Life-threatening	16 (0.1)	19 (0.1)
Any adverse event leading to withdrawal	31 (0.2)	24 (0.1)
Related[c]	13 (0.1)	7 (0.0)
Severe	13 (0.1)	7 (0.0)
Life-threatening	1 (0.0)	4 (0.0)
Death	0	2 (0.0)

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_pd2_bs_p3_saf

There were 19,067 participants with at least 2 months follow-up time after Dose 2, and similar to the 37,586 participants randomised before 9 October 2020 with a median of 2 months of safety follow up after Dose 2, most AEs reported after Dose 1 up to the safety data cut-off date were reactogenicity, in SOCs of:

- general disorders and administration site conditions (11.9% BNT162b2 vs 2.9% placebo)
- musculoskeletal and connective tissue disorders (5.5% BNT162b2 vs 2.1% placebo)
- nervous system disorders (4.2% BNT162b2 vs 2.1% placebo)
- infections and infestations (1.9% BNT162b2 vs 1.6% placebo)
- gastrointestinal disorders (2.6% BNT162b2 vs 1.8% placebo).

In the younger versus older BNT162b2 age groups, AE SOCs were:

- general disorders and administration site conditions (13.1% vs 10.4%)
- musculoskeletal and connective tissue disorders (6.0% vs 4.9%)

- nervous system disorders (4.8% vs 3.5%)
- infections and infestations (1.9% vs 1.9%)
- gastrointestinal disorders (2.7% vs 2.5%)

Most often occurring events by PT comprised vaccine typical reactions such as injection site pain, fever, fatigue as well as myalgia and arthralgia. Lymphadenopathy and nausea occurred respectively in 0.4% and 0.6% more cases in the vaccine compared to placebo arm.

Related AEs belonged overall to the same SOCs as described above, i.e. general disorders and administration site conditions (3426 cases, 20.8%), musculoskeletal reactions (1148 cases, 6.1%), and nervous system disorders (979 cases, 5.2%) and occurred overall more often in the vaccine than in the placebo arm (median follow up 2 months). Severe AEs occurred more often in the vaccine arm (1.2% vs. 0.6%) in the subset with a median follow up time of 2 months, reflecting a similar SOC pattern.

The following specific observations are made based on PTs:

Numerical disbalances are observed for several hypersensitivity terms ((drug)hypersensitivity/ immunisation events; 5/3 cases ≥ 2 months group, 13/6 cases whole population, 6/1 cases deemed related in the whole population, 4 cases deemed severe (whole population), in the SOC immune system disorders).

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study, 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and, among those, two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. The participant who received BNT162b2 had a history of allergy to tree pollen. This participant reported Drug hypersensitivity and Urticaria on the day of Dose 1. Both AEs were of moderate severity and lasted one day. The participant did not receive Dose 2 of the vaccine. The participant who received placebo had an allergy to shellfish and iodine. This participant reported Allergy to vaccine and Pharyngeal swelling 1 day after Dose 1. Both events were of moderate severity and lasted 13 days and 10 days, respectively. This participant did not receive Dose 2 of study intervention.

In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine.

Four cases of facial paralysis were observed in the vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole population). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days had no previous history of Bell ' s palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole population)). However, none of the cases considered related to study drug treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm, which where however balanced in frequency between vaccine and placebo arm.

An imbalance in PT connected to sleep disturbances was noted in the whole population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus the placebo arm).

A slight imbalance of hyperhidrosis/night sweats was noted in the whole population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole population).

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole population).

Stratification according to age did not reveal meaningful differences in the types of AEs.

A stratification according to serostatus was performed in individuals with a follow up of at least one month (median FUP 2 months) and ≥2 months. Most abundant SOCs are similar to the SOCs identified in the general population with ≥2 months follow-up. No additional safety concerns are detected when stratifying according to serostatus.

2.6.4. Serious adverse event/deaths/other significant events

SAEs

This section presents the SAEs reported up to the data cut-off (14-nov-20).

Among the 19,067 subjects (BNT162b2 n=9531; placebo n= 9536) with ≥2 months of follow-up post Dose 2, small percentages of subjects in the 30 µg BNT162b2 group (56 [0.6%]) and the placebo group (53 [0.6%]) reported any SAEs. Subjects in both the BNT162b2 group and placebo group, respectively, reported SAEs at similar rates for the observed SOCs. A similar frequency was observed for the entire study population and no clinically meaningful differences in SAEs were observed by age, baseline SARS-CoV-2 status, ethnicity, race or sex subgroups.

Among all included subjects (BNT162b2 n=21720; placebo n=21728) three SAEs were reported in the SOC immune system disorders. One SAE of anaphylactic reaction (related to bee sting) and one drug hypersensitivity (related to treatment with doxycycline) was reported in the BNT162b2 group. In addition, one SAE of anaphylactic shock (related to an ant bite) was reported in the placebo group.

In the subset of individuals aged 16-17 years old, one SAE (facial bone fracture) was reported.

After the cut-off date and up to 5-Dec-20, additional 22 SAEs have been reported (blinded data).

SAEs related to study intervention

Up to the cut-off date, four of the SAEs in the BNT162b2 group and none in the placebo group were assessed by the investigator as related to study intervention. One event of lymphadenopathy and one event of shoulder injury due to incorrected administration were considered related to BNT162b2.

It is not agreed that the event of ventricular arrythmia and the event of pain in the lower back/extremities/and radicular paraesthesia have been convincingly demonstrated to be related to study intervention, since the subjects had underlying conditions that could have caused the two SAEs, there is little biological plausibility, and the overall numbers of reported events do not allow for a causal inference.

Death

Six events of death (2 in the BNT162b2 group and 4 in the placebo group) were reported in the Phase 2/3 study up to the cut-off date of 14-Nov-20. None of the deaths were considered related to study intervention, which is agreed since other pre-existing diseases were more likely to have caused death than the vaccine. After the cut-off date and up to 5-Dec-20, one additional event of death due to aortic rupture were reported (data blinded).

2.6.5. Laboratory findings

Laboratory results are available for the two Phase 1 studies, but not for the Phase 2/3 trials. This is considered acceptable. Except for minor transient decrease in lymphocyte count observed for some of the subjects, no abnormal lab results were reported from the Phase 1 studies.

2.6.6. Safety in special populations

No clinically meaningful differences in AEs were observed by age, country (mostly Argentina, Brazil, USA), ethnicity (Hispanic/Latino, Non-Hispanic/Non-Latino), gender and race (With, Black or African American, all other races) subgroups.

Pregnancy

At the time of the data cut-off in the Phase 2/3 study (14 Nov 2020), a total of 23 participants had reported pregnancies in the safety database, including 9 participants who withdrew from the vaccination period of the study due to pregnancy. These participants are being followed for pregnancy outcomes. Thus, data on pregnancy are very limited at this stage.

Elderly

The Phase 2/3 study included >40% of subjects >55 years of age. In general, reactogenicity and AE rate were slightly lower in older compared to younger individuals (stratified according to median age 55 years). No differences in AE frequency were detected among subjects >70 years of age compared to the older age group >55 year. Thus, no specific safety concern is anticipated for the elderly.

Immunocompromised individuals

Per protocol, participants with chronic stable HIV infection were defined as HIV disease with a documented viral load <50 copies/mL and CD4 count >200 cells/mm3 within 6 months before enrolment, and on stable antiretroviral therapy for at least 6 months. Stratification by CD4 count, efficacy and immunogenicity data are not available at this time but will be provided post-authorisation.

Safety data are available for 196 participants with stable HIV infection. The most frequent AEs in the BNT162b2 group were reported in the General Disorders and Administrative Site Conditions SOC including injection site pain, pyrexia, chills, fatigue, injection site erythema, and injection site swelling.

Assessment of paediatric data on clinical safety

Paediatric individuals age 16 to 17 years of age are included in the Phase 2/3 study that constitutes the safety database in this assessment. The population of subjects aged 16-17 years are limited (n=283). No additional or new AEs were observed compared to adults).

There were no participants in the 16 to 17 years of age group with ≥2 months of safety follow-up at the time of the data cut-off (14 November 2020). The longest duration of follow-up in this age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study.

The reactogenicity subset of ~8000 participants (n=4093 BNT162b2; n=4090 placebo) contributing e-diary data included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) include reactogenicity data (local reactions and systemic events) collected via e-diary up to the safety cut-off date of 14 November 2020. The reported adverse events were primarily reactogenicity events with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

In the reactogenicity subset including individuals aged 12-15 years and the 8 individuals aged 16-17 years, the most frequently reported systemic reaction in both treatment groups were fatigue (59.2% in the BNT162b2 group and 25.5% in the placebo group), followed by headache (57.1% BNT162b2, 43.1% placebo). Fever ≥38°C was reported for 26.5% more participants who received BNT162b2 over placebo; two (4.1%) of these participants reported severe fever (>38.9°C to 40.0°C).

2.6.7. Safety related to drug-drug interactions and other interactions

Interaction studies with other vaccines have not been performed, which is acceptable given the need to use the vaccine in an emergency situation. The Applicant will conduct a study post-authorisation as indicated in the RMP (see section 2.7).

2.6.8. Discontinuation due to adverse events

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn from the study because of AEs. The results were similar to the AEs leading to withdrawal in the group randomised before 9 October 2020 with median follow up of 2 months. Among 19,067 participants with at least 2 months of follow-up time post Dose 2, 1 participant in the BNT162b2 group and no participants in the placebo group had an AE leading to withdrawal from the study.

No participants in the 16 to 17 years of age group experienced an AE leading to withdrawal. Among all 43,448 participants, no clinically meaningful differences in AEs leading to withdrawal were observed by age or other subgroups.

2.6.9. Post marketing experience

Post-marketing data are not yet available as the vaccine has not been approved in any country at the time of the data cut-off (14-Nov-20). After the cut-off date, it is noted that several countries have recently authorised the vaccine for emergency use (e.g. UK, Canada, US). Two cases of anaphylactoid reaction out of 138,000 persons vaccinated have been reported in individuals carrying Epipen after initiation of vaccination in one country, which resolved with standard therapy. One case of anaphylaxis was reported in another country (unknown denominator) in a subject without known history of

allergies, which required ICU and was then resolved. Post-marketing safety data are expected with the next monthly summary safety report.

2.6.10. Discussion on clinical safety

The safety database for BNT162b2 constitutes of two Phase 1 studies (BNT162-01[3] and C4591001[4]) and one Phase 2/3 study (C4591001) which is still ongoing. The cut-off date for safety data included in this assessment is 14 November 2020.

Up to the cut-off date ~44,000 subjects had been recruited and received at least one dose of either BNT162b2 (n=21,720) or placebo (n=21,728). The core safety database of this assessment constitutes of ~19,000 participants who have been followed ≥2 months after the 2nd dose of BNT162b2 (n=9531) or placebo (n=9536). The Applicant has also presented data from a subset of ~38,000 subjects randomised before 9 October 2020 with a median follow-up period of 2 months after Dose 2 of BNT162b2 (n=18,860) or placebo (n=18,846).

Demographic characteristics are considered well balanced between vaccine and placebo arm (median follow up 2 months). Subjects were mostly white (83%) and had a median age of 52 years. The younger and older age groups included 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Gender was balanced (51% male). Of note, 35% of individuals were obese in study arms. The demographic distribution was different between seropositive and seronegative individuals, with a median age of 43 years in seropositive and of 52 years in seronegative subjects. Furthermore, the seropositive group covered a higher rate of obese individuals (42.2% versus 34.7%). Demographic characteristics in all participants were roughly comparable to those with median follow up of 2 months.

Charlson co-morbidity diagnoses were balanced in both study arms (20%). Most prevalent co-morbidities were diabetes (7.8%), COPD (7.8%) and malignant disease (3.9% in the vaccine arm and 3.5% in the placebo arm). Other diagnoses accounted for ≤ 1% of subjects in both study arms (median follow up of 2 months).

In the Phase 2/3 study reactogenicity was evaluated in a subset of 8,183 subjects who received BNT162b2 (n=4093) or placebo (n=4090) according to the proposed dosing regimen. The number of subjects aged 16-17 years included in the reactogenicity subset was small (n=8; BNT162b2 n=5; placebo n=3). After each dose, all subjects were asked to report any local reactions, systemic events, and antipyretic/pain medication usage for 7 days, by using an e-diary.

Pain at the injection site was the most common local reaction reported in the vaccine group, slightly more frequently reported among subjects 16-55 years (~80%) compared to >55 years (~70%). In the placebo group 8-14% reported pain at injection site. In the vaccine group redness and swelling were overall reported at a frequency of 5-7% in both age groups (vs. placebo 0-1%). Use of antipyretic/pain medication was more common after Dose 2 than after Dose 1 in both age groups, and overall slightly lower among subjects >55 years regardless of the dose (younger group: 28% after dose 1 vs 45% after dose 2; older group: 20% vs 38%). The use of antipyretic/pain medication was less common in the placebo group (younger group: 34% after dose 1 vs 23% after dose 2; older group: 23% vs 18%).

Among the systemic reactions, headache and fatigue were the most common events, and the frequency was higher after Dose 2 compared to Dose 1 (16-55 YOA [47% vs 59%]; >55 YOA [34% vs 51%]). Fever also occurred more frequently after Dose 2 (16-55 YOA [4% vs 16%]; >55 YOA [1% vs

[3] Phase I: End of study 28 days after Dose 2.
[4] Phase I: participants enrolled in Phase1 in groups that do not proceed to Phase 2/3 (i.e. other doses than 30 µg) may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

11%]). None of the subjects >55 YOA in the placebo group reported events of fever and 1% of the subjects aged 16-55 years reported fever after the first dose.

Overall, the local and systemic reactions were transient and of short duration (resolved within few days after vaccination), the majority were of mild to moderate intensity, and milder and of slightly lower frequency among older subjects (>55 years of age).

In the group of 19,067 participants with 2 months follow up after dose 2, 21.4% and 12.6% (vaccine vs placebo) of the subjects reported at least one AE. 13.6%/3.6% reported at least 1 related AE. Rates were lower compared to the whole enrolled trial population (26.7% (vaccine) and 12.2% (placebo)).

AEs in subjects with a follow up of at least 2 months belonged most often to the SOCs "General disorders and administration site conditions" (11.9% vs 2.9%), "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%), occurring more often in the vaccine than in the placebo arm. PTs comprised most often vaccine typical reactions, i.e. injection site pain, redness and swelling, fever, chills, fatigue, headache as well as myalgia and arthralgia and malaise. Nausea also occurred more often in the vaccine arm (79 cases, i.e. 0.8%, in vaccine vs. 21 cases, i.e. 0.2%, in placebo). Lymphadenopathy was seen in 0.4% subjects in the vaccine arm (38 cases) vs. 0% in the placebo arm (3 cases).

Severe AEs were reported by a small number of subjects (≤1.1%) and equally distributed between the study arms. No differences were seen between age groups. Frequencies are comparable in the whole enrolled trial population and when stratifying according to serostatus.

Numerical imbalances are observed for several hypersensitivity/immunisation reaction preferred terms (5/3 cases in the ≥ 2 months follow up subset, 13/6 cases in the whole enrolled trial population subset, 4 cases deemed severe (whole enrolled trial population), in the SOC immune system disorders).

Lymphadenopathy, nausea, and hypersensitivity are reported more often with the vaccine arm. For these items there is a reasonable possibility of a causal relation to vaccination and they are as such included in the SmPC section 4.8.

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and among those two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. There are incoming reports of anaphylactoid reactions from ongoing vaccination campaigns. A warning is included in the SmPC addressing the need of adequate emergency material in place at the vaccination site, which is common practice with any vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

Four cases of peripheral facial paralysis were observed in vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole enrolled trial population, however the case of paresis was not considered for this calculation). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days

had no previous history of Bell´s palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician. Taken together, this was considered to indicate there is a reasonable possibility of a causal relation to the vaccine, and to justify inclusion of peripheral facial paralysis (Bell´s palsy) in the SmPC 4.8 with a frequency as 'rare'.

An imbalance in PT connected to sleep disturbances was noted in the whole enrolled trial population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus in the placebo arm). The occurrence of insomnia may plausibly be due to e.g. local/systemic reactogenicity that may occur after vaccination. The CHMP agreed to include insomnia in section 4.8. of the SmPC.

A slight imbalance of hyperhidrosis/night sweats was noted in the whole enrolled trial population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole enrolled trial population). These events may be plausibly associated to the injection of BNT162b2 and should therefore be included in the SmPC section 4.8.

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole enrolled trial population). In addition to pain at injection site, which was commonly reported, pain in the extremity is also considered plausibly related to the vaccination and should therefore be included in the SmPC section 4.8.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole enrolled trial population)), however these are considered not related to study treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm. These were numerically balanced in frequency between vaccine and placebo arm. Autoimmune events will be monitored post-authorisation as described in the RMP.

SAEs occurred at a low frequency in both BNT162b2 and the placebo group (0.6%, 56 cases in vaccine vs. 53 cases in placebo) in subjects with ≥2 months of follow-up post Dose 2, and a similar frequency was observed in the total study population. One SAE of lymphadenopathy and one SAE of shoulder injury were considered related to study intervention. No cases of related SAEs were reported in the adolescent group (only one case of facial bone fracture). Six events of death (2 in the BNT162b2 group and 4 in the placebo group) have been reported in the entire study population, all deemed unrelated to the vaccine.

The rate of subjects discontinuing participation in the study due to AEs was low in both study arms (0.2%/0.1%).

The subgroup of seropositive subjects is limited in size (n=545 BNT162b2; n=580 Placebo). A stratification according to serostatus for AE investigation was specifically performed in individuals with a follow up of at least one month (median Follow up 2 months) and ≥2 months. Most reported SOCs are similar to those identified in the ≥ 2 months population. AE rate in seropositive individuals was lower (22%) compared to seronegative individuals (27%) and no specific safety concern is detected in this subpopulation.

23 participants reported pregnancies in the safety database, nine of them were withdrawn from the study due to the pregnancy status. These participants will be followed up for pregnancy outcomes.

The Applicant has not provided a specific analysis of elderly individuals > 70 years included in the development program. In general, reactogenicity and AE rate were slightly lower in older compared to

younger individuals (stratified according to median age 55 years). Thus, no specific safety concern is anticipated for the elderly.

Data on immunocompromised individuals are limited, which was raised as missing information in the RMP and will be further followed up. 196 participants with stable HIV infection were included in the trial and reported AEs that were mostly reactogenicity-related with no SAEs. No specific safety concern is detected in this subpopulation.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics as applicable.

Assessment of paediatric data on clinical safety

The longest duration of follow-up in the 16-17 years of age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study, albeit is numerically lower (11.6%/4.8%, vaccine/placebo).

The reactogenicity subset included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) show reactogenicity events (local reactions and systemic events) with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

Overall, the safety of BNT162b2 in individuals 16-17 years of age is extrapolated from young adults in general.

Additional safety data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.6.11. Conclusions on the clinical safety

The safety evaluation is based on one ongoing Phase 2/3 study that at the time of data cut-off (14-Nov-20) included 43,448 subjects who received either two doses of BNT162b2 30µg (n=21 720) or placebo (n=21 728). Overall, the reported reactogenicity profile are in line with any authorised vaccine. In addition, the frequency of reported AEs and SAEs were low. The emerging safety profile is presently considered favourable. Long term safety data, interaction with other vaccines, data on use in pregnancy and other subgroups (e.g. frail subjects, or subjects with pre-existing autoimmune diseases) are missing at this stage.

The lack of long-term follow up renders the data provided non-comprehensive. Therefore, the delivery of the final C4951001 study report, including a 2-year follow up of the studied population, is classified as a specific obligation in the context of a conditional marketing authorisation.

The plan for the generation of further safety data post authorisation is described in the section below.

2.7. Risk Management Plan

Safety Specification

Summary of safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use during pregnancy and while breast feeding Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long term safety data

Risks considered important for inclusion of the summary of safety concerns

The review of available safety data, including post-marketing data emerging from use in the UK and US, the experience with biological products and other vaccines leads to the conclusion that anaphylaxis is an important identified risk for Comirnaty. This safety concern will be followed up via routine pharmacovigilance activities and in the planned and ongoing safety studies and reported in the monthly summary safety reports and PSURs.

Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease) should be taken into account. The Applicant has included VAED/VAERD as an important potential risk and will further investigate it in the ongoing pivotal study and a post-authorisation safety study.

Missing information

Since pregnant and breast-feeding women were excluded from the study, no information is available for those populations. It is agreed to include use during pregnancy and while breastfeeding as missing information in the RMP.

At the data cut-off of 14 Nov-20, 10-14 weeks safety data are available. Thus, long-term safety is included as missing information and will be characterised as part of the continuation of the pivotal clinical trial and the PASS.

Interaction with other vaccines, has not been evaluated in clinical trials and may be of interest to prescribers. As elderly individuals will be one target group for vaccination, and they often may need vaccination with other vaccines such as influenza and pneumococcus vaccines, further data is

requested. The Applicant commits to conduct a study of the co-administration of Comirnaty with inactivated quadrivalent influenza vaccine.

Data from use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders), is limited, and it is desirable to gather further data in these groups. Therefore, use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) has been included as missing information in the RMP. Furthermore, information is limited on the use in patients with autoimmune or inflammatory disorders, as well as in immunocompromised patients. Thus, these groups are also included as missing information. Such missing information will be collected in the post-authorisation safety studies.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine, and it is considered acceptable to not include those events in the list of safety specifications.

Pharmacovigilance Plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond the receipt and review and submission of ADRs include:

- A **web-based AE reporting portal** will be available for vaccine providers (*e.g.* pharmacists, nurses, physicians and others who administer vaccines) and recipients, to assist with anticipated high volume of reports (based on expectations of a large target population for vaccination). The portal will capture key adverse event data in the initial interaction and will provide automated intake into the Pfizer safety database via E2B for safety review.
- **Signal detection activities** for the lifecycle of vaccines consist of individual AE assessment at case receipt, regular aggregate review of cases for trends and statistically disproportionately reported product-adverse event pairs. Aggregated and statistical reviews of data are conducted utilizing Pfizer's software interactive tools. Safety signal evaluation requires the collection, analysis and assessment of information to evaluate potential causal associations between an event and the product and includes subsequent qualitative or quantitative characterization of the relevant safety risk to determine appropriate continued pharmacovigilance and risk mitigation actions. Signal detection activities for the COVID-19 mRNA vaccine, will occur on a weekly basis. In addition, observed versus expected analyses will be conducted as appropriate as part of routine signal management activity.
- Routine signal detection activities for the COVID-19 mRNA Vaccine will include routine and specific review of AEs consistent with the AESI list provided in the RMP.
- In addition, published **literature** will be reviewed weekly for individual case reports and broader signal detection purposes.
- Regulatory authority **safety alerts monitoring**, to detect and further investigate potential signals being raised on other areas outside of EU.
- A specific adverse reaction **follow-up questionnaire** intended to capture clinical details about the nature and severity of COVID-19 illness particularly in relation to potential cases of vaccine lack of effect or VAED.

- In addition to routine 6-monthly PSUR production, monthly summary safety reports will be compiled and submitted to EMA, to support timely and continuous benefit risk evaluations during the pandemic. Minimum data to be submitted include:
  - Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately);
  - Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women);
  - Interval and cumulative number of reports per HLT and SOC;
  - Summary of the designated medical events;
  - Reports per EU country;
  - Exposure data (including age-stratified);
  - Changes to reference safety information in the interval, and current CCDS;
  - Ongoing and closed signals in the interval;
  - AESI reports – numbers and relevant cases;
  - Fatal reports – numbers and relevant cases;
  - Risk/benefit considerations.
- The submission of monthly reports complements the submission of PSURs (requested initially every six months). The need and frequency of submission of the summary safety reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 submissions).
- Joint adverse event and product complaint (including available batch/lot information) trending reviews will be conducted routinely by the Applicant.

The proposed routine pharmacovigilance activities are considered appropriate for the safety profile of the product and the pandemic circumstances.

Traceability

Full traceability from manufacturing to vaccination administration site is crucial to ensure maintenance of the cold-chain as well as for pharmacovigilance purposes should assessment of a safety signal need to be performed by batch/lot.

The Applicant's proposal to ensure traceability include:

- SmPC 4.4 labelling to raise HCP awareness regarding the need to clearly record the name and batch of the vaccine to improve traceability;
- a tracking device on every vaccine shipping container that provides real-time monitoring of GPS location and temperature 24 hours per day, 7 days per week;
- vaccine carton labelling also containing a 2-D barcode which has the batch/lot and expiry embedded within
- additional tools for vaccinators to record manufacturer and lot/batch information at the time of vaccination including a Traceability and Vaccination Reminder Card and peel-off labels (stickers with brand name and lot/batch numbers), acknowledging that each Member State will decided if and how the tools will be used, in accordance with the national provisions for pharmacovigilance.

Each shipment to a vaccination site should be accompanied with a sufficient number of corresponding vaccinee traceability and vaccination reminder cards; the lot/batch numbers will be for the first batches distributed copied manually by the vaccinators, with the Applicant's commitment that by 31 January 2021 all batches shipped will be accompanied at the receipt point in the Member States by sufficient peel-off labels to facilitate the recording of brand name and lot/batch number both in the vaccinators' records and the vaccinee traceability and vaccination reminder cards, where the Member States will require it.

The Traceability and Vaccination Reminder will include:

- Space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine, and keep it thereafter;
- QR code that links to additional information;
- Adverse event reporting information.

Additional pharmacovigilance activities

The Applicant proposes the following 11 studies, of which 1 global, 3 in Europe only, 2 in Europe and US, and 3 in US only; the countries where 2 studies will be conducted are not available at this time. There are 6 interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, 1 study in high risk adults and 1 study addressing co-administration with another vaccine) and 5 non-Interventional studies (4 safety and 1 effectiveness):

Study (*study short name, and title*) **Status (*planned/on-going*)**	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
Category 2				
C4591001 *Ongoing*	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
			CSR submission 6 months post Dose 2:	31-Dec-2021
			Final CSR submission with supplemental follow-up:	31-Aug-2023
Category 3				
C4591011	Assessment of occurrence of safety events of interest, including severe or	Anaphylaxis	Interim reports submission:	30-Jun-2021

Planned	atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.	AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.		31-Dec-2021 30-Jun-2022 31-Dec-2022 31-Dec-2023
C4591012 *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission: Final CSR submission:	30-Jun-2021 31-Dec-2021 30-Jun-2022 31-Dec-2022 31-Dec-2023
C4591010 *Planned*	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final draft protocol submission for EMA review: Final CSR submission:	31-Jan-2021 31-Mar-2024

C4591015 *Planned*	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Use in pregnancy and while breast feeding.	Protocol draft submission: Final CSR submission:	28-Feb-2021 30-Apr-2023
C4591014 *Planned*	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified	-	Protocol draft submission: Final CSR submission:	31-Mar-2021 30-Jun-2023
BNT162-01 Cohort 13 *Ongoing*	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission: Final CSR submission:	30-Sep-2021 31-Dec-2022
C4591018 *Planned*	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Use in immunocompromised patients Use in patient with autoimmune or inflammatory disorders.	Protocol submission: IA submission:	28-Feb-2021 31-Dec-2021
Safety and immunogenicity in high risk adults *Planned*	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders).	Protocol submission: Final CSR submission:	30-Jun-2021 31-Dec-2022
ACCESS/VAC4EU *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders	Protocol submission: Final CSR submission:	28-Feb-2021 31-Jan-2024

		Long term safety data.		
Co-administration study with seasonal influenza vaccine *Planned*	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022

Non-Interventional Post Approval Safety Studies (4)

The Applicant proposes 4 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs.

Study C4591010 will be conducted in the EU using primary data collection to monitor a cohort of vaccinees and evaluate risk of safety events of interest reflecting the AESI list. A draft protocol C4591010 has been provided.

Additionally, Pfizer, on behalf of the Applicant, will sponsor one or more PASS using secondary electronic health records data sources in Europe based on a master surveillance protocol developed through the ACCESS project.

Two additional studies will be conducted using US data:

- 1 study using secondary data from EHR of active military and their families (C4591011),
- 1 study using secondary data from EHR of patients included in the Veterans Healthcare Administration system (C4591012).

The draft protocols for the proposed safety studies in the US (C4591011 and C4591012) have been provided.

Interventional studies (6)

The Applicant proposes 6 interventional studies, of which 2 are ongoing and 4 are planned.

- **Study C4591001** is an ongoing Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. At the time of the data cut-off date in Study C4591001 (14 November 2020), a total of 21,720 participants received at least one dose of the candidate vaccine.
- **Study BNT162-01 Cohort 13** is an ongoing multi-site (Germany), Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in 30 immunocompromised adults.
- **Study C4591015** is a planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID 19 mRNA vaccine.
- **Study C4591018** is a planned study of BNT162b2 in 100 adults receiving a stable dose of immunomodulators for the treatment of stable rheumatoid arthritis (RA), in two cohorts (50 tofacitinib, 50 TNF inhibitors). Subjects will be studied for safety, immunogenicity by neutralizing antibody titer, and evidence of asymptomatic infection by N-antigen antibodies.

- A planned **Phase II safety and immunogenicity study** (Safety and immunogenicity in high risk adults) in up to 150 immunocompromised adults (with a range of primary immunocompromising conditions and/or receiving immunocompromising treatments.
- **Co-administration study with seasonal influenza vaccine** study investigating the safety and immunogenicity of Comirnaty and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

Non-Interventional PASS in Pregnancy

The Applicant's proposed strategy to assess vaccination during pregnancy will be implemented in 2 stages. It is anticipated that initial use in pregnancy will be very limited; therefore, initially this information will derive from the 4 of the real-world safety studies (C4591010, C4591011, and ACCESS/VAC4EU), described in the preceding section. Study C4591012 is focused on patients in the Veterans Health Administration system and is not expected to capture many pregnancies given the demographics of the source population.

The findings from studies' interim analysis (where planned) will inform a strategy to assess pregnancy outcomes as vaccination in pregnancy expands. The Applicant will consider established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. The applicant's commitment and considerations are noted to evaluate pregnancy outcomes in a PASS using established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. Further feasibility analyses are awaited with RMP updates post-approval.

Non-Interventional Post-Approval Effectiveness study (1)

The Applicant will conduct at least one non-interventional study (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 illness in a real-world setting (C4591014). The effectiveness of COVID-19 mRNA vaccine will be estimated against laboratory confirmed COVID 19 illness requiring admission to the Emergency Department (ED) or hospital where SARS-CoV-2 is identified. These studies will allow to determine the effectiveness of Pfizer's vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups. The studies proposed below are under evaluation as potential commitments; studies are presented by geographical area (US and EU).

Overall conclusions on the Pharmacovigilance Plan

The proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

None proposed.

Risk minimisation measures

Routine Risk Minimisation Measures

Potential Medication Errors

The Applicant included a discussion on potential medication errors which is endorsed:

Large scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to: reconstitution and administration, vaccination scheme, storage conditions, errors associated with a multi-dose vial, and once other COVID-19 vaccines are available, confusion with other COVID-19 vaccines. These potential medication errors are mitigated through the information in the SmPC and further materials for healthcare providers which will be made available to the Member States to be integrated in the national campaign for communication, as needed.

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the COVID-19 mRNA vaccine.
- A poster with step-by-step instruction for vaccine storage, dose planning and preparation, and administration is available, which can be conspicuously displayed in settings where vaccine is to be administered for ongoing reference.
- Brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.
- Medical information call centres will be available for healthcare providers to obtain information on use of the vaccine.
- Traceability and Vaccination Reminder card will be provided with the pre-printed manufacturer name, dates of vaccination, batch/lot as a mitigation effort for potential confusion between vaccines.
- Peel-off labels with lot/batch number

These available resources will inform healthcare providers on the proper preparation and administration of the vaccine and reduce the potential for medication errors in the context of a mass vaccination campaign. Additionally, the patient information leaflet and, in those MSs where applicable, a Traceability and Vaccination Reminder card informs patients of the vaccine received so that a series is completed with the same product.

Summary of additional risk minimisation measures

None proposed.

The Applicant stated that Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. This is acceptable.

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks		
Anaphylaxis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Important Potential Risks		
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591001 (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Missing information		
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC section 4.6; PL section 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	Additional risk minimisation measures: No risk minimisation measures.	Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591015 (30-Apr-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in immunocompromised patients	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR or IA Due Date) • BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Dec-2022) • C4591018 (IA: 31-Dec-2021) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date submission) • C4591001 subset (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024) • Safety and immunogenicity in high risk adults (31-Dec-2022).

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591018 (31-Dec-2021) • ACCESS/VAC4EU (31-Jan-2024).
Interaction with other vaccines	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • Co-administration study with seasonal influenza vaccine (31-Dec-2022).
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date or IA CSR submission) • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Summary of the risk management plan

The public summary of the RMP is acceptable.

Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan **version 1.0** is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. Furthermore, During the duration of the COVID-19 pandemic situation, the MAH shall submit summary safety reports submitted to EMA, including spontaneously reported data and data from compassionate use and expanded access programs. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

The following exemptions from labelling and serialization requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the *Questions and Answers on labelling flexibilities for COVID-19 vaccines* (EMA/689080/2020 rev.1, from 16 December 2020)[5] document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

Labelling exemptions

US packaging specific derogations (valid for December '20 and January '21)

All EU Members States (MSs), as well as Norway and Iceland, have agreed to grant a temporary

[5] Available at https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid19-vaccines_en.pdf, last consulted on 21 December 2021.

exemption to allow the placing in the EU market of the US packaging, under the following conditions:

a. The validity is only temporary and the MAH shall switch to the EU labelling requirements by February '21;

b. The US pack will have included a Quick Response (QR) code which the vaccine recipient could scan and gain access to the package leaflet (PL) in his/her national language;

c. The MAH shall supply a separate printed PL in the national language(s) of those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine.

EU packaging specific derogations (from February '21 onwards)

a. Outer and immediate labelling will be provided in English only.

The MAH shall provide outer and immediate labelling in all EU languages by 2nd Q 2022. This exemption is justified on the deep-frozen storage/shipping requirements and the necessity to label batches ahead of time. Production of different vaccine packs in different languages will significantly reduce the supply chain efficiency. The multiple changes on packaging lines will result in significant time and capacity losses and would slow down the rapid deployment of COVID-19 vaccines. Moreover, English only labelling will better help to manage a shortage situation in one country by using immediately the supply from another country.

b. A printed package leaflet will be provided in the national language(s) for those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine. In addition, a QR code printed on the outer label and the PL will provide access to the package leaflet in the national language(s).

The MAH shall provide a printed package leaflet in all EU languages by 2nd Q 2022.

The MAH shall engage with the National Competent Authorities (other than the 6 mentioned above) to discuss and speed up the provision of PLs in the respective national language(s) of the MSs concerned. The MAH shall also contact MSs directly to agree on the exact numbers of PLs to be distributed, again in line with the published Q&A on labelling flexibilities.

c. The Blue Box will be omitted for the initial batches. The MAH shall provide the Blue Box via a QR code at a later stage following agreement on exact timing of implementation with the National Competent Authorities in each MS.

d. The inclusion of the EU Marketing Authorisation number in the labelling will be implemented with the switch from US packaging to EU compliant packs in February 2021.

Exemption from the obligation of serialisation

US packaging specific derogations (valid for December '20 and January '21)

a. It is acceptable that the US pack will be placed in the EU market without serialisation according to the EU FMD requirements. Only the Global Trade Item Number (GTIN) will be common for US & EU and this will be printed on the US pack.

EU packaging specific derogations (from February until March '21)

- All EU Member States have accepted a temporary derogation from serialisation for the EU pack from February until the end of March 2021.

- The MAH shall provide two progress reports on the serialisation: a first by 1st of February '21 and a second by 1st of March '21 referring to details on the progress achieved in terms of ensuring compliance, e.g. proof of acquiring the relevant equipment, the date for the validation, the proof of contract to connect to the European Medicines Verification Organisation.

- The MAH shall provide additional mitigating measures, e.g. immediate reporting of any stolen product during the period of exemption, reporting of any counterfeit or falsified vaccine in the EU or third countries in the legal supply or internet, reconciliation of product distributed and used in the respective territory.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- The Summary of Product Characteristics
- The Package Leaflet
- Safe Handling Guidelines for Dry Ice
- Shipping and Handling Guidelines Brochure
- Preparation and Administration Video
- Storage and Handling Video
- Returning the Thermal Shipping Container video
- How to prepare and Administer Poster
- Traceability and vaccination reminder card
- Returning the thermal Shipping Container brochure
- Dry Ice Replenishment Brochure
- Link to Adverse Event Reaction Reporting

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation (EC) No 726/2004, Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS). The pandemic is ongoing despite unprecedented efforts to control the outbreak. According to ECDC histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

As of 1 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

Comirnaty is intended for active immunisation against SARS-CoV-2, thereby preventing COVID-19.

3.1.2. Available therapies and unmet medical need

There is currently no approved vaccine in the EU available to prevent COVID-19. Several development programs are ongoing globally and currently other applications are under evaluation by regulatory authorities worldwide. There is a very high global demand for vaccines to help contain the pandemic and decrease morbidity and mortality in at risk groups.

3.1.3. Main clinical studies

The clinical development consists of one FIH phase 1 study (BNT162-01) in younger and older adults (18-55 years and 56-85 years) comparing 4 vaccine candidates, and one pivotal clinical study, C4591001 (or BNT162-02).

The pivotal study is a phase 1/2/3 placebo-controlled, randomised, observer-blind, dose finding, multicentre study performed in the US (start date 4 May 2020), Argentina, Brazil, Turkey, Germany, and South Africa, to evaluate the safety, immunogenicity and efficacy of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 in healthy adults. The phase 1 part of the study was designed for dose evaluation of 2 vaccines: BNT162b1 and BNT162b2 in younger (18-55 years) and older (65-85 years) adults. The Phase 2 part was designed to confirm safety and immunogenicity of the selected vaccine, BNT162b2, in the first 360 subjects enrolled in the Phase 2/3 part of the study.

The Phase 2/3 part of the study was designed to enrol up to 43,998 subjects (randomised 1:1 to BNT162b2 or placebo) to receive BNT162b2 at the dose of 30 µg, given as 2 IM injections 21 day apart (within 19 to 42 days), for an efficacy assessment in addition to safety and exploratory immunogenicity assessments.

The primary endpoint was symptomatic COVID-19 incidence per 1000 person-years of follow-up based on centrally or locally confirmed nucleic acid amplification test (NAAT) in subjects without serological or virological evidence of SARS-CoV-2 infection before and during vaccination regimen (cases confirmed ≥7 days after Dose 2), and in subjects with and without evidence of SARS-CoV-2 infection before and during vaccination regimen. The study was event-driven, i.e. the final efficacy analysis was to be triggered by 162 cases; in practice 170 cases were reached.

3.2. Favourable effects

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9) in subjects ≥16 years of age without prior evidence of SARS-CoV2 infection and 94.6% (95% CI 89.6, 97.6) in all subjects regardless of prior evidence of SARS-CoV-2 infection (primary endpoint). This outcome met the pre-specified success criteria.

Vaccine efficacy after dose 1 to before dose 2 was 52.4% (95% CI 29.5, 68.4). Vaccine efficacy from 10 days after dose 1 to before dose 2 was estimated to be 86.7% (95% CI 68.6, 95).

The efficacy analyses in the all-available efficacy population (including participants who had protocol violations), showed consistent results with those in the primary analysis population. The efficacy analyses using CDC defined symptoms to identify a COVID-19 case gave similar efficacy results as the primary endpoints.

The VE in each demographic subgroup analysed, as defined by age (including subjects >65 years), sex, race, ethnicity, and country and in individuals with comorbidities including obesity, diabetes, hypertension and cardiopulmonary diseases was >90%. In the obese population, VE was 95.4% (CI 95% 86.0%, 99.1%).

VE among 65-74-year-olds was 92.9% (CI95% 53.1%, 99.8%). VE among >75-year-olds was 100% (CI95% -13.1%, 100.0) with 0 cases in the vaccine group and 5 cases in the placebo group. VE among >65 years and at risk of severe COVID-19 was 91.7% (95% 44.2%, 99.8%).

Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, but the number of cases after second dose was very low, 1 case in the vaccine group and 4 cases in placebo group. Counting cases from after dose 1, there were 1 case in the vaccine group and 9 cases in the placebo group.

Phase 1 and phase 2 immunogenicity data from both the pivotal study C4591001 and supportive study BNT162-01 have shown robust humoral responses after vaccination with 2 doses of BNT162b2 at 30 µg in both younger (18-55 years) and older adults (age groups 56-85 years and 65-85 years), and both in terms of neutralising antibodies and IgG-antigen binding antibodies. The second dose given 21 days post-dose 1 induced a marked boosting effect in both younger and older adults. Responses were generally faster and higher in younger adults than in older adults. The levels of neutralizing antibodies titres were moderate 21 days after dose 1. The peak of neutralizing antibodies titres was reached 14 days post-dose 2 in older adults versus 7 days post-dose 2 in younger adults. Immune responses were maintained up to 1-month post-dose 2 in both age groups based on available data.

Study BNT162-01 provides evidence for T cell-mediated immune response, with antigen-induced IFNγ expression demonstrating a Th1 CD4+ and CD8+ phenotype following the second dose of vaccine. For the 30 µg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults.

The immunogenicity results are only considered supportive at this stage, as no correlate of protection has been established. The immune responses support the need for two doses, as neutralising antibody

levels increased substantially following the second dose compared to the first dose. Cell mediated immune responses were demonstrated in very few subjects in phase 1 but confirm a Th1 dominated cytokine pattern.

3.3. Uncertainties and limitations about favourable effects

Based on the available limited data, no reliable conclusion on the efficacy of the vaccine against severe COVID-19 can be drawn from 7 days after the second dose (secondary endpoint). The estimated efficacy against severe COVID-19 occurring at least 7 days after dose 2 was 66.4%, with a large and negative lower bound CI (95% CI: -124.8%; 96.3%). Only a limited number of events occurred at the cut-off date of analysis (1 and 4 cases in the vaccine and placebo groups respectively). The posterior probability for the true vaccine efficacy ≥ 30% (74.29%) did not meet the pre-specified success criterion. Consequently, the efficacy against the severe disease across subgroups, notably certain populations at high-risk of severe COVID-19 cannot be estimated (elderly and subjects with comorbidities).

Efficacy against asymptomatic infection is not available but, notwithstanding all the limitations, will be assessed through seroconversion of N-binding antibodies in BNT162b2 and placebo recipients who did not experience COVID-19.

The pivotal study was not designed to assess the effect of the vaccine against transmission of SARS-CoV-2 from subjects who would be infected after vaccination. The efficacy of the vaccine in preventing SARS-CoV-2 shedding and transmission, in particular from individuals with asymptomatic infection, can only be evaluated post-authorisation in epidemiological or specific clinical studies.

Duration of protection has currently been followed up for approximately 100 days after dose 1. Data on longer term protection are anticipated to the extent that the ongoing phase 3 study can continue as planned with a placebo group. The assessment of efficacy over a period of at least 6 months is expected to determine the need and the appropriate time of a booster dose.

There seems to be at least a partial onset of protection after the first dose, but this remains unconfirmed at this stage.

There are very limited or no data in immunocompromised subjects and in pregnant women. Efficacy in subjects aged 16-17 years is extrapolated from young adults as no cases of disease were reported in this small group at this stage.

Available data do not suffice to establish efficacy in subjects seropositive for SARS-CoV-2 at baseline, and subjects with a known history of COVID-19. However, efficacy is anticipated in this group; to the extent that they are not naturally protected against re-infection, which is presently incompletely characterised.

3.4. Unfavourable effects

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies (BNT162-01 and C4591001) that included 21,744 participants that have received at least one dose of Comirnaty.

In Study C4591001, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study C4591001, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older. Reactogenicity was evaluated in a subset of 8183 subjects (n=4093 vaccinated; n=4090 placebo) up to 7 days after each dose.

Regarding reactogenicity, the most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%). All reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. The frequency of headache, fatigue and fever was higher after Dose 2 in both age groups.

Regarding AEs, at least one AE was reported in 21% of the vaccinated subjects and in 13% of the placebo arm. The frequency of severe AEs was low (<1%) in both study arms. The most frequently reported SOC were "General disorders and administration site conditions (11.9% vs 2.9%)", "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%). PTs comprised mainly of vaccine typical reactions such as injection site pain, headache, fever, fatigue, malaise as well as myalgia and arthralgia.

For subjects with a follow-up of ≥2 months, SAE were reported at a low frequency (0.5-0.6%) in both the vaccine and the placebo group, with no clinically meaningful differences by age, baseline serostatus, ethnicity, race or sex. Lymphadenopathy and nausea were reported to occur more often in the vaccine group compared to the placebo group in the whole enrolled trial population (respectively 0.4% and 0.6% higher rate than placebo). Numerical imbalances in reporting were observed for insomnia, injection site pruritus and pain in extremity. Since these are supported by a biologically plausible relation to vaccination, these AEs are reflected in the SmPC.

Acute peripheral paralysis was reported in 4 vs. 0 cases (vaccine vs placebo) in the whole study population, of which 2 cases were deemed related to study treatment (see section 2.6.10). For acute peripheral paralysis, there is a reasonable possibility of a causal relation to vaccination and should therefore be included in the SmPC.

In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. Three reports of anaphylaxis were identified during vaccination campaigns by the time this report was written.

Few cases of hypersensitivity/immunisation reaction events have been observed with the vaccine (13 vs 6 cases) in the whole study population. Hypersensitivity should be annotated in the SmPC, section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

Long term safety data is not available at this stage, however the Phase 2/3 study will follow the included subjects up to 2 years post vaccination, so these data are expected post-authorisation.

AEs were slightly lower in subjects seropositive to SARS-CoV-2 at baseline (22% vs. 27% in seronegatives), however the number of such subjects was limited (vaccinated n=558; placebo n=590).

Data on immunocompromised individuals is limited, as only 196 participants with stable HIV infection were included in the study. No specific safety concern was detected.

Data from exposure during pregnancy is very limited. Up to the cut-off date 23 pregnancies have been reported in the Phase 2/3 trial and will be followed up for outcome.

Multiple long-term pharmacoepidemiology safety studies are planned to be conducted in order to confirm the safety profile in the already studied population as well as in a broader population including pregnant, immunocompromised and very elderly subjects.

There is no data available on interaction with other vaccines given in co-administration.

In the Phase 2/3 study, the total number of included subjects aged 16-17 years was smaller compared to other age groups (n=138 BNT162b; n=145 placebo), however no safety concerns were identified.

Uncertainties remain regarding causality association of acute peripheral paralysis to vaccination due to the limited number of cases, which are consistent with background rates. Nevertheless, facial paralysis will be included as an adverse event of special interest (AESI) for pharmacovigilance monitoring and in the active surveillance study protocols.

While apart from facial paralysis, whose aetiology is currently unknown, no possible autoimmune adverse events where identified as causally related to vaccination, rare events of this nature cannot be excluded based on the size of the available data set.

There is a theoretical risk, based on non-clinical data with MERS and SARS vaccines, of vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), however no cases were identified in clinical studies with COVID-19 vaccines, including Comirnaty, and the characterisation of the immune response does not indicate a risk profile in this regard (Th1 skewed).

This vaccine contains two new components (cationic lipid ALC-0315 and PEGylated liquid ALC-0159) in the LNP, for which there is limited experience. Some uncertainties remain regarding the ALC-0315 long half-life. Regarding PEG related toxicity which is known to depend on the dose, dose frequency, duration of treatment and molecular weight of the PEG protein, immunogenicity is not expected to be an issue due to the low molecular weight of this PEG (<2KDa). The scientific data available at this stage do not raise noticeable concerns regarding immunogenicity or immunotoxicity of the PEG, but current evidence is not definitive.

3.6. Effects Table

Table 20 Effects Table for Comirnaty intended for active immunisation to prevent COVID-19 caused by against SARS-CoV-2 in individuals 16 years of age and older (data cut-off: 14 Nov 2020)

Effect	Short Description	Unit	BNT162b2 (30 µg)	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Vaccine efficacy	First COVID-19 occurrence from 7	**% (95% CI)**	**95.0** (90.0, 97.9)			

Effect	Short Description	Unit	BNT162b2 (30 µg)	Placebo	Uncertainties / Strength of evidence	References
	days after Dose 2, without prior SARS-COV-2, **overall**	**Cases/** Number of subjects at risk for the endpoint	**8/** 17411	**162/** 17511	Robust data with similar efficacy confirmed in all age sub-groups (16-64YOA, >65YOA, 65-74YOA, >75YOA)	Evaluable efficacy population (7 days post dose 2) - Study C495100
		% **(95% CI)**	**94.7** (66.7, 99.9)			
	Patients aged ≥65	**Cases/** Number of subjects at risk for the endpoint	**1**/3848	**19**/3880		
Unfavourable Effects						
Lymphadenopathy		% (denominator)	0.3% (n=21720)	0% (N=21728)		
Facial paralysis		Number of cases	4	1	Small number of cases, short duration of follow-up	All enrolled Phase 2/3 participants
Hypersensitivity/immunisation reaction		Number of cases	13	6		
			Post dose 1	**Post dose 2**	**Post dose 1**	**Post dose 2**		
Pain at injection site	16-55 years	%	83%	79%	14%	12%	Transient events, majority mild to moderate intensity	Reactogenicity subset of study C495100
	>55 years		71%	66%	9%	8%		
Headache	16-55 years		42%	52%	34%	24%		
	>55 years		25%	39%	18%	14%		
Fatigue	16-55 years		25%	39%	25%	39%		
	>55 years		34%	51%	23%	17%		

Abbreviations:
COVID-19: Coronavirus disease, SARS-CoV-2: Severe Acute Respiratory Syndrome, CI: Confidence Interval

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, substantial efficacy in preventing symptomatic COVID-19 infection has been demonstrated, as well as an acceptable safety profile in a large phase 3 study. Uncertainties relate to the

characterization of active substance and finished product. Given the comparable immunogenicity from 10 to 30µg doses, an impact on efficacy of the acceptance of somewhat lower levels of intact mRNA in the commercial product is not considered likely. Furthermore, based on low levels and biological plausibility, an impact of mRNA impurities on safety is deemed unlikely (see section 3.7.3).

Due to the limited extent of safety follow-up, the delivery of final data from the full 2-year follow up in the pivotal clinical trial are considered important to confirm the current knowledge.

With regards to the balance of efficacy and safety benefits and risks, it is overwhelmingly positive for subjects at risk of severe COVID-19, including the elderly and those with comorbid conditions, which are known to increase the risk of complication and death due to infection.

Uncertainties concerning the pharmaceutical characterization of the commercial product are compatible with a positive benefit/risk balance. This pertains not only to adults but, by extrapolation, to individuals 16-17 years of age.

Data are limited in individuals seropositive against SARS-CoV-2 at baseline. Available data however do not indicate any specific safety concerns, and efficacy is anticipated also in this subset.

There are no data on use in pregnant women, but a protective effect is anticipated. In the light of the reassuring data from the DART study, noting that pregnancy as such is a risk factor for severe COVID-19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis.

Based on biological plausibility no risk in breastfeeding is anticipated.

While there was no indication of an excess risk of severe allergic reactions such as anaphylaxis in the clinical study program, three post marketing cases, of which 2 in patients carrying adrenaline pens and one in a person with no known history of allergies, have been reported during vaccination campaigns, and all resolved with standard treatment. Hypersensitivity to the active substance or to any of the excipients is a contraindication. However, there is presently no substantial evidence of a negative benefit/risk balance in a subject with severe allergy to substances absent in the vaccine. For all subjects, the vaccine should be administered in settings where resuscitation facilities are available, as specified in the SmPC and in line with other vaccines. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

There are no efficacy data in immunocompromised individuals. Such patients may not be protected as well as immunocompetent individuals by vaccination. While there are limited safety data too in the immunocompromised subjects (a broad and disparate category), no particular safety issues are anticipated, and the benefit/risk balance of vaccination of such subjects is deemed positive, also in light of the underlying excess risk of COVID-19.

Studies to monitor potential safety concerns (autoimmune disorders, VAED) are planned.

3.7.2. Balance of benefits and risks

Overall, the available data are supportive of a positive B/R in the proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

Given the emergency situation, it is considered that the identified uncertainties can be addressed post-authorisation in the context of a conditional MA, including further characterisation of the active substance and finished product, the continuation of the pivotal study as long as possible, and post-approval effectiveness studies and routine disease surveillance.

Conditional marketing authorisation

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine (Process 1). The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities.

Data demonstrates the presence of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are not sufficiently characterised, and although the limited data provided for protein expression does not fully address uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein, the amount of any such proteins, is expected to be too low to elicit an immune response of biological relevance.

Indeed, considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell it cannot be excluded that different proteins than the intact full-length spike will be expressed. The risk of unwanted immunological events is considered low based on the following observations and considerations:

- Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
- The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA able to be translated into a specific protein or peptide.
- The level of any individual fragment of mRNA species would anyway be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the truncated proteins would be non-significant.

Also, lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

Regarding the proposed control strategy for active substance and finished product, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Considering the above and the current public health emergency, the characterisation of the active substance and finished product are considered acceptable, and the proposed specifications for RNA integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product, and considering clinical experience, are considered important to confirm the adequacy of these specifications, and these data should be provided post-approval as specific obligations to the MA.

Therefore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

Studies are underway to complete the characterisation of the active substance and finished product, and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment by the CHMP in order to complete all proposed specific obligations. Based on the Applicant's plans and documentation, it is expected that data to fulfil all quality SOs will be submitted gradually between March and July 2021.
Furthermore, the applicant will continue the ongoing pivotal Phase 3 randomized, placebo-controlled, observer-blind study C4591001 to obtain 2-year long-term data and to ensure sufficient follow-up in order to confirm the efficacy and safety of Comirnaty.

- Unmet medical needs will be addressed

There is no approved or widely available COVID-19 vaccine, and COVID-19 remains associated with substantial morbidity and mortality. While care for patients who have COVID-19 has improved over time and with clinical experience, no medications to cure COVID-19 are available and there remains an urgent need for a prophylactic vaccine during the ongoing pandemic.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Convincing efficacy evidence including the elderly and those with comorbid conditions has been provided and long-term effectiveness and safety data will be provided post-authorisation. Taking all this into account, it would not be considered appropriate to withhold a highly beneficial vaccine considering the severity of COVID-19 disease and the current global pandemic situation, since the demonstrated benefits in the current emergency setting clearly outweigh the uncertainties of the available data as outlined above.

3.8. Conclusions

The overall benefit/risk balance of Comirnaty is positive.

As available data are non-comprehensive, granting of a conditional marketing authorisation is relevant, and in line with provisions of Article 14-a of Regulation (EC) No 726/2004 it is supported.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Comirnaty is favourable in the following indication:

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions and specific obligations:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

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Vaccines and Related Biological Products Advisory Committee Meeting
December 10, 2020

FDA Briefing Document

Pfizer-BioNTech COVID-19 Vaccine

Sponsor:
Pfizer and BioNTech

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Glossary

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	Che
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
modRNA	nucleoside-modified messenger RNA
NAAT	nucleic acid amplification-based test
PVP	Pharmacovigilance Plan
RBD	receptor binding domain
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On November 20, 2020, Pfizer and BioNTech (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older." The proposed dosing regimen is 2 doses, 30 µg each, administered 21 days apart.

The EUA request includes safety and efficacy data from an ongoing phase 3 randomized, double-blinded and placebo-controlled trial of BNT162b2 in approximately 44,000 participants. The primary efficacy endpoint is incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen. In a mid-November analysis of 36,621 participants randomized 1:1 to vaccine or placebo who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination regimen, efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.

Safety data from approximately 38,000 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. Available safety data from all participants enrolled through the November 14, 2020 data cut-off (N=43,252, which includes late enrollment of additional adolescent and adult participants), was consistent with the safety profile for the approximately 38,000 participants with median follow-up of 2 months and also did not raise specific safety concerns. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ≥55 years of age (≤ 2.8%) as compared to younger participants (≤4.6%). The frequency of serious adverse events was low (<0.5%), without meaningful imbalances between study arms. Among non-serious unsolicited adverse events, there was a numerical imbalance of four cases of Bell's palsy in the vaccine group compared with no cases in the placebo group, though the four cases in the vaccine group do not represent a frequency above that expected in the general population. Otherwise, there were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations on whether:

- based on the totality of scientific evidence available, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 in individuals 16 years of age and older, and
- the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks for use in individuals 16 years of age and older.

The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

2. Background

2.1. SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of November 30, 2020, has caused more than 60 million cases of COVID-19 and claimed the lives of 1.5 million people worldwide. In the United States, over 13 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 260,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is a main target for neutralizing antibody, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain (RBD), as the immunogenic determinant.

2.2. EUA Request for the Pfizer and BioNTech COVID-19 Vaccine BNT162b2

Pfizer, in partnership with BioNTech Manufacturing GmbH, is developing a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNP). The Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2) is administered intramuscularly as a 2-dose series spaced 21 days apart at a dose of 30 µg each. The vaccine is supplied as a multi-dose vial (5 doses) containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for five 0.3 mL doses. The vaccine is preservative free.

A phase 3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. Vaccine efficacy for the primary endpoint against confirmed COVID-19 occurring at least 7 days after the second dose was 95.0% with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group. Data from about 38,000 participants randomized 1:1 with a median of 2 months of follow-up after the second dose of vaccine showed a favorable safety profile at a dose of 30 µg in participants 16 years of age and older. On November 20, 2020, Pfizer and BioNTech submitted an EUA request to FDA for its investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by SARS-CoV-2.

2.3. U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and it would be under further investigation (under an Investigational New Drug Application) until it is licensed under a Biologics License Application (BLA). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4. Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" (Appendix C, page 53) describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.

2.5. Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[6]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing phase 3 studies.

Phase 3 Follow-up

Data from phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[7] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.6. Continuation of clinical trials following issuance of an EUA for a COVID-19 vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Some developers have proposed maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[8-10]

2.7. Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session, to discuss, in general, the development, authorization and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents

- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
  - Further evaluate safety, effectiveness and immune markers of protection
  - Evaluate the safety and effectiveness in specific populations.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on December 10, 2020, to discuss and provide recommendations on whether:

- based on the totality of scientific evidence available, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 in individuals 16 years of age and older, and
- the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks for use in individuals 16 years of age and older.

The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

4. Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

4.1. Vaccine Composition, Dosing Regimen

The Pfizer-BioNTech COVID-19 Vaccine is a white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection. The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen [between -80°C to -60°C (-112°F to -76°F)] multi-dose (5-dose) vial. The vaccine must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 5 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution.

The Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 21 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. As such, FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2. Proposed Use Under EUA

The proposed indication and use of the vaccine under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older."

5. FDA Review of Clinical Safety and Effectiveness Data

5.1. Overview of Clinical Studies

Data from two ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study C4591001 is a multi-center, multi-national Phase 1,2,3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study BNT162-01 is a Phase 1 study that explored various vaccine candidates and dose levels and will not be discussed in detail. A brief summary of the BNT162-01 study design and results to date is found in Appendix A, page 51.

Table 1: Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Pfizer-BioNTech COVID-19 Vaccine

Study Number/ Country	Description	BNT162b2 (30 µg)* participants (N)	Placebo participants (N)	Study Status
C4591001 USA, Argentina, Brazil, Germany, S. Africa, Turkey	Phase 1,2,3 randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 24 Phase 2/3: 21823	Phase 1: 6 Phase 2/3: 21828	Ongoing
BNT162-01 Germany	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity, dose escalation	12	0	Ongoing

N= total number of randomized participants as of November 14, 2020. Placebo: saline.
*Phase 1 studies included additional participants vaccinated with other dose levels and other mRNA vaccine candidates.
Studies C4591001 and BNT162-01 started in April 2020 (first participant, first visit).

5.2. Study C4591001

5.2.1. Design

Study C4591001 is an ongoing, randomized, placebo-controlled, phase 1/2/3 study being conducted in the US, Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a phase 1/2 study in healthy adults in the US for vaccine candidate and dosage selection, immunogenicity and preliminary efficacy, but the protocol was revised to expand the study design for inclusion of a phase 2/3 portion to evaluate clinical disease endpoint efficacy in individuals 12 years of age and older in the US and additional sites outside of the US.

In phase 1, two age groups were evaluated in separate cohorts, younger participants 18 through 55 years of age (N=45) and older participants 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received escalating dose levels with progression to subsequent dose levels and evaluation of escalating dose levels in the older age group (65 through 85 years), based on recommendations from an internal review committee that reviewed safety and immunogenicity data. For each vaccine candidate and dose

level, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from phase 1, in combination with data from Study BNT162-01 (See Section 10), supported the final vaccine candidate and dose level (BNT162b2 at 30 µg, given 21 days apart) to proceed into phase 2/3.

In phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) and a goal of 40% enrollment in the older adult age group. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study, so the age strata were revised as follows: 12 through 15 years of age, 16 through 54 years of age, and 55 years of age and older. The study population for phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19 disease, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. The phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants enrolled early-on, and these participants also contribute to the overall efficacy and safety data in the phase 3 portion. The ongoing phase 3 portion of the study is evaluating the safety and efficacy of BNT162b2 for the prevention of COVID-19 disease occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (midturbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (e.g., Cepheid; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001) Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design includes planned interim analyses of the first primary efficacy endpoint at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases), and all primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued (see Statistical Analysis section, below). Participants are expected to participate for a maximum of approximately 26 months.

Primary Efficacy Endpoints

Study C4591001 has two primary endpoints:

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Secondary Efficacy Endpoints

Study C4591001 has secondary endpoints based on different approaches to COVID-19 case evaluation criteria as follows:

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2

CDC-defined COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was the presence of at least one of the following symptoms and a positive SARS-CoV-2 NAAT within 4 days of the symptomatic period:

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

For a secondary efficacy endpoint, a second definition, which may be updated as more is learned about COVID-19, included the following additional symptoms defined by CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

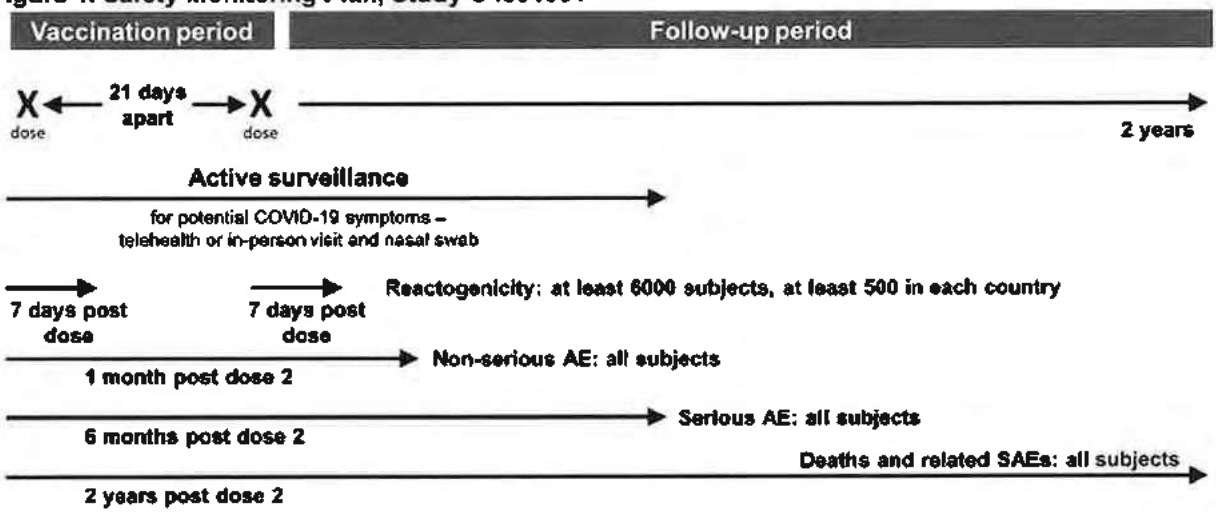
For another secondary endpoint, the case definition for a severe COVID-19 case was a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of BNT162 vaccine(s) in healthy adults after 1 or 2 doses. All phase 1 participants (n=30), and then 6653 U.S. participants (360 phase 2, 6293 phase 3) and the first ~500 phase 3 participants/per country with enrollment through October 9, 2020 (Argentina, Brazil and South Africa) recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from Dose 1 to 1 month after the last dose and serious AEs (SAEs) from Dose 1 to 6 months after the last dose. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study C4591001



Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), and antipyretic/pain medication use were recorded in an e-diary. At the data cutoff date for the EUA, reactogenicity events were not collected from adolescents 16 to 17 years of age (enrolled prior to the implementation of Protocol Amendment 9, finalized on 29 October 2020) using an e-diary but were detected and reported as unsolicited AEs. For any phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as unsolicited AEs. HIV-positive participants and adolescents 12 through 15 years of age were included in the reactogenicity subset with implementation of protocol amendment 6 (finalized on September 8, 2020) and amendment 7 (finalized on October 6, 2020), respectively. Solicited reactogenicity data in adolescents 16-17 years of age are not available for the reporting period. Reactogenicity data from a total of 100 adolescents 12 through 15 years of age enrolled in C4591001 phase 2/3 were provided in the EUA submission. However, the Sponsor did not request inclusion of this age group in the EUA because the available data, including number of participants and follow-up duration, were insufficient to support favorable a benefit-risk determination at this time. Therefore, the reactogenicity data for participants 12 through 15 years of age are not presented in this document.

Clinical laboratory tests were assessed in phase 1 at 1-week postvaccination. The planned safety follow-up for currently enrolled adolescents and adults is through 24 months after vaccination #2.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

In phase 2/3, monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants, and alert criteria were triggered when this probability was less than 11%.

Analysis Populations

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed informed consent document.
Randomized	All participants who are assigned a randomization number.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.

Phase 2/3 safety analysis populations were as follows:

- Phase 2/3 all-enrolled population: composed of a total of 43,448 (21720 vaccine, 21728 placebo) participants ≥16 years of age, regardless of duration of follow-up, for whom written informed consent was obtained. Initial enrollment included individuals 18 years and older, then included individuals as young as 16 years of age and individuals with known HIV (protocol amendment 6; finalized on September 8, 2020). As of November 14, 2020, 43.9% and 79.5% of vaccine recipients completed at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks) were similar to the vaccine group.

- Phase 2/3 safety population (median follow-up time of 2 months after vaccination #2): comprised of a total of 37586 (18801 vaccine,18785 placebo) participants >16 years of age enrolled by October 9, 2020 and received at least 1 dose of study vaccine or placebo; overall, 98.1% of participants completed the 2-dose series. As of November 14, 2020, 50.6% and 91.6% of vaccine recipients completed at least 2 months (>8 weeks) and at least 1 month (>4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (>8 weeks) and at least 1 month (>4 weeks) were similar to the vaccine group. A total of 283 (138 vaccine,145 placebo) individuals were 16 to <18 years of age. HIV-positive individuals were included in the all-enrolled population, but not the phase 2/3 safety population because the number of participants enrolled by October 9, 2020 was small (n=120) and the median duration of safety follow-up was short.

5.2.2. FDA Assessment of Phase 2/3 Follow-Up Duration

Study C4591001 initially enrolled approximately 30,000 participants and then several months later began enrollment of approximately 14,000 additional participants, including adolescents and participants with chronic, stable HIV, hepatitis B, or hepatitis C infections. Because of the gap in enrollment, the entire enrolled study population had a median follow-up of less than 2 months as of the EUA submission data cut-off date of November 14, 2020. However, the analyses submitted to support this EUA request meet the expectation for median duration of follow-up time, as follows:

- Submitted safety analyses for participants enrolled through October 9, 2020, and followed through November 14, 2020 (referred to by Pfizer and in this document as the phase 2/3 safety population and including a total of 37,586 participants), represent a median follow-up of 2 months. Additionally, this safety database is larger than for the initial planned enrollment of approximately 30,000 participants.

- The date for data cut-off for the first interim analysis for efficacy was November 4, 2020, when a total of 94 confirmed COVID-19 cases were accrued. All of the participants included in the first interim efficacy analysis had at least 7 days of follow-up after Dose 2, and thus were enrolled no later than October 7, 2020. All participants in the first interim efficacy analysis were therefore included in the phase 2/3 safety population defined above. Although the median follow-up duration for participants included in the first interim efficacy analysis was slightly less than 2 months as of November 4, 2020, these participants were also included in the final efficacy analyses with data cut-off of November 14, 2020, which extended the median follow-up for these participants to greater than 2 months. The results of the final efficacy analysis on data to November 14, 2020, indicate that the conclusions from the first interim efficacy analysis would not change when including additional follow-up to November 14, 2020.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued. As noted above, the median follow-up duration after completion of the full vaccination regimen for all participants enrolled at that time was less than 2 months for both safety and efficacy populations, due to a gap in enrollment. Because the data for the final efficacy analysis could be submitted in support of the EUA request and could provide data from a greater number of participants than from the interim analysis, FDA has focused its review on the efficacy data from the final efficacy analyses. Additional safety analyses from this larger database of all enrolled participants were also reviewed to evaluate for differences compared with the smaller phase 2/3 safety population.

5.2.3. Subject Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 2 (efficacy analysis populations) and Table 3 (phase 2/3 safety population). Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. Of 43,448 participants in the phase 2/3 all-enrolled population, 94.2% of vaccine recipients and 94.1% of placebo recipients completed 2 doses (data not shown).

Table 2. Efficacy Populations, Treatment Groups as Randomized

	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Participants without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Participants excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Participants without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Participants without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Participants excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Participants excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Participants excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

[a]n = Number of participants with the specified characteristic.
[b]These values are the denominators for the percentage calculations.
[c]Participants may have been excluded for more than 1 reason.
Note: 100 participants 12 through 15 years of age with limited follow-up are included in the randomized population (49 in the vaccine group and 51 in the placebo group). Some of these subjects were included in the denominators of efficacy analyses, depending on the population analyzed, but did not contribute primary endpoint cases and do not affect efficacy conclusions for ages 16 years and above.

Table 3. Disposition of All Randomized Participants, Phase 2/3 Safety Population

Treatment Group	BNT162b2 N=18904 n (%)	Placebo N=18892) n (%)	Total N=37796 n (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Vaccinated			
Completed 1 dose	18858 (99.8)	18849 (99.8)	37707 (99.8)
Completed 2 doses	18555 (98.2)	18533 (98.1)	37088 (98.1)
Withdrawn from Study	180 (1.0)	259 (1.4)	439 (1.2)
Reason for Withdrawal			
Adverse Event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	4 (0.0)	6 (0.0)
Withdrawal by Subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to Follow-up	80 (0.4)	86 (0.5)	166 (0.4)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)

Source: EUA 27036, amendment 3, Table 2; c4591001-safety-tables-cos-reacto.pdf, page 43.
Note: One participant was randomized but did not sign informed consent and therefore not included in any analysis population.
Note: 120 HIV-positive participants included in this table. HIV population analyses were summarized separately from analyses based on the phase 2/3 safety population, but included in the all-enrolled poplation analyses presented in this briefing document.
%:n/N. n = number of subjects with the specified characteristic. N = number of participants ≥16 years of age enrolled by October 9, 2020, including 120 HIV-positive participants, and received at least 1 dose of study vaccine or placebo. N is the denominator used for the percentage calculations.
Data analysis cutoff date: November 14, 2020

The numbers of randomized participants contributing to efficacy analyses presented in this document include 100 participants 12 through 15 years of age (49 in the vaccine group and 51 in the placebo group) who had limited follow-up at the time of the November 14, 2020 data cut-off. However, the sponsor did not include this age group in the EUA request. The numbers of participants presented and used as denominators for efficacy calculations were not adjusted to remove participants 12 through 15 years of age. Because the number of participants 12 through 15 years of age is very small relative to the overall efficacy analysis populations, and no primary endpoint COVID-19 cases occurred in this age group, the vaccine efficacy conclusions are not impacted. No participants 12 through 15 years of age are included in the safety analyses. However, the safety disposition table includes 120 HIV-positive participants who were not included in the phase 2/3 safety population analyses.

5.2.4. Demographics and Other Baseline Characteristics

Overall, the phase 2/3 evaluable efficacy population included 49.4% females, 81.9% White, 9.8% African American, 4.4% Asian participants, and <3% from other racial groups; 26.2% of participants were Hispanic/Latino; 21.4% of participants were ≥65 years of age. The median age was 51 years. The most frequently reported comorbidities were obesity (35.1%), diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-available efficacy population were similar to the evaluable efficacy population. Please refer to the table below.

Table 4. Demographic Characteristics, Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Characteristic	BNT162b2 (N[a]=20033) N[b] (%)	Placebo (N[a]=20244) N[b] (%)	Total (N[a]=40277) N[b] (%)
Sex: Female	9794 (48.9)	10107 (49.9)	19901 (49.4)
Sex: Male	10239 (51.1)	10137 (50.1)	20376 (50.6)
Age at Vaccination: Mean years (SD)	50.3 (15.73)	50.1 (15.78)	50.2 (15.76)
Age at Vaccination: Median (years)	51.0	51.0	51.0
Age at Vaccination: Min, max (years)	(12, 89)	(12, 91)	(12, 91)
Age Group: 16 to <18 years	77 (0.4)	76 (0.4)	153 (0.4)
Age Group: 16 to 55 years	11589 (57.8)	11743 (58.0)	23332 (57.9)
Age Group: >55 years	8396 (41.9)	8454 (41.8)	16850 (41.8)
Age Group: ≥65 years	4294 (21.4)	4319 (21.3)	8613 (21.38)
Age Group: ≥75 years	860 (4.3)	852 (4.2)	1712 (4.3)
Race: American Indian or Alaska Native	131 (0.7)	122 (0.6)	253 (0.6)
Race: Asian	880 (4.4)	883 (4.4)	1763 (4.4)
Race: Black or African American	1957 (9.8)	1972 (9.7)	3929 (9.8)
Race: Native Hawaiian or Other Pacific Islander	54 (0.3)	29 (0.1)	83 (0.2)
Race: White	16387 (81.8)	16619 (82.1)	33006 (81.9)
Race: Multiracial	523 (2.6)	493 (2.4)	1016 (2.5)
Race: Not reported	101 (0.5)	126 (0.6)	227 (0.6)
Ethnicity: Hispanic or Latino	5272 (26.3)	5281 (26.1)	10553 (26.2)
Ethnicity: Not Hispanic or Latino	14652 (73.1)	14847 (73.3)	29499 (73.2)
Ethnicity: Not reported	109 (0.5)	116 (0.6)	225 (0.6)
Comorbidities[c]: Yes	9278 (46.3)	9314 (46.0)	18592 (46.2)
Comorbidities: No	10755 (53.7)	10930 (54.0)	21685 (53.8)
Comorbidity: Obesity	6934 (34.6)	7093 (35.0)	14027 (34.8)

[a].N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b].n = number of participants with the specified characteristic.
[c]. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity only (BMI ≥30 kg/m^2).

Overall, the phase 2/3 safety population included 83.1% White, 9.1% African American, 4.3% Asian participants, and <3% from other racial groups; 28.0% of participants were Hispanic/Latino; 21.6% of participants were >65 years of age. The median age was 52 years, and safety data from a total of 103 participants 16 and 17 years of age were included in this submission. The most frequently reported comorbidities were obesity (35.1%), diabetes (without chronic complications, 7.8%) and chronic pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2.0% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-enrolled population were similar and were also enrolled from sites in Germany (1%) and Turkey (1%). There were no significant imbalances in demographic and other baseline characteristics between the all-enrolled population and phase 2/3 safety population with median 2-month follow-up.

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Table 5. Demographics and Other Baseline Characteristics, Phase 2/3 Safety Population

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Age (years)									
Mean [SD]	16.40 [0.49]	44.99 [12.66]	68.84 [2.80]	78.07 [2.78]	16.36 [0.48]	44.78 [12.72]	68.84 [2.78]	78.10 [2.81]	50.38 [15.70]
Median	16	46	68	77	16	46	69	77	52
Min, max	16-17	18-64	65-74	75-89	16-17	18-64	65-74	75-91	16-91
Sex									
Male	33 (0.2)	7385 (39.3)	1714 (9.1)	470 (2.5)	24 (0.1)	7153 (38.1)	1724 (9.2)	498 (2.7)	19001 (50.6)
Female	20 (0.1)	7305 (38.9)	1513 (8.0)	361 (1.9)	26 (0.1)	7539 (40.1)	1511 (8.0)	310 (1.7)	18585 (49.4)
Race									
White	37 (0.2)	11895 (63.3)	2908 (15.5)	775 (4.1)	38 (0.2)	11891 (63.3)	2930 (15.6)	756 (4.0)	31230 (83.1)
African American	11 (0.1)	1477 (7.9)	186 (1.0)	20 (0.1)	7 (0.0)	1505 (8.0)	189 (1.0)	21 (0.1)	3416 (9.1)
Asian	0 (0.0)	693 (3.7)	81 (0.4)	26 (0.1)	0 (0.0)	715 (3.8)	72 (0.4)	19 (0.1)	1606 (4.3)
Multiracial	3 (0.0)	417 (2.2)	21 (0.1)	7 (0.0)	3 (0.0)	379 (2.0)	18 (0.1)	5 (0.0)	853 (2.3)
Not reported	0 (0.0)	82 (0.4)	11 (0.1)	0 (0.0)	1 (0.0)	98 (0.5)	10 (0.1)	5 (0.0)	207 (0.6)
American Indian or Alaska native	0 (0.0)	84 (0.4)	15 (0.1)	2 (0.0)	1 (0.0)	83 (0.4)	11 (0.1)	2 (0.0)	198 (0.5)
Nat. HI or other Pac. Isl.	2 (0.0)	42 (0.2)	5 (0.0)	1 (0.0)	0 (0.0)	21 (0.1)	5 (0.0)	0 (0.0)	76 (0.2)
Ethnicity									
Hispanic or Latino	6 (0.0)	4595 (24.4)	549 (2.9)	103 (0.5)	5 (0.0)	4616 (24.6)	558 (3.0)	90 (0.5)	10522 (28.0)
Non-Hispanic/non-Latino	47 (0.2)	10009 (53.2)	2658 (14.1)	722 (3.8)	44 (0.2)	10004 (53.3)	2652 (14.1)	707 (3.8)	26843 (71.4)
Not reported	0 (0.0)	86 (0.5)	20 (0.1)	6 (0.0)	1 (0.0)	72 (0.4)	25 (0.1)	11 (0.1)	221 (0.6)
Baseline Body Mass Index (BMI)									
Obese	3 (0.0)	5200 (27.7)	1079 (5.7)	248 (1.3)	14 (0.1)	5242 (27.9)	1147 (6.1)	235 (1.3)	13168 (35.0)
Overweight	14 (0.1)	4901 (26.1)	1278 (6.8)	368 (2.0)	9 (0.0)	4857 (25.9)	1255 (6.7)	340 (1.8)	13022 (34.6)

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**>75**	**16 to <18**	**18 to <65**	**65 to <75**	**>75**	
Baseline Evidence of Prior SARS-CoV-2 Infection									
Negative	48 (0.3)	13879 (73.8%)	3109 (16.5)	805 (4.3)	47 (0.3%)	13858 (73.8%)	3115 (16.6%)	788 (4.2%)	35649 (94.8%)
Positive	3 (0.0)	473 (2.5%)	53 (0.3)	16 (0.1)	3 (0.0%)	520 (2.8%)	52 (0.3%)	5 (0.0%)	1125 (3.0%)
Missing	2 (0.0)	338 (1.8%)	65 (0.3)	10 (0.1)	0 (0.0%)	314 (1.7%)	68 (0.4%)	15 (0.1%)	812 (2.2%)
Comorbidities									
No	48 (0.3)	12353 (65.7%)	2081 (11.1)	444 (2.4)	37 (0.2%)	12412 (66.1%)	2118 (11.3%)	470 (2.5%)	29963 (79.7%)
Yes	5 (0.0)	2337 (12.4%)	1146 (6.1)	387 (2.1)	13 (0.1%)	2280 (12.1%)	1117 (5.9%)	338 (1.8%)	7623 (20.3%)
Diabetes Without Chronic Complication	0 (0.0)	814 (4.3%)	497 (2.6)	156 (0.8)	1 (0.0%)	849 (4.5%)	491 (2.6%)	132 (0.7%)	2940 (7.8%)
Chronic Pulmonary Disease	5 (0.0)	1093 (5.8%)	286 (1.5)	89 (0.5)	12 (0.1%)	1060 (5.6%)	309 (1.6%)	66 (0.4%)	2920 (7.8%)
Myocardial Infarction	0 (0.0)	82 (0.4%)	71 (0.4)	41 (0.2)	0 (0.0%)	73 (0.4%)	83 (0.4%)	31 (0.2%)	381 (1.0%)
Peripheral Vascular Disease	0 (0.0)	26 (0.1%)	67 (0.4)	31 (0.2)	0 (0.0%)	29 (0.2%)	52 (0.3%)	33 (0.2%)	238 (0.6%)
Liver Disease (mild, moderate or severe)	0 (0.0)	83 (0.4%)	34 (0.2)	7 (0.0)	0 (0.0%)	67 (0.4%)	17 (0.1%)	6 (0.0%)	214 (0.6%)
Diabetes With Chronic Complication	0 (0.0)	47 (0.2%)	36 (0.2)	15 (0.1)	0 (0.0%)	47 (0.3%)	47 (0.3%)	18 (0.1%)	210 (0.6%)
Congestive Heart Failure	0 (0.0)	44 (0.2%)	26 (0.1)	17 (0.1)	0 (0.0%)	36 (0.2%)	30 (0.2%)	16 (0.1%)	169 (0.4%)
AIDS/HIV	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)

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Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Hypertension only	0 (0.0)	2569 (13.7%)	1528 (8.1)	488 (2.6)	1 (0.0%)	2621 (14.0%)	1569 (8.4%)	432 (2.3%)	9208 (24.5%)

Source: FDA-generated table.
Abbreviations: n = number of participants with the specified characteristic; N = number of participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo, N is denominator for the percentage calculations; SD = standard deviation; min, max = minimum, maximum; Nat. HI = Native Hawaiian; Pac. Isl. = Pacific Islander
Data analysis cutoff date: November 14, 2020.

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5.2.5. Vaccine Efficacy

Primary Efficacy Analyses

Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 6). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively (Table 7). The posterior probability was >99.99% for the true VE being greater than 30%. The 95% credible interval for the vaccine efficacy was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

Table 7. Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants With And Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.9, 97.3)[e]	Yes
16 to 55 years	6 1.309 (10653)	120 1.317 (10738)	95.0 (88.7, 98.2)[f]	NA
>55 years and older	3 1.022 (7892)	49 1.028 (7956)	93.8 (80.9, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy >30% conditioning on the available data is >99.5% at the final analysis
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Subgroup Analyses of Vaccine Efficacy

Subgroup analyses of the second primary efficacy endpoint provide additional information about the VE for participants with and without evidence of infection prior to vaccination in specific populations enrolled, which is the endpoint considered to represent the general population who may receive the vaccine, as baseline evidence of prior infection may not be known by all people who might receive the vaccine. The results are displayed below in Table 8. The VE point estimates for the subgroup analyses were comparable to results for the first primary efficacy endpoint.

VE point estimates were uniformly high across the subgroups examined with the exception of participants identifying as multiracial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 cases occurred to interpret efficacy data for these subgroups. Additionally, the numbers of participants and cases in some other specific subgroups, such as the adolescent age group and racial subgroups, limits the interpretability of the VE results because of the wide credible intervals, but are displayed for completeness.

Table 8: Subgroup Analyses of Second Primary Endpoint: First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup, Participants With and Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Overall	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.6, 97.6)
Age group (years)			
16 to 17	0 0.003 (58)	1 0.003 (61)	100.0 (-3969.9, 100.0)
18 to 64	8 1.799 (14443)	149 1.811 (14566)	94.6 (89.1, 97.7)
65 to 74	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)
≥75	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)
At risk[f]			
Yes	4 1.083 (8584)	87 1.084 (8609)	95.4 (87.8, 98.8)
No	5 1.250 (9975)	82 1.261 (10099)	93.8 (85.0, 98.1)
Age group (years) and at risk			
16-64 and not at risk	5 1.012 (8172)	75 1.019 (8239)	93.3 (83.6, 97.9)
16-64 and at risk	3 0.790 (6329)	75 0.794 (6388)	96.0 (87.8, 99.2)
≥65 and not at risk	0 0.238 (1794)	7 0.241 (1849)	100.0 (29.5, 100.0)
≥65 and at risk	1 0.293 (2250)	12 0.290 (2218)	91.7 (44.2, 99.8)
Obese[g]			
Yes	3 0.810 (6445)	68 0.832 (6582)	95.5 (86.2, 99.1)
No	6 1.522 (12108)	101 1.513 (12120)	94.1 (86.7, 97.9)
Age group (years) and obese			
16-64 and not obese	5 1.163 (9380)	89 1.162 (9422)	94.4 (86.4, 98.2)
16-64 and obese	3 0.637 (5116)	61 0.651 (5199)	95.0 (84.6, 99.0)
≥65 and not obese	1 0.358 (2715)	12 0.351 (2685)	91.8 (44.7, 99.8)
≥65 and obese	0 0.172 (1328)	7 0.180 (1382)	100.0 (27.4, 100.0)
Sex			
Female	5 1.149 (9102)	84 1.176 (9366)	93.9 (85.2, 98.1)
Male	4 1.183 (9457)	85 1.170 (9342)	95.3 (87.6, 98.8)
Ethnicity			
Hispanic or Latino	3 0.637 (5074)	55 0.638 (5090)	94.5 (83.2, 98.9)

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Not Hispanic or Latino	6 1.681 (13380)	114 1.693 (13509)	94.7 (88.1, 98.1)
Race			
American Indian or Alaska native	0 0.011 (104)	1 0.010 (104)	100.0 (-3511.0, 100.0)
Asian	1 0.095 (796)	4 0.097 (808)	74.4 (-158.7, 99.5)
Black or African American	0 0.187 (1758)	7 0.188 (1758)	100.0 (30.4, 100.0)
Native Hawaiian or other Pacific Islander	0 0.006 (50)	1 0.003 (29)	100.0 (-2112.1, 100.0)
White	7 1.975 (15294)	153 1.990 (15473)	95.4 (90.3, 98.2)
Multiracial	1 0.047 (467)	1 0.042 (424)	10.4 (-6934.9, 98.9)
Not reported	0 0.010 (90)	2 0.013 (112)	100.0 (-581.6, 100.0)
Baseline SARS-CoV-2 Status			
Positive[h]	1 0.056 (526)	1 0.060 (567)	-7.1 (-8309.9, 98.6)
Negative[i]	8 2.237 (17637)	164 2.242 (17720)	95.1 (90.1, 97.9)
Unknown	0 0.039 (396)	4 0.043 (421)	100.0 (-68.9, 100.0)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.
[f] At risk is defined as having at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity (BMI ≥30 kg/m^2).
[g] Obese is defined as BMI ≥30 kg/m^2.
[h] Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[i] Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 9.

Table 9. Demographic Characteristics, Participants With Protocol Defined Case (Without Evidence of Infection Prior to 7 Days After Dose 2)

Characteristic	BNT162b2 (N[a]=8) n[b] (%)	Placebo (N[a]=162) n[b] (%)	Total (N[a]=170) n[b] (%)
Sex: Female	5 (62.5)	81 (50.0)	86 (50.6)
Sex: Male	3 (37.5)	81 (50.0)	84 (49.4)
Age at Vaccination: Mean years (SD)	51.4 (12.47)	47.4 (15.21)	47.6 (15.09)
Age at Vaccination: Median (years)	51	48	48
Age at Vaccination: Min, max (years)	(30, 69)	(18, 79)	(18, 79)
Age Group: 16 to < 18 years	0	0	0
Age Group: 18 to < 65 years	7 (87.5)	143 (88.3)	150 (88.2)
Age Group: ≥ 65 to < 75 years	1 (12.5)	14 (8.6)	15 (8.8)
Age Group: ≥ 75 years	0	5 (3.1)	5 (2.9)
Race: American Indian or Alaska Native	0	1 (0.6)	1 (0.6)
Race: Asian	1 (12.5)	4 (2.5)	5 (2.9)
Race: Black or African American	0	7 (4.3)	7 (4.1)
Race: Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.6)
Race: White	7 (87.5)	146 (90.1)	153 (90.0)
Race: Multiracial	0	1 (0.6)	1 (0.6)
Race: Not reported	0	2 (1.2)	2 (1.2)
Ethnicity: Hispanic or Latino	3 (37.5)	53 (32.7)	56 (32.9)
Ethnicity: Not Hispanic or Latino	5 (62.5)	109 (67.3)	114 (67.1)
Ethnicity: Not reported	0	0	0
Comorbidities[c]: Yes	4 (50.0)	86 (53.1)	90 (52.9)
Comorbidities: No	4 (50.0)	76 (46.9)	80 (47.1)
Comorbidity: Obesity	3 (37.5)	67 (41.4)	70 (41.2)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = Number of participants with the specified characteristic.
[c] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity only (BMI ≥30 kg/m^2).

Only 3% of participants had evidence of prior infection at study enrollment, and additional analyses showed that very few COVID-19 cases occurred in these participants over the course of the entire study (9 in the placebo group and 10 in the BNT162b2 group, only 1 of which occurred 7 days or more after completion of the vaccination regimen – data not shown). The placebo group attack rate from enrollment to the November 14, 2020, data cut-off date was 1.3% both for participants without evidence of prior infection at enrollment (259 cases in 19,818 participants) and for participants with evidence of prior infection at enrollment (9 cases in 670 participants). While limited, these data do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the vaccine efficacy, by comorbidity status. VE point estimates were uniformly high across the comorbidities examined, though for some interpretation of the results is limited by small numbers of participants and/or cases.

Table 10. Vaccine Efficacy: First COVID-19 Occurrence From 7 Days After Dose 2, by Comorbidity Status, Among Participants Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

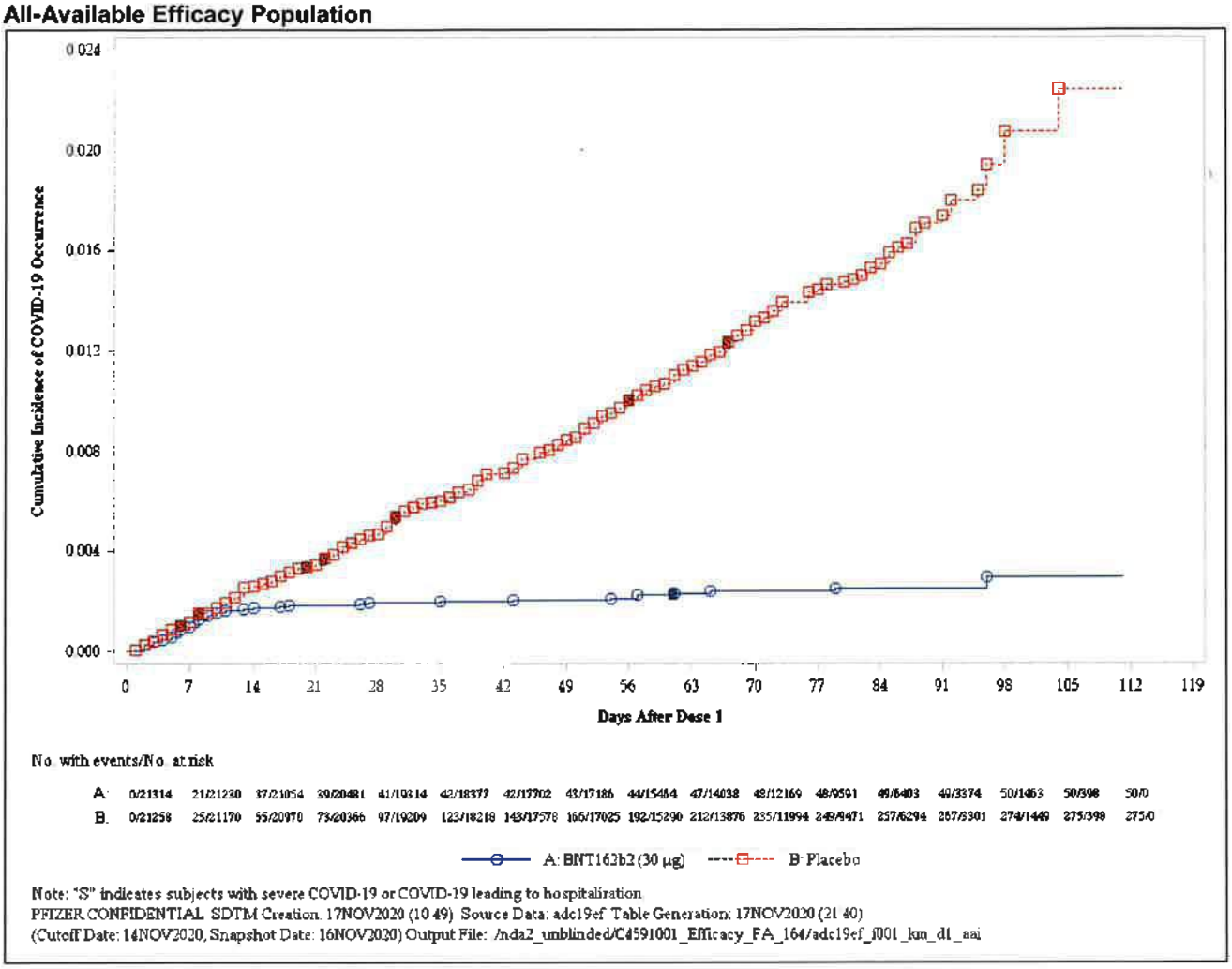
Efficacy Endpoint Subgroup	BNT162b2 (30 µg) N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Overall	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.0, 97.9)
Comorbidity			
No comorbidity	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Any comorbidity[f]	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
Any malignancy	1 0.092 (704)	4 0.090 (681)	75.7 (-145.8, 99.5)
Cardiovascular	0 0.067 (534)	5 0.062 (492)	100.0 (-0.8, 100.0)
Chronic pulmonary disease	1 0.175 (1374)	14 0.171 (1358)	93.0 (54.1, 99.8)
Diabetes	1 0.176 (1372)	19 0.176 (1374)	94.7 (66.8, 99.9)
Obese (BMI≥30.0 kg/m^2)	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
Hypertension	2 0.567 (4413)	44 0.567 (4437)	95.4 (82.6, 99.5)
Diabetes (including gestational diabetes)	1 0.177 (1381)	20 0.178 (1384)	95.0 (68.7, 99.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f] Subject who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or BMI ≥30 kg/m2.

Cumulative Incidence Curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1, (Figure 2), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the BNT162b2 group, and there does not appear to be evidence of waning protection during the follow-up time of approximately 2 months following the second dose that is being evaluated at this point in time.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 17NOV2020 (21:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: /nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_i001_km_d1_aai

Secondary Efficacy Analyses

The secondary efficacy endpoints evaluate the VE of BNT162b2 for the prevention of COVID-19 disease from 14 days after Dose 2 and based on the CDC's definition of COVID-19 disease from 7 and 14 days after Dose 2. The case splits and VE for each of these secondary efficacy endpoints were each similar to the primary efficacy endpoints described above.

Severe COVID-19 Cases

In the final analysis of the evaluable efficacy population (7 days), four participants had severe COVID-19 disease at least 7 days after Dose 2 (one subject who received BNT162b2 and three participants who received placebo). The vaccine recipient who had severe COVID-19 disease met the severe case definition because oxygen saturation at the COVID-19 illness visit was 93% on room air. The subject was not hospitalized, did not seek further medical care, and did not have risk factors for severe disease. The three placebo recipients who had severe COVID-19 disease met the severe case definition for the following reasons: one subject had an oxygen saturation of 92% on room air without other severe disease criteria, one subject was

hospitalized for noninvasive positive pressure ventilation with bilateral pneumonia, and one subject had an oxygen saturation of 92% and ICU admission for heart block. One of these placebo recipients with severe disease also had a body mass index > 30 kg/m^2 as a risk factor, while the other two participants did not have any risk factors for severe disease. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 11.

Table 11. First Severe COVID-19 Occurrence from 7 Days after Dose 2 - Evaluable Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
First severe COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection	1 2.215 (17411)	3 2.232 (17511)	66.4 (-124.8, 96.3)[e]	No

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >98.6% at the final analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

In the all-available efficacy population, ten participants had severe COVID-19 disease after Dose 1 (one subject who received BNT162b2 and nine participants who received placebo). Five of the remaining six placebo recipients who had severe COVID-19 disease were hospitalized, two of whom were admitted to an intensive care unit. Five of these remaining six placebo recipients who had severe disease had at least one risk factor for severe disease. The total number of severe cases is small, which limits the overall conclusions that can be drawn; however, the case split does suggest protection from severe COVID-19 disease.

Table 12. First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First severe case occurrence after Dose 1	1 4.021 (21314)	9 4.006 (21259)	88.9 (20.1, 99.7)[f]
After Dose 1 to before Dose 2	0	4	100.0 (-51.5, 100.0)
Dose 2 to 7 days after Dose 2	0	1	100.0 (-3800.0, 100.0)
≥7 Days after Dose 2	1	4	75.0 (-152.6, 99.5)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Additional Efficacy Analyses

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 2 (Table 13).

Table 13. Primary Efficacy Endpoint –All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after	50	275	82.0
Dose 1 – Dose 1	4.015 (21314)	3.982 (21258)	(75.6, 86.9)[f]
After Dose 1 to before Dose 2	39	82	52.4 (29.5, 68.4)
Dose 2 to 7 days after Dose 2	2	21	90.5 (61, 98.9)
≥7 Days after Dose 2	9	172	94.8 (89.8, 97.6)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 82%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 21 days after a single dose.

Efficacy Summary

The data submitted in this EUA request were consistent with the recommendations set forth in the FDA Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 and met the prespecified success criteria established in the protocol. In the planned interim and final analyses, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the group of participants with or without prior infection. Efficacy outcomes were consistently robust (⩾93%) across demographic subgroups.

Efficacy against severe COVID-19 occurring after the first dose was 88.9% (95% CI 20.1, 99.7), with an estimated VE of 75.0% (95% CI -152.6, 99.5) (1 case in BNT162b2 group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.

Among all participants (regardless of evidence of infection before or during the vaccination regimen), 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2. The efficacy observed after Dose 1 and before Dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the time of observation is limited by the fact that most of the participants received a

second dose after three weeks. The trial did not have a single-dose arm to make an adequate comparison.

5.2.6. Safety

Overview of Adverse Events

Table 14 below presents an overview of all adverse events in the phase 2/3 safety population. A higher proportion of vaccine recipients reported adverse events compared with placebo recipients, and this imbalance was driven by reactogenicity (solicited adverse events) reported in the 7 days following vaccination and unsolicited adverse events corresponding to reactogenicity symptoms among participants not in the reactogenicity subset (see presentation of unsolicited adverse events in a later section). Proportions of participants with serious adverse events, deaths, and withdrawals due to adverse events were balanced between treatment groups.

Table 14. Study C4591001 Safety Overview- Ages 16 years and older

Participants Experiencing at Least One:	BNT162b2 n/N (%)	Placebo n/N (%)
Immediate unsolicited AE Within 30 minutes after vaccination[a]		
Dose #1	78/18801 (0.4)	66/18785 (0.4)
Dose #2	52/18494 (0.3)	39/18470 (0.2)
Solicited injection site reaction within 7 days[b]		
Dose #1	3216/4093 (78.6)	525/4090 (12.8)
Dose #2	2748/3758 (73.1)	396/3749 (10.6)
Solicited systemic AE within 7 days[b]		
Dose #1	2421/4093 (59.1)	1922/4090 (47.0)
Dose #2	2627/3758 (69.9)	1267/3749 (33.8)
From Dose 1 through 1 month after Dose 2[a]		
Unsolicited non-serious AE	5071/18801 (27.0)	2356/18785 (12.5)
SAE	103/18801 (0.5)	81/18785 (0.4)
From Dose 1 through cutoff date (safety population)		
SAE	124/18801 (0.7)	101/18785 (0.5)
From Dose 1 through cutoff date (all-enrolled)[c]		
Withdrawal due AEs	37/21621 (0.6)	30/21631 (0.5)
SAE	126/21621 (0.6)	111/21631 (0.5)
Deaths	2/21621 (0.0)	4/21631 (0.0)

Source: c4591001-safety-tables-ae3.pdf pages 216,446,459,463; c4591001-safety-tables-cos-reacto.pdf, pages 113-114.
n= number of participants with the specified reaction or AE.
[a] N: number of participants in the phase 2/3 safety population.
[b] N: number of participants in the reactogenicity subset of the phase 2/3 safety population.
[b] N: number of participants in the all-enrolled population.
Data analysis cutoff date: November 14, 2020.

Solicited Local Reactions and Systemic Adverse Events

As of the cutoff date, solicited reactogenicity data in participants 16 and 17 years of age were not collected by e-diary and are not available. Symptoms consistent with solicited reactogenicity that were reported by these participants were collected and analyzed as unsolicited adverse events and are discussed with review of those data.

Solicited Local Reactions

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of local reactions in the vaccine group was 0 (day of vaccination) to 2 days after either dose and lasted a median duration between 1 and 2 days.

For both age groups, injection site pain was the most frequent solicited local adverse reaction. After dose 2, the younger age group reported any pain more frequently than the older age group (77.8% vs 66.1%) and pain characterized as moderate (27.1% vs. 18.0%); a similar pattern was observed after Dose 1. Injection site redness and swelling after each dose were generally similar for both age groups.

Subgroup analyses by age

Table 15. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Local Reaction	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Pain[a]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)
Redness[b]				
Any	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[b]				
Any	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)

Source: adapted from EUA 27034, amendment 3, Table 17.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, >55 Years of Age and Older

Local Reaction	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Pain[a]				
Any	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)
Redness[b]				
Any	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[b]				
Any	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)

Source: EUA 27036, amendment 3, Table 21.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Solicited Systemic AEs

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of systemic AEs in the vaccine group in general was 1 to 2 days after either dose and lasted a median duration of 1 day.

The frequency and severity of systemic AEs were higher in the younger than the older age groups. Within each age group, the frequency and severity of systemic AEs was higher after Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar regardless of dose. For both age groups, fatigue, headache and new/worsened muscle pain were most common.

Subgroup analyses by age

Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Adverse Event	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
>38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)

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Adverse Event	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Fatigue[a]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	46 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[a]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[a]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[b]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[c]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[a]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[a]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

Source: adapted from EUA 27036, amendment 3, Table 19.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 18. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population*, >55 Years of Age and Older

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
>38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[a]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)
Headache[a]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[a]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[b]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[c]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[a]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[a]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

Source: EUA 27036, amendment 3, Table 23.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Unsolicited (non-serious) AEs

A higher frequency of unsolicited, non-serious adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local reactions and systemic adverse events in subjects not in the reactogenicity subset and are consistent with solicited reactions/events reported by reactogenicity subset participants during the first 7 days following vaccination. Table 19 below presents unsolicited adverse events reported by at least 1% of participants in any treatment group for the phase 2/3 safety population.

Reports of lymphadenopathy were imbalanced with notably more cases in the vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Bell's palsy was reported by four vaccine participants and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days postvaccination) was reported as resolved with sequelae within three days after onset, and the other three were reported as continuing or resolving as of the November 14, 2020 data cut-off with ongoing durations of 10, 15, and 21 days, respectively. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and there is no clear basis upon which to conclude a causal relationship at this time, but FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories (system organ class or preferred term) of non-serious adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Table 19. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1-month After Dose 2, Phase 2/3 Safety Population*, 16 Years of Age and Older

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
General disorders and administration site conditions	3521 (18.7)	737 (3.9)	4258 (11.3)
Injection site pain	2125 (11.3)	286 (1.5)	2411 (6.4)
Fatigue	1029 (5.5)	260 (1.4)	1289 (3.4)
Pyrexia	1146 (6.1)	61 (0.3)	1207 (3.2)
Chills	999 (5.3)	87 (0.5)	1086 (2.9)
Pain	455 (2.4)	36 (0.2)	491 (1.3)
Musculoskeletal and connective tissue disorders	1387 (7.4)	401 (2.1)	1788 (4.8)
Myalgia	909 (4.8)	126 (0.7)	1035 (2.8)
Arthralgia	212 (1.1)	82 (0.4)	294 (0.8)
Nervous system disorders	1158 (6.2)	460 (2.4)	1618 (4.3)
Headache	973 (5.2)	304 (1.6)	1277 (3.4)
Gastrointestinal disorders	565 (3.0)	368 (2.0)	933 (2.5)
Diarrhoea	194 (1.0)	149 (0.8)	343 (0.9)
Nausea	216 (1.1)	63 (0.3)	279 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Subgroup analyses by age

16 and 17 years of age: the table below represents an FDA-generated summary of unsolicited AEs consistent with reactogenicity and AEs that occurred at ≥1% and higher in the BNT162b2 Vaccine Group, classified by MedDRA System Organ Class and Preferred Term.

Table 20. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 16 and 17 Years of Age

System Organ Class Preferred Term	BNT162b2 N=53 n (%)	Placebo N=50 n (%)	Total N=103 n (%)
General disorders and administration site conditions	7 (13.2)	3 (6.0)	10 (9.7)
Injection site pain	5 (9.4)	2 (4.0)	7 (6.8)
Pyrexia	5 (9.4)	0	5 (4.9)
Pain	2 (3.8)	0	2 (1.9)
Chills	1 (1.9)	0	1 (1.0)
Injury, poisoning and procedural complications	1 (1.9)	0	1 (1.0)
Concussion	1 (1.9)	0	1 (1.0)
Facial bones fracture	1 (1.9)	0	1 (1.0)
Road traffic accident	1 (1.9)	0	1 (1.0)
Investigations	1 (1.9)	0	1 (1.0)
Body temperature increased	1 (1.9)	0	1 (1.0)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 21. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 65 Years and Older

System Organ Class Preferred Term	BNT162b2 (N=4058) n (%)	Placebo (N=4043) n (%)	Total (N=8101) n (%)
General disorders and administration site conditions	577 (14.2)	118 (2.9)	695 (8.6)
Injection site pain	361 (8.9)	39 (1.0)	400 (4.9)
Fatigue	175 (4.3)	44 (1.1)	219 (2.7)
Chills	143 (3.5)	19 (0.5)	162 (2.0)
Pyrexia	148 (3.6)	10 (0.2)	158 (2.0)
Pain	60 (1.5)	7 (0.2)	67 (0.8)
Musculoskeletal and connective tissue disorders	231 (5.7)	83 (2.1)	314 (3.9)
Myalgia	125 (3.1)	23 (0.6)	148 (1.8)
Arthralgia	42 (1.0)	21 (0.5)	63 (0.8)
Pain in extremity	33 (0.8)	10 (0.2)	43 (0.5)
Nervous system disorders	179 (4.4)	87 (2.2)	266 (3.3)
Headache	127 (3.1)	45 (1.1)	172 (2.1)
Gastrointestinal disorders	127 (3.1)	72 (1.8)	199 (2.5)
Diarrhea	49 (1.2)	26 (0.6)	75 (0.9)
Nausea	40 (1.0)	13 (0.3)	53 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

FDA independently conducted standard MedDRA queries (SMQs) using FDA-developed software (MAED) to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions. The SMQs, conducted on the phase 2/3 all-enrolled safety population, revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137 [0.63%]) compared with the placebo group (111 [0.51%]). No imbalances between treatment groups were evident for any of the other SMQs evaluated.

Immediate AEs (phase 2/3 safety population)
The frequency of immediate AEs reported in the vaccine group was 0.4% after Dose 1 and <0.3% after Dose 2 and were mainly consistent with solicited reactogenicity events. In both study groups, the most frequently reported immediate AE was injection site pain (BNT162b2 vaccine 0.3%, placebo 0.2%).

Study Withdrawals due to an AE (all-enrolled population)
Of 43,448 enrolled participants, 37 (0.2%) vaccine recipients and 30 (0.1%) placebo recipients (0.1%), and no adolescents 16 to <18 years of age, withdrew from the study due to an AE. AEs in the SOC of General Disorders and Administration Site Conditions (7 vaccine, 3 placebo) was common, with injection site pain the most frequent (2 vaccine, 0 placebo).

Serious Adverse Events

Deaths

A total of six (2 vaccine, 4 placebo) of 43,448 enrolled participants (0.01%) died during the reporting period from April 29, 2020 (first participant, first visit) to November 14, 2020 (cutoff date). Both vaccine recipients were >55 years of age; one experienced a cardiac arrest 62 days after vaccination #2 and died 3 days later, and the other died from arteriosclerosis 3 days after vaccination #1. The placebo recipients died from myocardial infarction (n=1), hemorrhagic stroke (n=1) or unknown causes (n=2); three of the four deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

Non-fatal SAEs

In the all-enrolled population of (total N=43,448), the proportions of participants who reported at least 1 SAE during the time period from Dose 1 to the data cutoff date (November 14, 2020) were 0.6% in the BNT162b2 vaccine group and 0.5% in the placebo group. The most common SAEs in the vaccine group which were numerically higher than in the placebo group were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), and syncope (0.02%). Occurrence of SAEs involving system organ classes and specific preferred terms were otherwise balanced between treatment groups, including no imbalance overall in cardiovascular serious adverse events.

Appendicitis was reported as a SAE for 12 participants, and numerically higher in the vaccine group: 8 vaccine participants ([appendicitis [n=7], appendicitis perforated [n=1]) and 4 placebo participants (appendicitis [n=2], appendicitis perforated [n=1], complicated appendicitis [n=1]). All of the vaccine participants (n=8) and 2 placebo participants were younger than 65 years of age. The cases were considered unrelated to vaccination by the study investigators and occurred no more frequently than expected in the given age groups. FDA agrees that there is no clear basis upon which to suspect that this imbalance represents a vaccine-related risk.

Three SAEs reported in the BNT162 group were considered by the investigator as related to vaccine or vaccine administration: shoulder injury, ventricular arrhythmia, and lymphadenopathy. The investigator and the sponsor thought that the shoulder injury was related to vaccine administration. Two SAEs in the BNT162b2 group and none in the placebo group were considered by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally following vaccination (n=1). In FDA's opinion following review of the adverse event narratives, two of these events were considered as possibly related to vaccine: shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. For lymphadenopathy, the event was temporally associated and biologically plausible.

Among participants 16 to 17 years of age, there was 1 participant in the vaccine group who experienced an SAE of facial bones fracture, which was not considered related to study intervention by the investigator.

Suspected COVID-19 Cases

As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness. Two serious cases of suspected but unconfirmed COVID-19 were reported, both in the vaccine group, and narratives were reviewed. In one case, a 36-year-old male with no medical comorbidities experienced fever, malaise, nausea, headache and myalgias beginning on the day of Dose 2 and was hospitalized 3 days later for further evaluation of apparent infiltrates on chest radiograph and treatment of dehydration. A nasopharyngeal PCR test for SARS-CoV-2 was negative on the day of admission, and a chest CT was reported as normal. The participant was discharged from the hospital 2 days after admission. With chest imaging findings that are difficult to reconcile, it is possible that this event represented reactogenicity following the second vaccination, a COVID-19 case with false negative test that occurred less than 7 days after completion of the vaccination series, or an unrelated infectious process. In the other case, a 66-year-old male with no medical comorbidities experienced fever, myalgias, and shortness of breath beginning 28 days post-Dose 2 and was hospitalized one day later with abnormal chest CT showing a small left-sided consolidation. He was discharged from the hospital 2 days later, and multiple nasopharyngeal PCR tests collected over a 10-day period beginning 2 days after symptom onset were negative. It is possible, though highly unlikely, that this event represents a COVID-19 case with multiple false negative tests that occurred more than 7 days after completion of the vaccination regimen, and more likely that it represents an unrelated infectious process.

Among 3410 total cases of suspected but unconfirmed COVID-19 in the overall study population, 1594 occurred in the vaccine group vs. 1816 in the placebo group. Suspected COVID-19 cases that occurred within 7 days after any vaccination were 409 in the vaccine group vs. 287 in the placebo group. It is possible that the imbalance in suspected COVID-19 cases occurring in the 7 days postvaccination represents vaccine reactogenicity with symptoms that overlap with those of COVID-19. Overall though, these data do not raise a concern that protocol-specified reporting of suspected, but unconfirmed COVID-19 cases could have masked clinically significant adverse events that would not have otherwise been detected.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Female study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Twenty-three pregnancies were reported through the data cut-off date of November 14, 2020 (12 vaccine, 11 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (4 vaccine, 2 placebo), within 30 days after LMP in 8 participants (4 vaccine, 6 placebo), >30 days after LMP in 1 participant (0 vaccine, 2 placebo), and date of LMP not known in 5 participants (4 vaccine, 1 placebo). Unsolicited AEs related to pregnancy include spontaneous abortion and retained products of conception, both in the placebo group. Pregnancy outcomes are otherwise

unknown at this time.

Clinical Laboratory Evaluations

Clinical laboratory tests (hematology, chemistries) were assessed in study BNT162-01 and C4591001 phase 1. The only common laboratory abnormality reported throughout the studies was transient decreases in lymphocytes 1-3 days after Dose 1, which increased in frequency with increasing dose, were mostly Grade 1-2, generally normalized at the next laboratory assessment 6-8 days after Dose 1 and did not occur after Dose 2. Among C4591001 phase 1 participants who received the 30 µg dose of BNT162b2, transient decreases in lymphocytes post-Dose 1 occurred in 5 of 12 participants 18-55 years of age and in 4 of 12 participants 65-85 years of age. These transient hematological changes were not associated with clinical symptoms.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of BNT162b2 in the context of the proposed indication and population for intended use under EUA. The number of participants in the phase 2/3 safety population (N=37586; 18801 vaccine,18785 placebo) meets the expectations in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy, and the median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series meets the agency's expectations in FDA's Guidance on its Emergency Use Authorization for Vaccines to Prevent COVID-19. The all-enrolled population contained more participants >16 years of age, regardless of duration of follow-up (43448; 21720 vaccine, 21728 placebo). The demographic and baseline characteristics of the all-enrolled population and the safety population were similar. Although the overall median duration of follow-up in the all-enrolled population was less than 2 months, because the protocol was amended to include subpopulations such as individuals with HIV and adolescents, the data from both populations altogether provide a comprehensive summary of safety.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in adults ≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). Among adverse events of special interest, which could be possibly related to vaccine, lymphadenopathy was reported in 64 participants (0.3%): 54 (0.5%) in the younger (16 to 55 years) age group; 10 (0.1%) in the older (>55 years) age group; and 6 in the placebo group. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff. Bell's palsy was reported by four vaccine participants. From Dose 1 through 1 month after Dose 2, there were three reports of Bell's palsy in the vaccine group and none in the placebo group. This observed frequency of reported Bell's palsy is consistent with the expected background rate in the general population. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine.

A total of six deaths occurred in the reporting period (2 deaths in the vaccine group, 4 in placebo). In the vaccine group, one participant with baseline obesity and pre-existing atherosclerosis died 3 days after Dose 1, and the other participant experienced cardiac arrest

60 days after Dose 2 and died 3 days later. Of the four deaths in the placebo arm, the cause was unknown for two of them, and the other two participants died from hemorrhagic stroke (n=1) and myocardial infarction (n=1), respectively; three deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

The frequency of non-fatal serious adverse events was low (<0.5%), without meaningful imbalances between study arms. The most common SAEs in the vaccine arm which were numerically higher than in the placebo arm were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), atrial fibrillation (0.02%) and syncope (0.02%). Appendicitis was the most common SAE in the vaccine arm. There were 12 participants with SAEs of appendicitis; 8 in the BNT162b2 group. Of the 8 total appendicitis cases in the BNT162b2 group, 6 occurred in the younger (16 to 55 years) age group and 2 occurred in the older (>55 years) age group (one of the cases in the older age group was perforated). One of the 6 participants with appendicitis in the younger age group also had a peritoneal abscess. Cases of appendicitis in the vaccine group were not more frequent than expected in the general population.

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

The Sponsor plans to offer vaccination to participants ⩾16 years of age who originally received placebo and who become eligible for receipt of BNT162b2 according to local or national recommendations. The Sponsor proposes that these participants will be unblinded upon request and will have the opportunity to receive BNT162b2 as part of the study. The Sponsor also proposes that all placebo recipients ⩾16 years of age will be offered BNT162b2 after completing 6 months of follow-up after Dose 2, if they did not request and receive vaccine previously. The participants will provide consent to receive vaccination and to continue follow-up. For these participants, the Sponsor plans a total follow up period of 18 months, with one visit 1-month postvaccination and subsequent phone contacts at 1, 6, and 18 months postvaccination. Safety and efficacy monitoring during this period will include collection of AEs, SAEs, and screening and diagnosing COVID-19 cases.

7. Pharmacovigilance Activities

Pfizer submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with Pfizer-BioNTech COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. Use in pregnancy and lactation and vaccine effectiveness are areas the Sponsor identified as missing information. In addition to the safety concerns specified by the Sponsor, FDA requested that the Sponsor update their PVP to include missing information in pediatric participants less than 16 years of age.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following three planned active surveillance studies. Of note, the Sponsor will submit plans for a clinical study to assess safety and immunogenicity in pregnant women and has proposed active surveillance studies designed to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA.

- Study Protocol Number C4591008. The Sponsor proposes to survey 20,000 U.S. health care workers enrolled in the COVID-19 HERO registry as well as health care workers in certain participating health care facilities about adverse events of special interest, and other clinically significant events of interest after vaccination with the Pfizer-BioNTech COVID-19 Vaccine. Incidence rates of these events in this cohort will be compared to expected rates. The respondents would receive follow-up surveys for a 30-month period.
- Study Protocol Number C4591011. This study is an active safety surveillance evaluation conducted within the Department of Defense Health System Databases using data derived from electronic health records and medical service claims among covered U.S. military and their families. Rates of safety events of interest in vaccinated participants will be compared to unvaccinated comparators. The study will be conducted for 30 months.
- Study Protocol Number C4591012. This study is an active surveillance study for adverse events of special interest and other clinically significant events associated with the Pfizer-BioNTech COVID-19 Vaccine using the Veteran's Health Administration electronic medical record database. Vaccinated participants will be compared to unvaccinated participants or to recipients of seasonal influenza vaccine. The study will be conducted for 30 months.

Currently, the primary objective of all three proposed studies above is descriptive, and the list of adverse events in the studies has not been finalized. FDA will provide feedback on these studies after further review.

Reporting to VAERS and Pfizer, Inc.

Providers administering the Pfizer-BioNTech COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to Pfizer the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1. Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2
- Reduction in the risk of confirmed COVID-19 after Dose 1 and before Dose 2
- Reduction in the risk of confirmed severe COVID-19 any time after Dose 1

The protocol-specified 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 7 days after completion of the vaccination regimen. Additional primary efficacy analyses in the all-available efficacy population, including participants who had protocol violations, showed consistency with outcomes in the primary analysis population. Efficacy findings were also consistent across various subgroups, including racial and ethnic minorities, participants aged 65 years and older, and those with one or more of the following conditions: obesity, diabetes, hypertension, and chronic cardiopulmonary diseases. While limited, available data suggest that individuals with previous SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination.

Among participants with no evidence of COVID-19 prior to vaccination, the vaccine was effective in reducing the risk of COVID-19 and severe COVID-19 after Dose 1. Fewer severe cases were also observed in the vaccine recipients relative to recipients of placebo during the follow up period after Dose 1. The findings post Dose 1, from a post-hoc analysis, cannot be the basis to assess the potential efficacy of the vaccine when administered as a single dose because the period of observation is limited by the fact that most participants received a second dose three weeks after the first one.

8.2. Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subset of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) is too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

The primary endpoint was evaluated in individuals without prior evidence of COVID-19 disease, and very few cases of confirmed COVID-19 occurred among participants with evidence of infection prior to vaccination (although more cases occurred in the placebo group compared with the vaccine group). Therefore, available data are insufficient to make conclusions about benefit in individuals with prior SARS-CoV-2 infection. However, available data, while limited, do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Effectiveness in pediatric populations

The representation of pediatric participants in the study population is too limited to adequately evaluate efficacy in pediatric age groups younger than 16 years. No efficacy data are available from participants ages 15 years and younger. Although adolescents 16 to 17 years of age were included in the overall efficacy analysis, only one confirmed COVID-19 case was reported in this age group. However, it is biologically reasonable to extrapolate that effectiveness in ages 16 to 17 years would be similar to effectiveness in younger adults. Efficacy surveillance continued beyond November 14, 2020, and the Sponsor has represented that additional data will be provided in a BLA.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27 to November 14, 2020, in various geographical locations. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine against asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[11-14] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3. Known Risks

The vaccine has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%). Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of subjects reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs. 111 [0.51%]). Severe adverse reactions occurred in 0.0-4.6% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in older adults (>55 years of age) (≤2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination.

Serious adverse events, while uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study. Three SAEs in the BNT162b2 group were considered related by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally related following vaccination (n=1). We considered two of the events as possibly related to vaccine: the shoulder injury possibly due to vaccine administration or the vaccine itself and lymphadenopathy. Lymphadenopathy was temporally associated and biologically plausible.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Although participants 16 to 17 years of age were enrolled in the phase 3 trial, safety data for this age group is limited. However, available data are consistent with the safety profile in the adult population, and it is biologically reasonable to extrapolate the greater safety experience in adults, in particular younger adults, to the oldest pediatric age group of 16 to 17 years.

8.4. Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 16 years of age, pregnant and lactating individuals, and immunocompromised individuals.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of nearly 44,000 participants over the period of follow up at this time. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

A numerically greater number of appendicitis cases occurred in the vaccine group but occurred no more frequently than expected in the given age groups and do not raise a clear concern at this time for a causal relationship to study vaccination. Although the safety database revealed an imbalance of cases of Bell's palsy (4 in the vaccine group and none in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

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10. Appendix A. Study BNT162-01

Design

Study BNT162-01 is an ongoing, first-in-human, phase 1 dose-level finding study conducted in Germany to evaluate the safety and immunogenicity of several different candidate vaccines, including BNT162b2. Twelve adults 18 to 55 years of age received 30ug BNT162b2.

Secondary and exploratory objectives were specified to describe the immune response, measured by functional antibody titer, antibody binding assay, and cell-mediated immune responses (cytokines associated with Th1 and Th2 responses to assess for the induction of a balanced versus Th1 or Th2 dominant immune response) at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as in study C4591001.

Results

No SAEs were reported in the BNT162-01 safety database included in the EUA submission, and the safety profile for BNT162b2 in this study was similar to that in the much larger study, C4591001.

Evaluable ELISPOT data were available from 39 participants across dose levels of BNT162b2 (data cutoff date was 17 September 2020). Evaluable intracellular cytokine staining and FACS data were available from 36 participants across dose levels of BNT162b2 (cutoff date was 04 September 2020). Data for serology results for serum neutralizing titers were available for 45 participants across dose levels of BNT162b2 (data cutoff date was 18 September 2020). Most participants who received both doses of BNT162b2 had evidence of SARS-CoV-2 S protein-specific CD4+ (39/39, 100%) and CD8+ (35/39, 89.7%) T cell responses. These T cell responses were directed against different parts of the antigen, including epitopes in the RBD, indicating the induction of multi-epitope responses by BNT162b2. Functionality and polarization of S-specific BNT162b2-induced SARS-CoV-2 T cells were assessed by intracellular accumulation of cytokines IFNγ, IL-2, and IL-4 measured after stimulation with overlapping peptide pools representing the full-length sequence of the whole SARS-CoV-2 S protein. For benchmarking, PBMC fractions from 15 convalescent patients with virologically confirmed COVID-19 were used. The Th1 polarization of the T helper response was characterized by the IFNγ and IL-2 production, and only minor IL-4, production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation. The SARS-CoV-2 neutralizing geometric mean titer (GMTs) increased over baseline after Dose 1, with a boost effect after Dose 2 that was most pronounced at the 30 µg dose level.

Thus, the immunogenicity results from Study BNT162-01 showed evidence of antibody-mediated SARS-CoV-2 neutralization and a Th1 polarization in the cell-mediated cellular immune responses in healthy adults 18 to 55 years of age, which supports the final dose selection and prospect of benefit for the enrollment of larger numbers of participants in Study C4591001.

11. Appendix B. Charlson Comorbidity Index

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, HIV/AIDS.

Reference: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

Emergency Use Authorization for Vaccines to Prevent COVID-19

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Vaccines and Related Biological Products Advisory Committee Meeting
December 17, 2020

FDA Briefing Document

Moderna COVID-19 Vaccine

Sponsor:
ModernaTX, Inc.

Moderna COVID-19 Vaccine
VRBPAC Briefing Document

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Glossary

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
mRNA	messenger RNA
NAAT	nucleic acid amplification-based test
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On November 30, 2020, ModernaTX (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (mRNA-1273) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is 2 doses, 100 µg each, administered 1 month apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3 randomized, double-blinded and placebo-controlled trial of mRNA-1273 in approximately 30,400 participants. The primary efficacy endpoint is the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2. In an interim analysis conducted using a data cutoff of November 7, 2020, a total of 27,817 participants randomized 1:1 to vaccine or placebo with a median 7 weeks of follow-up post-dose 2 were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to vaccination. Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5.0% (95% CI 86.5%, 97.8%) with 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 (11 protocol-defined severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group), in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for some of these outcomes did not allow for firm conclusions. Efficacy data from the final scheduled analysis of the primary efficacy endpoint (data cutoff of November 21, 2020, with a median follow-up of >2 months post-dose 2) demonstrated a VE of 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group and was consistent with results obtained from the interim analysis. The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to <65 years of age and 86.4% (95% CI: 61.4%, 95.5%) for participants ⩾65 years of age. A final secondary efficacy analysis also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 cases in the vaccine group.

Safety data from a November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomized 1:1 to vaccine or placebo with a median of 7 weeks of follow-up after the second dose supported a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. These safety data are the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Key safety data from this later submission, including death, other serious adverse events, and unsolicited adverse events of interest were independently verified and confirmed not to change the safety conclusions from the interim safety analysis.

The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and

chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ⩾65 years of age as compared to younger participants. Among unsolicited adverse events of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff, lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Lymphadenopathy (axillary swelling and tenderness of the vaccination arm) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there were three reports of facial paralysis (Bell's palsy) in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

The frequency of serious adverse events was low (1.0% in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

With the exception of more frequent, generally mild to moderate reactogenicity in participants <65 years of age, the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations on whether, based on the totality of scientific evidence available, the benefits of the mRNA-1273 COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of December 11, 2020, has caused more than 71 million cases of COVID-19 and claimed the lives of more than 1.6 million people worldwide. In the United States, more than 16 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 296,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S.

President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is the main target for neutralizing antibodies, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

2.2 EUA Request for the Moderna COVID-19 Vaccine mRNA-1273

ModernaTX, Inc. (Sponsor) is developing a vaccine to prevent COVID-19 that is based on the pre-fusion stabilized SARS-CoV-2 spike glycoprotein (S) antigen encoded by mRNA and formulated in a lipid nanoparticle (LNP). The Moderna COVID-19 Vaccine (also referred to as mRNA-1273) is a 2-dose series of 100-µg intramuscular injections administered 1 month apart. The vaccine is supplied as a multi-dose vial (10 doses) containing a frozen suspension -25° to -15°C) of mRNA-1273 that must be thawed prior to administration. The vaccine does not contain a preservative.

A Phase 3 randomized and placebo-controlled trial using mRNA-1273 in approximately 30,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. A prespecified interim efficacy analysis from 27,817 participants using a data cutoff date of November 7, 2020, demonstrated vaccine efficacy (VE) of 94.5% (95% CI: 86.5%, 97.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. At the time of this interim analysis, the median efficacy follow-up was 7 weeks post completion of the 2-dose series. Safety data from a November 11, 2020, interim analysis with a median of 7 weeks follow-up after the second dose of vaccine were reported to demonstrate an acceptable tolerability profile with no significant safety concerns. On November 30, 2020, ModernaTX submitted an EUA request to FDA, based on the interim analyses described above, for use of mRNA-1273 to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

On December 7, 2020, the Sponsor submitted an amendment to the EUA request with additional accrued safety data on all participants with a median of 2 months (9 weeks) follow-up after the second dose, using a data cutoff date of November 25, 2020, and data from the prespecified final efficacy analysis using a data cutoff of November 21, 2020, which met the median follow-up of 2 months after dose 2 and demonstrated vaccine efficacy of 94.1% (95%

CI: 89.3%, 96.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. Although the complete datasets and analyses from the primary efficacy analysis and associated safety analyses submitted on December 7, 2020, have not been independently verified by the FDA to the same extent as the data for the interim efficacy analyses and associated safety analyses submitted on November 30, 2020, based on comprehensive independent review of the data from the interim analysis, and the consistency of findings across the two analysis time points, FDA considers that the totality of available data are sufficient to support an evaluation of this product for EUA.

2.3 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and would continue under further investigation (under an Investigational New Drug Application). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4 Alternatives for Prevention of COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. However, the Pfizer-BioNTech COVID-19 vaccine is not an approved product, and furthermore is not available in quantity sufficient to vaccinate all persons in the U.S. for whom the vaccine is authorized for use. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use authorization, but not FDA approved, for treatment of COVID-19. Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.5 Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6]

2.6 Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.7 Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Regardless of when vaccination of placebo recipient would occur, there may be advantages to maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[9-11]

2.8 Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session to discuss, in general, the development, authorization, and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents
- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine

- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
  - Further evaluate safety, effectiveness and immune markers of protection
  - Evaluate the safety and effectiveness in specific populations.

On December 10, 2020, the VRBPAC met in open session to discuss the EUA request of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age older. Topics discussed at the meeting but not voted upon included Pfizer's plan for continuation of blinded, placebo-controlled follow-up in ongoing trials in the event that the vaccine is made available under EUA and gaps in plans for further evaluation of vaccine safety and effectiveness in populations that receive the Pfizer-BioNTech Vaccine under an EUA. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the proposed vaccine outweigh its risks for use in individuals 16 years of age and older.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on December 17, 2020, to discuss and provide recommendations on whether based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The Committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

4. Moderna COVID-19 Vaccine (mRNA-1273)

4.1 Vaccine Composition, Dosing Regimen

The Moderna COVID-19 Vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

The Moderna COVID-19 Vaccine is provided as a frozen suspension [stored between -25° to -15°C (-13° to 5°F)] multi-dose vial containing 10 doses. The vaccine must be thawed prior to administration. After thawing, a maximum of 10 doses (0.5 mL each) can be withdrawn from each vial. Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F) and discarded after 6 hours.

The Moderna COVID-19 Vaccine, mRNA-1273 (100 µg) is administered intramuscularly as a series of two doses (0.5 mL each), given 28 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2 Proposed Use Under EUA

The proposed use of the vaccine under an EUA is for the prevention of COVID-19 in adults 18 years of age and older.

5. FDA Review of Clinical Safety and Effectiveness Data

5.1 Overview of Clinical Studies

Data from three ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study mRNA-1273-P301 is a multi-center, Phase 3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study mRNA1273-P201 is a Phase 2 dose-confirmation study that explored 2 dose levels of mRNA-1273 and will not be discussed in detail. Study 20-0003 is a Phase 1 open label, dose-ranging, first-in-human study of mRNA-1273 and will also not be discussed in detail. A brief summary of the P201 and 20-0003 study designs and results to date is found in Appendix A, page 53.

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Moderna COVID-19 Vaccine mRNA-1273

Study Number	Type of Study (Efficacy, Safety, Nonclinical)	Participants randomized (N)	Study Design & Type of Control	Test Product(s); Dosing Regimens	Study Status
P301	Efficacy, Safety	30418	A Phase 3, randomized, stratified, observer-blind, placebo-controlled study	mRNA-1273 100 µg	Ongoing-vaccine efficacy demonstrated at the 1st interim analysis
P201	Safety, Immunogenicity	600	A Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study	mRNA-1273 50ug,100µg	Ongoing-Day 57 primary analysis have completed
20-0003*	Safety, Immunogenicity	120	A Phase 1 Open-label dose-ranging study	mRNA-1273 25ug 50ug,100ug 250ug	Ongoing-Day 119 (25ug, 100ug, 250ug), Day 57 (50ug)

*Sponsor: Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health

5.2 Study mRNA-1273-P301

5.2.1 Design

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 years of age and older. The study took place in 99 sites in the United States. Participants (N=30,351) were randomized 1:1 to receive intramuscular injections of either 100 µg of mRNA-1273 vaccine (n=15,181) or placebo

(n=15,170) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19, 18 to <65 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 41.4% of the study population. Participants were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. The study included 24,907 (82.1%) participants considered at occupational risk for acquiring SARS-CoV-2 infection, of whom 7,613 (25.1%) were healthcare workers. Other essential workers were also represented. The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS CoV-2 at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (Viracor; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the final scheduled efficacy analysis. Two interim analysis timepoints were pre-specified; the first upon accrual of 53 cases and the second upon accrual of 106 cases. The expected duration of study participation is approximately 25 months.

Primary Efficacy Endpoint

The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). The primary analysis was based on the Per-Protocol Set, defined as all randomized, baseline SARS-CoV-2 negative participants who received planned doses per schedule and have no major protocol deviations. For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was defined as:

- At least TWO of the following systemic symptoms: Fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), or
- At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; and
- NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Vaccine efficacy was defined as the percent reduction (mRNA-1273 vs. placebo) in the hazard of the primary endpoint, i.e. VE =1 – Hazard Ratio (HR). A stratified Cox proportional hazard (PH) model using Efron's method to handle ties and with treatment group as the independent variable was used to estimate the HR, where the same stratification factor used for randomization was applied. The primary objective would be met if the null hypothesis of H0: VE ≤30% is rejected at any of the interim or primary analyses at the respective significance level.

The final scheduled efficacy analysis of the primary endpoint was planned when a total of 151 adjudicated cases occurring at least 14 days after the second injection had been accrued. In addition, two interim analyses were planned when 35% (53 cases) and 70% (106 cases) of the

total target number of cases had been accrued. The Lan-DeMets spending function was used for approximating O'Brien-Fleming efficacy bounds to preserve the overall Type I error rate at a one-sided α =0.025, yielding nominal one-sided α of 0.0002, 0.0073, and 0.0227 at the first and second interim and the primary analyses, respectively. As conducted, the first and only interim analysis in the study occurred at 95 adjudicated cases of the primary endpoint, where the null hypothesis of H0: VE ≤30% was evaluated at a one-sided alpha of 0.0047.

Secondary Efficacy Endpoints

Secondary endpoints based on the Per-Protocol Set included the VE of mRNA-1273 to prevent the following:

- Severe COVID-19 (as defined below)
- COVID-19 based on a less restrictive definition of disease (defined below) occurring at least 14 days after the second dose of vaccine
- Death due to COVID-19
- COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the second dose)

One additional secondary endpoint was based on the Full Analysis Set (FAS): VE of mRNA-1273 to prevent COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection.

One of the secondary efficacy endpoints assessed COVID-19 as defined by a less restrictive definition: a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR **and** one of the following systemic symptoms:

- fever (temperature ≥38°C), or
- chills,
- cough,
- shortness of breath or difficulty breathing,
- fatigue,
- muscle aches or body aches,
- headache,
- new loss of taste or smell,
- sore throat,
- nasal congestion or rhinorrhea,
- nausea or vomiting, or diarrhea

Another secondary endpoint assessed cases of severe COVID-19, defined as a case of confirmed COVID-19 plus at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg);
- Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death

Vaccine efficacy of secondary endpoints was estimated from the Cox proportional-hazards model when the primary endpoint reached statistical significance. Estimates based on the Per-Protocol Set were presented with nominal two-sided 95% confidence intervals.

Analysis Populations

For the purposes of analysis, the following populations are defined:

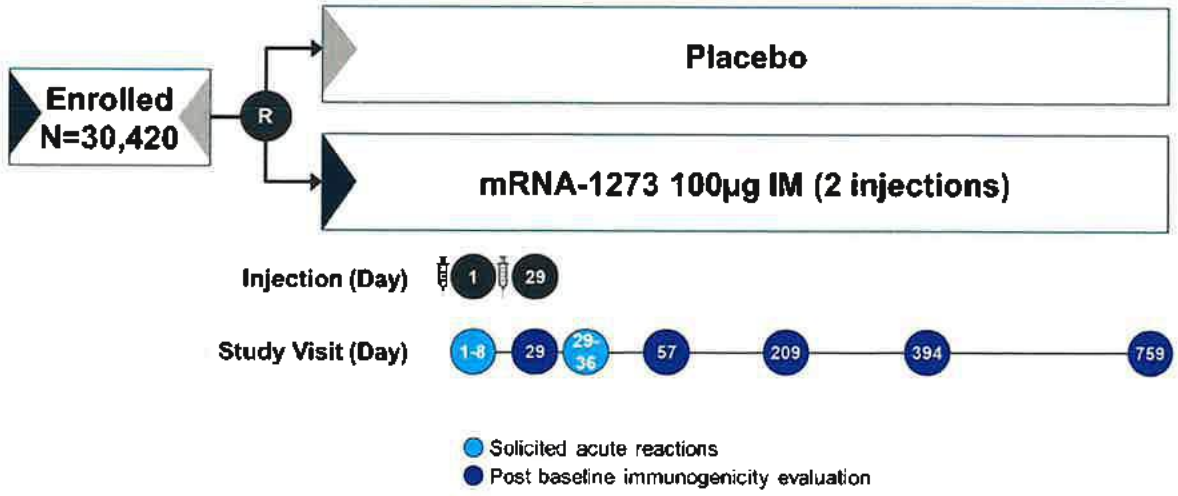
Table 2. Efficacy Set Definitions

Population	Description
Randomized	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set	All randomized participants who received at least one dose of Investigational Product (IP).
mITT Set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 (i.e., negative NP swab test at Day 1 and/or bAb against SARS-CoV-2 nucleocapsid below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1 before the first dose of IP.
Per Protocol Set	All participants in the mITT Set who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to DBL and unblinding, that impact critical or key study data.
Safety Set	All randomized participants who received at least one dose of IP.
Solicited Safety Set	All randomized participants who received at least one dose of IP and contributed any solicited adverse reaction data.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of mRNA-1273 after 1 or 2 doses. In all studies, participants recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from dose 1 to 28 after the last dose and medically attended adverse events (MAAEs) and serious AEs (SAEs) from dose 1 to the end of the study. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study 301



Safety assessments included the following:

- Solicited local and systemic adverse reactions (AR) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR.
- AEs leading to discontinuation from vaccination and/or study participation from Day 1 through Day 759 or withdrawal from the study.
- Medically Attended Adverse Events (MAAE) from Day 1 through Day 759 or withdrawal from the study.
- Serious Adverse Events (SAEs) from Day 1 through Day 759 or withdrawal from the study.
- Abnormal vital sign measurements.
- Physical examination findings.
- Pregnancy and accompanying outcomes.

Safety laboratory evaluations were not assessed in Study P301 but were collected in the phase 2 Study P201. See Appendix A on page 53.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. Such illnesses were evaluated and reported as SAEs.

Monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

The table below shows the Phase 3 safety analyses populations that were used to determine the proportions of study participants who experienced adverse events, including solicited adverse reactions after each dose, unsolicited adverse events, medically attended adverse events, and serious adverse events.

Table 3. Safety Set Definitions

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants treatment status in the study.
Safety Set	All randomized participants who received at least one dose of investigational product. The safety set was used for all analyses of safety except solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set	All randomized participants who received at least one dose of investigational product and contributed any solicited adverse reaction data. The solicited safety set was used for the analyses of solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set-1st Injection	All randomized participants who received the 1st dose and provided any solicited reaction data.

Population	Description
Solicited Safety Set-2nd Injection	All randomized participants who received the 2nd dose and provided any solicited reaction data.

5.2.2 FDA Assessment of Phase 3 Follow-Up Duration

As of the interim analysis cutoff (November 7, 2020, for efficacy, November 11, 2020, for safety), the proportion of participants across groups who received one dose of vaccine or placebo was 100%, and the proportion of participants who received two doses was 91.9% (92.1% vaccine, 91.7% placebo). The median follow-up after dose 2 was 7 weeks across groups. (For participants who did not receive a second dose of vaccine or placebo, follow-up after dose 2 was zero. Among participants who received dose 2, the median follow-up after the second dose was 50.0 days.) The proportion of participants with at least 1 month of follow-up after dose 2 was 76.7% (77.2% vaccine, 76.2% placebo) and with at least 2 months follow-up after dose 2 was 25.3% (25.7% vaccine, 24.9% placebo). FDA has completed its independent validation and evaluation of the datasets from which the Sponsor's interim safety and efficacy analyses were derived.

A second safety data cutoff was performed on November 25, 2020, and final efficacy analysis performed with a data cutoff of November 21, 2020, when 196 primary endpoint cases accrued. These data include a median follow-up of 2 months (9 weeks) for both efficacy and safety. The proportion of participants with at least 1 month of follow-up after dose 2 was 87.9% (88.2% vaccine, 87.7% placebo) and with at least 2 months follow-up after dose 2 was 53.6% (53.8% vaccine, 53.5% placebo). The Sponsor submitted analyses from the final efficacy analysis (Tables, Figures and Listings) on December 4, 2020, and safety analyses (Tables, Figures and Listings) on December 7, 2020, for FDA review under the EUA. Datasets were also submitted on December 7, 2020 and validated by FDA by December 8, 2020. The review of the second dataset submission for the final scheduled efficacy analysis and safety data through November 25, 2020, was not as comprehensive as that of the interim efficacy data and safety data first submitted in support of the EUA. However, preliminary assessments of safety and efficacy data and analyses from second data cutoff do not demonstrate any notable differences compared with the efficacy and safety analyses from November 7, 2020, and November 11, 2020, respectively, and key safety and efficacy data (e.g., the primary analysis, cases of severe COVID-19, and serious adverse events) from the December 7, 2020, submission were verified. FDA therefore considers the totality of submitted data to satisfy the expectation of a median of 2 months follow-up after completion of the full vaccination regimen.

5.2.3 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 4 (Per-Protocol Set) and Table 5 (Safety Set). The proportion of participants excluded from the Per-Protocol Set was balanced between treatment groups, with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the per protocol population, 26.3% of vaccine recipients and 25.7% of placebo recipients completed at least 2 months follow-up after dose 2.

Table 4. Efficacy Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Full Analysis Set	15180 (99.8)	15170 (99.7)	30350 (99.8)
Modified Intent-to-Treat Set	14312 (94.1%)	14370 (94.5%)	28682 (94.3)
Participants excluded from PP set	1274 (8.4%)	1327 (8.7%)	2601 (8.6%)
Randomized but received no Investigational Product (IP)	28 (0.2%)	40 (0.3%)	68 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	868 (5.7%)	800 (5.3%)	1668 (5.5)
Received IP other than what the participant was randomized to	5 (<0.1)	7 (<0.1)	12 (<0.1)
Discontinued study or study vaccine without receiving the second dose	136 (0.9)	203 (1.3)	339 (1.1)
Did not receive second dose of IP	144 (0.9)	155 (1.0)	299 (1.0)
Received vaccine out of window	81 (0.5)	98 (0.6)	179 (0.6)
Major protocol deviation	12 (<0.1)	24 (0.2)	36 (0.1)
Per Protocol Set	13934 (91.6)	13883 (91.3)	27817 (91.4)
Completed 1 dose**	13934 (100)	13883 (100)	27817 (100)
Completed 2 doses**	13218 (94.9)	13164 (94.8)	26382 (94.8)
Completed at least 7 weeks follow-up after dose 2**	7293 (52.3)	7304 (52.6)	14597 (52.5)
Completed at least 2 months follow-up after dose 2**	3669 (26.3)	3568 (25.7)	7237 (26.0)
Discontinued from Study**	24 (0.2)	34 (0.2)	58 (0.2)
Reason for Discontinuation**			
Adverse Event	0	0	0
Death	0	1 (<0.1)	1 (<0.1)
Withdrawal by Participant	18 (0.1)	22 (0.2)	40 (0.1)
Lost to Follow-up	2 (<0.1)	9 (<0.1)	11 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	2 (<0.1)	0	2 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2
[a] EUA request (interim analysis): November 11, 2020 cutoff
*Percentage based on number of participants in the Safety Set
**Percentage based on number of participants in the Per-Protocol Set

Based on the November 11, 2020 safety data cutoff, an overview of participant disposition is presented in the table below. The proportion of randomized participants who discontinued from the study was 0.9% (288 participants) across study groups, with a greater number in the placebo group (168) compared with the vaccine group (120). The most frequently reported reason was withdrawal of consent (67 participants in the vaccine group, 120 in the placebo group). In addition, 51 participants were lost to follow-up (20 in the vaccine group, 31 in the placebo group). In the vaccine group, 3 participants withdrew due to an adverse event (<0.1%, including 1 participant who withdrew due to a SAE) and 3 participants died during the study. In the placebo group, no participants withdrew due to an adverse event, and 4 participants died during the study.

Table 5. Safety Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Completed 1 dose	15180 (99.8)	15170 (99.7)	30350 (99.8)
Completed 2 doses	13982 (91.9)	13916 (91.5)	27898 (91.7)
Exposed (Safety Set)	15184	15166	30350 (99.8)
Discontinued from Study	120 (0.8)	168 (1.1)	288 (0.9)
Reason for Discontinuation			
Adverse Event	3 (<0.1)	0	3 (<0.1)
Death	3 (<0.1)	4 (<0.1)	7 (<0.1)
Withdrawal by Participant	67 (0.4)	120 (0.8)	187 (0.6)
Lost to Follow-up	20 (0.1)	31 (0.2)	51 (0.2)
Protocol Deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician Decision	17 (0.1)	2 (<0.1)	19 (<0.1)
Other	9 (<0.1)	10(<0.1)	19 (<0.1)
Completed ≥1 month f/up*	14354 (94.5)	14345 (94.6)	28700 (94.6)
Completed ≥2 months f/up*	12021 (79.2)	11974 (79.0)	23995 (79.1)
Completed ≥1 month f/up after dose 2*	11717 (77.2)	11559 (76.2)	23276 (76.7)
Completed ≥2 months f/up after dose 2*	3894 (25.7)	3773 (24.9)	7667 (25.3)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2.
[a] EUA request (interim analysis): November 11, 2020 cutoff

5.2.4 Demographics and Other Baseline Characteristics

The Per-Protocol Set included 47.4% females and 25.3% of individuals ≥65 years of age. There were 36.5% of participants considered as representing communities of color with 9.7% African American, 4.7% Asian, and <3% from other racial groups; 20% of participants were Hispanic/Latino. A majority of the participants (82%) were considered at occupational risk for SARS-CoV-2 exposure, with 25.4% of participants being healthcare workers. At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.3% of participants, and 4% of participants had two or more high risk conditions. The protocol-specified risk factors were those conditions that placed an individual at increased risk for severe complications of COVID-19 and were selected based on CDC recommendations[12] from March 2020. These conditions included the following:

- Chronic lung disease (e.g., emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- HIV infection

There was a similar distribution of demographic characteristics between the treatment groups as well as between the all randomized population, Full Analysis Set, and the Per-Protocol Set.

Table 6. Demographic Characteristics[a], Per-Protocol Set

Characteristic	Vaccine Group (N=13934) n (%)	Placebo Group (N=13883) n (%)	Total (N=27817) n (%)
Sex			
Female	6661 (47.8)	6514 (46.9)	13175 (47.4)
Male	7273 (52.2)	7369 (53.1)	14642 (52.6)
Age (years)			
Mean (SD)	51.6 (15.45)	51.5 (15.55)	51.6 (15.50)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age- subgroups (years)			
18 to <65	10407 (74.7)	10384 (74.8)	20791 (74.7)
65 and older	3527 (25.3)	3499 (25.2)	7026 (25.3)
Race			
American Indian or Alaska Native	107 (0.8)	110 (0.8)	217 (0.8)
Asian	616 (4.4)	684 (4.9)	1300 (4.7)
Black or African American	1369 (9.8)	1338 (9.6)	2707 (9.7)
Native Hawaiian or Other Pacific Islander	33 (0.2)	30 (0.2)	63 (0.2)
White	11078 (79.5)	11005 (79.3)	22083 (79.4)
Other	298 (2.1)	293 (2.1)	591 (2.1)
Ethnicity			
Hispanic or Latino	2783 (20.0)	2769 (19.9)	5552 (20.0)
Not Hispanic or Latino	11019 (79.1)	10987 (79.1)	22006 (79.1)
Race and Ethnicity			
Non-Hispanic white	8858 (63.6)	8755 (63.1)	17613 (63.3)
Communities of color	5054 (36.3)	5102 (36.7)	10156 (36.5)
Occupational Risk*	11397 (81.8)	11408 (82.2)	22805 (82.0)
Healthcare worker	3541 (25.4)	3531 (25.4)	7072 (25.4)
High Risk Condition**			
No high risk condition	11820 (77.9)	11788 (77.7)	23608 (77.8)
One high risk condition present	3116 (22.4)	3075 (22.1)	6191 (22.3)
Two or more high risk conditions present	561 (4.0)	554 (4.0)	1115 (4.0)
Age and Health Risk for Severe COVID-19***			
18 to <65 years and not at risk	8309 (59.6)	8323 (60.0)	16632 (59.8)
18 to <65 years and at risk	2098 (15.1)	2061 (14.8)	4159 (15.0)
≥65 years	3527 (25.3)	3499 (25.2)	7026 (25.3)

Source: Sponsor's Table14.1.3.4.2. [a] EUA request (interim analysis): November 11, 2020 data cutoff.
Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.
** High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
*** Age and health risk for severe COVID-19 is used as stratification factor for randomization.

The demographic characteristics among vaccine and placebo participants in the safety population were similar. There were no significant imbalances in demographic and other baseline characteristics between the per-protocol population and the safety population, with median 7-week follow-up.

Table 7. Demographic Characteristics[a], Safety Set

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Sex			
Female	7255 (47.8)	7100 (46.8)	14355 (47.3
Male	7929 (52.2)	8065 (53.2)	15995 (52.7)
Age (years)			
Mean (SD)	51.4 (15.50)	51.3 (15.60)	51.4 (15.55)
Median	53.0	52.0	52.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
≥18 to <65	11414 (75.2)	11415 (75.3)	22830 (75.2)
65 and older	3770 (24.8)	3750 (24.7)	7520 (24.8)
Race			
American Indian or Alaska Native	110 (0.7)	120 (0.8)	230 (0.8)
Asian	653 (4.3)	732 (4.8)	1385 (4.6)
Black or African American	1562 (10.3)	1528 (10.1)	3090 (10.2)
Native Hawaiian or other Pacific islander	34 (0.2)	32 (0.2)	66 (0.2)
White	12032 (79.2)	11990 (79.1)	24023 (79.2)
Other	321 (2.1)	315 (2.1)	636 (2.1)
Multiracial	315 (2.1)	319 (2.1)	634 (2.1)
Ethnicity			
Hispanic or Latino	3121 (20.6)	3112 (20.5)	6234 (20.5)
Not Hispanic or Latino	11920 (78.5)	11914 (78.6)	23834 (78.5)
Race and Ethnicity			
Non-Hispanic White	9534 (62.8)	9458 (62.4)	18992 (62.6)
Communities of color	5624 (37.0)	5680 (37.5)	11305 (37.2)
Occupational Risk*	12420 (81.8)	12487 (82.3)	24907 (82.1)
Healthcare worker	3787 (24.9)	3826 (25.2)	7613 (25.1)
High Risk Condition**			
One high risk condition present	3360 (22.1)	3382 (22.3)	6742 (22.2)
No high risk condition	11824 (77.9)	11783 (77.7)	23608 (77.8)
Age and Health Risk for Severe COVID-19***			
≥18 to <65 years and not at risk	8889 (58.5)	8884 (58.6)	17773 (58.6)
≥18 to <65 years and at risk	2530 (16.7)	2534 (16.7)	5065 (16.7)
≥65 years	3765 (24.8)	3747 (24.7)	7512 (24.8)

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Baseline SARS CoV-2 status****			
Negative	14316 (94.3%)	14366 (94.7)	26862 (94.5%)
Positive	341 (2.2%)	334 (2.2%)	675 (2.2%)
Missing	527 (3.5%)	465 (3.5%)	993 (3.3%)

Source: Sponsor's Table 14.1.3.2.2 ª EUA request (interim analysis): November 11 2020 cutoff.
* Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.**
**High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human immunodeficiency virus (HIV) infection

The following table provides the proportions of participants randomized to each of the protocol-specified strata based on presence or absence of protocol-defined risk factors for severe COVID-19 disease, including age ⩾65 years. The presence of these risk factors was assessed at screening via review of the participants medical history. The protocol specified that at least 25% (and up to 50%) of enrolled participants were to be either ⩾65 years of age or 18 through <65 years of age with a protocol-defined risk factor. As of the November 11, 2020 cutoff, ~25% of participants were age ⩾65 years, and 16.7% of participants were age 18 to <65 years with a protocol-defined risk factor. The remainder of participants (58.6%) were age 18 to <65 years without risks. The proportions of participants in each of these three strata randomized to vaccine or placebo are shown in the table below.

Table 8. Protocol-Defined Risk for Severe COVID-19 Disease, Safety Seta

Participants Risk Categories	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Without Any Protocol Risk for Severe COVID-19	11824 (77.9)	11783 (77.7)	23608 (77.8)
With Any Protocol Risk for Severe COVID-19	3360 (22.1)	3382 (22.3)	6742 (22.2)
Chronic Lung Disease	707 (4.7)	741 (4.9)	1448 (4.8)
Significant Cardiac Disease	742 (4.9)	741 (4.9)	1483 (4.9)
Severe Obesity	986 (6.5)	978 (6.4)	1964 (6.5)
Diabetes	1427 (9.4)	1431 (9.4)	2858 (9.4)
Liver Disease	100 (0.7)	96 (0.6)	196 (0.6)
HIV Infection	90 (0.6)	86 (0.6)	176 (0.6)

Source: Sponsor's Table 14.1.3.2.2. ª EUA request (interim analysis): November 11, 2020 cutoff

5.2.5 Vaccine Efficacy

Interim Primary Efficacy Analysis

The interim primary efficacy analysis was based on the Per-Protocol Set, which consisted of all participants with negative baseline SARS-CoV-2 status (i.e., negative RT-PCR for SARS-CoV-2 at Day 1 and/or negative serology against SARS-CoV-2 nucleocapsid) and who received 2 doses of investigational product per schedule with no major protocol deviations. The primary efficacy endpoint was vaccine efficacy (VE) in preventing protocol defined COVID-19 occurring at least 14 days after dose 2. Cases were adjudicated by a blinded committee. The primary

efficacy success criterion would be met if the null hypothesis of VE ≤30% was rejected at the O'Brien Fleming boundary at either the interim or primary analysis. The efficacy analysis presented is based on the data at the first pre-specified interim analysis timepoint consisting of 95 adjudicated cases. As shown in Table 9, in participants ≥18 years of age, there were 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group, with a VE of 94.5%, a lower bound of the 95% CI of 86.5%, and a one-sided p-value of <0.0001 for testing H0: VE ≤30%, which met the pre-specified success criterion. In participants ≥65 years of age in the Per-Protocol Set, there were no COVID-19 cases in the vaccine group and 15 COVID-19 cases in the placebo group.

Table 9. Interim Analysis[a] for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
All participants	5 (<0.1) 1.840	90 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1.
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose. All potential COVID-19 cases starting 14 days after the 2nd dose in the clinical database as of 07-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (07-Nov-2020 is the data cutoff date for efficacy). One case (in the placebo group) was assessed as a case by the adjudication committee but did not meet case definition based on statistical analysis plan (participant had body aches, nasal congestion, rhinorrhea, which were not protocol defined symptoms).
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/placebo) and 95% CI from the stratified Cox proportional hazard model.
**The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary: the one-sided nominal alpha of 0.0049 based on 95 cases using the Lan-DeMets O'Brien-Fleming spending function.

There were an additional 18 COVID-19 cases which met the protocol-defined primary efficacy endpoint but were not able to be adjudicated in time for the interim analysis. Of these 18 cases, one was in the vaccine group, and 17 were in the placebo group. Vaccine efficacy for the primary efficacy endpoint including these unadjudicated cases was similar to the results presented above.

Interim Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the primary efficacy endpoint include VE based on age, sex, race and ethnicity, risk factor, and baseline SARS-CoV-2 status and provide additional information on the applicability of these results across the general population. In general, VE among the subgroups are similar to the VE seen in the overall study population. The small number participants and cases in some subgroups, such as participants ≥75 years of age and participants in certain racial subgroups, limits the interpretability of the individual VE results, but are displayed for completeness.

Table 10. Subgroup Analyses of Vaccine Efficacy[a], COVID-19 14 Days After Dose 2 Per Adjudication Committee Assessments, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Age (years)			
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)
65 to <75	0 / 2904	12/ 2823 (0.4) 20.883	100%
75 and older	0 / 623	3 / 676 (0.4) 21.726	100%
Age and risk for severe COVID-19**			
18 and <65 and not at risk	4 / 8309 (<0.1) 2.524	57 / 8323 (0.7) 36.034	93.0% (80.8%, 97.5%)
18 and <65 and at risk	1 / 2098 (<0.1) 2.428	18 / 2061 (0.9) 44.673	94.6% (59.4%, 99.3%)
≥65	0 / 3527	15 / 3499 (0.4) 21.046	100%
Sex			
Female	3 / 6661 (<0.1) 2.271	45 / 6514 (0.7) 34.991	93.5% (79.2%, 98.0%)
Male	2 / 7273 (<0.1) 1.433	45 / 7369 (0.6) 31.883	95.5% (81.5%, 98.9%)
Race and Ethnicity			
Non-Hispanic white	5 / 8858 (<0.1) 2.657	70 /8755 (0.8) 37.721	93.0% (82.6%, 97.2%)
Communities of color	0 / 5054	20 / 5102 (0.4) 23.892	100%
Ethnicity			
Hispanic or Latino	0 / 2783	12 / 2769 (0.4) 26.346	100%
Not Hispanic or Latino	5 / 11019 (<0.1) 2.243	77 / 10987 (0.7) 34.729	93.6% (84.1%, 97.4%)
Race			
American Indian or Alaska Native	0 / 107	0 / 110	
Asian	0 / 616	3 / 684 (0.4) 26.549	100%
Black or African American	0 / 1,369	4 / 1338 (0.3) 18.566	100%
Native Hawaiian or Other Pacific Islander	0 / 33	0 / 30	
White	5 /11078 (<0.1) 2.215	80 / 11005 (0.7) 35.821	93.8% (84.8%, 97.5%)
Multiple	0 / 293	1 / 304 (0.3)	100%

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Other	0 / 298	2 / 293 (0.7) 45.645	100%

Source: Sponsor's Table 14.2.2.1.1.6.1.1, Table 14.2.2.1.1.6.3.1, Table 4.2.2.1.1.6.7.1, Table 14.2.2.1.1.6.10.1, Table 14.2.2.1.1.6.4.1, Table 14.2.2.1.1.6.2.1, Table 14.2.2.1.1.6.5.1, Table 14.2.2.1.1.6.6.1
[a] EUA request (interim analysis): November 7, 2020 data cutoff.
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic f ibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
**used as stratification factor for randomization

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 11.

Table 11. Demographic Characteristics[a], Participants With COVID-19 Starting 14 Days After Dose 2, Per Adjudication Committee Assessments, Per-Protocol Set

Characteristic	Vaccine (N[a]=5) N[b] (%)	Placebo (N[a]=90) N[b] (%)	Total (N[a]=95) N[b] (%)
Sex			
Female	3 (60)	45 (50)	48 (50.5)
Male	2 (40)	45 (50)	47 (49.5)
Age group			
18 to <65 years	5 (100)	75 (83.3)	80 (84.2)
≥65 to <75 years	0	12 (13.3)	12 (12.6)
≥75 years	0	3 (3.3)	3 (3.2)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	3 (3.3)	3 (3.2)
Black or African American	0	4 (4.4)	4 (4.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	5 (100)	80 (88.9)	80 (84.2)
Multiracial	0	1 (1.1)	1 (1.1)
Other	0	2 (2.2)	2 (2.1)
Ethnicity			
Hispanic or Latino	0	12 (13.3)	12 (12.6)
Not Hispanic or Latino	5 (100)	77 (85.6)	82 (86.3)
Not reported	0	1 (1.1)	1 (1.1)
At risk for severe COVID-19			
Yes	1 (20)	24 (26.7)	25 (26.3)
No	4 (80)	66 (73.3)	70 (73.7)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. [a] EUA request (interim analysis): November 07 2020 efficacy data cutoff. [a] EUA request (interim analysis): November 07 2020 cutoff.
[b] n = Number of participants with the specified characteristic.

Only 2.2% of participants had evidence of prior infection at study enrollment, and there was only one COVID-19 case starting 14 days after dose 2 reported from this subgroup, which was in a participant in the placebo group. There is insufficient data to conclude on the efficacy of the vaccine in previously infected individuals.

Table 12. Vaccine Efficacy by Baseline SARS-CoV-2 Status[a]: First COVID-19 From 14 Days After Dose 2 Per Adjudication Committee Assessment, Full Analysis Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6/15180	92/15170	93.5% (85.2, 97.2)
Positive	0/341	1/334 (0.3) 17.038	100%
Negative	6/14312 (<0.1) 2.154	90/14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0/527	1/465 (0.2)	100%

* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

Additional subgroup analyses of the interim primary efficacy analysis were conducted to evaluate the vaccine efficacy, by risk factor for severe COVID-19. VE point estimates were consistent with the efficacy observed for the overall study population, though interpretation of the results is limited by small numbers of participants and cases.

Table 13. Vaccine Efficacy by Risk Factor: First COVID-19 Occurrence From 14 Days After Dose 2, Per Adjudication Committee Assessment, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
At risk for severe COVID-19 due to comorbidity, regardless of age			
Yes	1 / 3116 (<0.1) 1.604	24 / 3075 (0.8) 39.177	95.9% (69.7%, 99.4%)
Chronic Lung Disease	0/661	6/673 (0.9) 42.950	100%
Significant Cardiac Disease	0/686	3/678 (0.4) 21.463	100%
Severe Obesity (BMI ≥40 kg/m^2)	1/901 (0.1) 5.524	11/884 (1.2) 62.851	91.2% (32.0%, 98.9%)
Diabetes	0/1338	7/1309 (0.5) 27.148	100%
Liver Disease	0/93	0/90	
HIV infection	0/80	1/76 (1.3) 91.108	100%
No	4 / 10818 (<0.1) 1.911	66 / 10808 (0.6) 31.657	94.0% (83.5%, 97.8%)
Obesity (BMI >30 kg/m^2)**	2/5269 (<0.1%)	46/5207 (0.9)	95.8% (82.6, 99.0)

[a] EUA request (interim analysis): November 7, 2020 efficacy data cutoff
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
** Post hoc analysis.

Interim Secondary Efficacy Analyses

Severe COVID-19 Cases

All 11 cases of severe COVID-19 at least 14 days after second dose as assessed by the adjudication committee were in the placebo group. Of these 11 participants, 5 had risk factors for severe COVID-19 and 6 did not. Three severe COVID-19 cases resulted in hospitalization and 8 did not. Nine of these cases met the severe COVID-19 case definition based on low oxygen saturation ≤93% on room air without any other severe disease criteria. One participant had low oxygen saturation as well as systolic blood pressure <90 mmHg. One participant had low oxygen saturation and missing data on whether other criteria were met. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 14.

Table 14. Severe COVID-19 Cases Starting 14 Days After Second Dose Based on Adjudication Committee Assessment, Per-Protocol Set

	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)*
Severe COVID-19	0	11 (<0.1); 4.072	100%

[a] EUA request (interim analysis): Novemer 07 2020 efficacy data cutoff.
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented when the lower bound was not evaluable by the statistical methods used for the analysis.

One participant in the mRNA-1273 group, a participant >65 years of age who had risk factors for severe COVID-19, was hospitalized due to oxygen saturation of 88% on room air 2 months after receiving the second dose of vaccine. There was a verbal report of a positive SARS-CoV-2 RT-PCR test 3 days prior to hospitalization; however, NP swab collected during hospitalization was negative for SARS-CoV-2. Due to absence of a confirmed RT-PCR result at the time of data snapshot, this case was not referred for adjudication and not captured. The pre-hospitalization RT-PCR result was later reported to be positive from an external CLIA-certified laboratory and may represent a severe COVID-19 case with hospitalization in the vaccine group.

There were 4 additional severe COVID-19 cases which met the protocol-defined severe COVID-19 endpoint but were not able to be adjudicated in time for the interim analysis. All 4 cases were in the placebo group.

Other Secondary Efficacy Endpoints

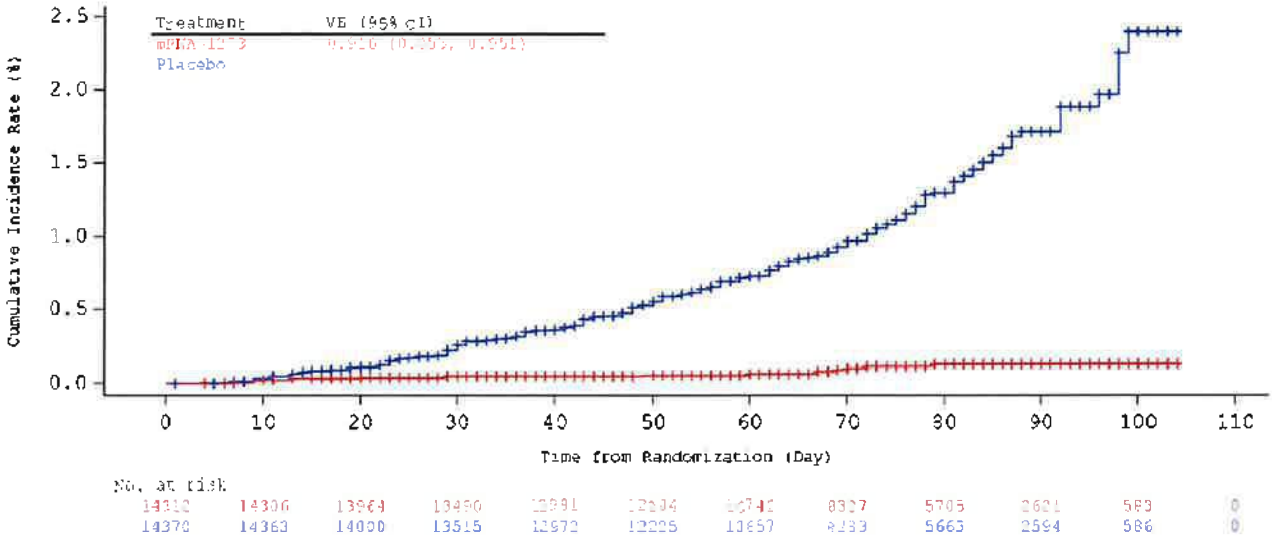
The secondary efficacy endpoint of VE of mRNA-1273 for the prevention of COVID-19 disease based on a less restrictive definition of COVID-19 disease from 14 days after dose 2 showed similar case splits and VE to the primary efficacy endpoints described above. Efficacy against COVID-19 occurring at least 14 days after the first dose of vaccine, including cases that occurred after the second dose, was also similar to the primary endpoint. There were no deaths due to COVID-19 at the time of the interim analysis to enable an assessment of vaccine efficacy against death due to COVID-19.

Cumulative Incidence Curves – Interim Efficacy Analysis

Based on the cumulative incidence curve for cases in the mITT efficacy population after randomization (same as date of dose 1), COVID-19 cases appear to have occurred similarly at low rates for both the mRNA-1273 and placebo groups until around Day 14 after dose 1. The

curves then diverge, with more cases accumulating in the placebo group than the mRNA-1273 group.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



Additional Interim Efficacy Analyses

Additional analyses were done to assess efficacy against COVID-19 after one dose of mRNA-1273. In participants in the mITT set who only received one dose of the vaccine at the time of the interim analysis, VE after one dose was 80.2% (95% CI 55.2%, 92.5%). These participants had a median follow-up time of 28 days (range: 1 to 108 days). The small, non-random sample and short median follow-up time limits the interpretation of these results. There appears to be some protection against COVID-19 disease following one dose; however, these data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Table 15. Vaccine Efficacy[a] of mRNA-1273 to Prevent COVID-19 From Dose 1 by Time Period in Participants Who Only Received One Dose, mITT Set

First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Case n (%)	Placebo Group N=1079 Case n (%)	VE (%) (95% CI)*
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (68.8%, 99.1%)

Surveillance time in person years for given endpoint across all participants within each group at risk for the endpoint
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years
**Participants who were not at risk (cases or censored at prior time period) are excluded from this analysis
[a] Based on interim analysis: November 7, 2020 efficacy data cutoff.

A similar analysis was conducted to look at vaccine efficacy against severe COVID-19 after one dose. In participants in the mITT group who received only one vaccine, 2 participants in the mRNA-1273 group and 4 participants in the placebo group developed severe COVID-19. Both participants in the vaccine group met the case definition for severe COVID-19 based on oxygen saturation ≤93% on room air. These results should be interpreted cautiously given the small sample size and case number and the short follow-up duration.

Table 16. Vaccine Efficacy[a] of mRNA-1273 to Prevent Severe COVID-19 After Dose 1 in Participants Who Only Received One Dose in mITT Set

	Vaccine Group N=996 Case n (%)	Control Group N=1079 Case n (%)	Vaccine Efficacy (95% CI)
Number of participants with severe COVID-19 starting after dose 1	2 (0.2)	4 (0.4)	42.6% (-300.8, 94.8)

[a] Based on interim analysis : EUA request (interim efficacy analysis): November 7, 2020 efficacy data cutoff.

Final Scheduled Efficacy Analysis

Data from the final scheduled efficacy analysis were submitted as an amendment to the EUA request on December 7, 2020. Analyses of efficacy endpoints beyond those presented below have not been independently verified by the FDA. The median efficacy and safety follow-up for participants in the study at of the time of the final scheduled efficacy analysis (November 21, 2020 efficacy data cutoff) was 9 weeks. Vaccine efficacy against COVID-19 starting 14 days after the second dose was 94.1% (95% CI 89.3%, 96.8%) and was consistent with results obtained from the interim analysis. The VE in participants ≥65 years of age appears to be lower than in younger adults 18 to <65 years (86.4% compared to 95.6%) and lower than observed in the interim analysis (100% based on a total of 15 cases).

Table 17. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence Rate per 1,000 person-years)*	Placebo Group N=13883 Cases n (%) (Incidence Rate per 1,000 person-years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All participants	11 (<0.1) 3.328	185 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years[1]	7/10551 (<0.1) 2.875	156/10521 (1.5) 64.625	95.6%; (90.6%, 97.9%)	NA
65 years and older[2]	4/3583 (0.1); 4.595	29/3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose. All potential COVID-19 cases starting 14 days after the second dose in the clinical database as of 21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy). One case (in the vaccine group) was adjudicated as a COVID-19 case by the committee but did was meet the case definition per statistical analysis plan due to documented symptoms and positive PCR being more than 14 days apart.
21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy).
* Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
**VE and 95% CI from the stratified Cox proportional hazard model
***The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary.
[1] Percentage based on number of participants in the 18 to <65 years of age group.
[2] Percentage based on number of participants in the ≥65 years of age group.

Severe COVID-19 Cases

In the primary efficacy analysis, there were an additional 19 cases of severe COVID-19 (one of which resulted in death from COVID-19), for a total of 30 severe COVID-19 cases starting 14 days after dose 2, per adjudication committee assessment. All 30 cases were in the placebo group. Nine of the total 30 severe COVID-19 cases resulted in hospitalization. Of the 19 additional severe cases since the interim analysis, 12 cases met the severe case definition due to low oxygen saturation ≤93% with no other criteria met. The remaining participants met the definition based on the following reasons: death (1 participant), ARDS requiring ECMO (1 participant), low oxygen saturation and renal and neurologic dysfunction (1 participant), low oxygen saturation and low blood pressure (2 participants), need for high flow oxygen (1 participant), low blood pressure only (1 participants). The COVID-19 case which resulted in death was in a 54-year-old participant with diabetes. The possible severe COVID-19 case in a mRNA-1273 vaccine recipient described with the interim efficacy analysis (negative SARS-CoV-2 PCR per the study central laboratory but reported positive PCR per a CLIA-certified external lab) is not included in the per-protocol analysis below.

Table 18. Secondary Efficacy Analysis, Severe COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All participants	0	30 (0.2) 9.138	100%

[a] EUA request (primary analysis): November 21, 2020 efficacy data cutoff.

Efficacy Summary

The data from the planned interim efficacy analysis, with a cutoff date of November 7, 2020, and median follow-up for efficacy of 7 weeks post-dose 2, met the prespecified success criteria established in the study protocol. Efficacy of the vaccine to prevent COVID-19 occurring at least 14 days after dose 2 was 94.5%, (95% CI 86.5%; 97.8%) in participants without prior evidence of SARS-CoV-2 infection. VE was >93% in the group of participants with or without prior infection, although interpretation of data in participants with positive SARS-CoV-2 status at baseline is limited by the small sample size and case numbers in this subgroup. Efficacy outcomes across demographic subgroups were consistent with the efficacy seen in the overall study population. All 11 cases of severe COVID-19 occurring 14 days after the second dose

were in the placebo group, although one severe COVID-19 may have occurred in the vaccine group but did not meet criteria for the protocol-specified case definition. Among participants in the mITT set who only received one dose of vaccine or placebo at the time of the interim analysis, efficacy against COVID-19 starting after dose 1 was 80.2% (95% CI: 55.2%, 92.5%). The efficacy observed after dose 1 and before dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the numbers of participants and time of observation are limited. The trial did not have a single-dose arm to make an adequate comparison.

Data from a final efficacy analysis (data cutoff November 21, 2020) was submitted as an amendment after the initial EUA request. The FDA has not independently verified the complete efficacy data from this dataset, beyond those analyses presented above. The final scheduled efficacy analysis on the primary endpoint, demonstrating a VE point estimate of 94.1% (95% CI: 89.3%, 96.8%), appear to align with the data obtained from the interim analysis, except for a lower efficacy observed in participants ≥65 years of age compared to that in younger adults 18 to <65 years of age and compared to the efficacy estimate from the interim analysis.

5.2.6 Safety

The safety analyses presented in this review are largely derived from the November 11, 2020 dataset that was the basis for the November 30, 2020 EUA request. FDA has not independently verified the complete safety dataset and analyses from the cutoff date of November 25, 2020. However, all new deaths, SAEs, unsolicited adverse events of interest, and pregnancies were reviewed using the cutoff date of November 25, 2020. No additional safety concerns were raised based on the additional data reviewed by FDA or analyses presented by the Sponsor. The safety analyses from the November 25, 2020 cutoff date, as presented by the Sponsor, appear to align with results from the interim analysis in terms of overall rates and types of solicited and unsolicited adverse events.

Adverse events were reported in a higher proportion of vaccine recipients than placebo recipients, and this imbalance was driven by reactogenicity (solicited AEs) reported in the 7 days following each dose of vaccine. The proportions of participants with SAEs, death, and withdrawals due to adverse events were balanced across the study groups. Overall, rates of AEs were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. The tables below provide an overview of the rates of AEs by treatment groups and baseline SARS-CoV-2 status.

Table 19. Participants Reporting at Least One Adverse Event, Among All Participants and by Baseline SARS-COV2 Status (Safety Set)[a]

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set	**N=15176**	**N=15162**
Solicited adverse reactions after any injection	14338/15176 (94.5)	9027/15162 (59.5)
Baseline SARS-COV-2 negative	13566/14309 (94.8%)	8576/14363 (59.7)
Baseline SARS-COV-2 positive	279 /340 (82.1%)	151/334 (45.2)
Solicited local adverse reaction	13,962/15176 (92.0)	4,381/15161 (28.9)
Baseline SARS-COV-2 negative	13211/14309 (92.3)	4147/14362 (28.9)
Baseline SARS-COV-2 positive	268/340 (78.8)	74/334 (22.2)
Grade 3 solicited injection site reaction[a]	1386/15176 (9.1)	143/15161 (0.9)
Baseline SARS-COV-2 negative	1307/14309 (9.1)	131/14362 (0.9)
Baseline SARS-COV-2 positive	23/340 (6.8)	5/334 (1.5)
Solicited systemic adverse reaction	12553/15176 (82.7)	8032/15,162 (53.0)
Baseline SARS-COV-2 negative	11893/14309 (83.1)	7628/14363(53.1)
Baseline SARS-COV-2 positive	237/340 (69.7)	137/334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction	2,501/15,176 (16.5)	560/15,162 (3.7)
Baseline SARS-COV-2 negative	2383/14309 (16.7)	529/14363 (3.7)
Baseline SARS-COV-2 positive	37/340 (10.9)	13/334 (3.9)
Safety Set	**N=15184**	**N=15165**
Unsolicited adverse event up to 28 days after any injection	3325/15184 (21.9)	2949/15165 (19.4)
Baseline SARS-COV-2 negative	3204/14316 (22.4)	2846/14366 (19.8)
Baseline SARS-COV-2 positive	49/341 (14.4)	56/334 (16.8)
Unsolicited adverse event	3283/15184 (21.6)	2902/15165 (19.1)
Grade 3 unsolicited adverse event	187/15184 (1.2)	148/15165 (1.0)
Related** unsolicited adverse events	1127/15184 (7.4)	609/15165 (4.0)
Baseline SARS-COV-2 negative	1095/14316 (7.6)	585/14366 (4.1)
Baseline SARS-COV-2 positive	16/341 (4.7)	14/334 (4.2)
Related** Grade 3 unsolicited adverse event	69/15184 (0.5)	28/15165 (0.2)
Medically attended adverse Event	1215/15184 (8.0)	1276/15165 (8.4)
Baseline SARS-COV-2 negative	1167/14316 (8.2)	1243/14366 (8.7)
Baseline SARS-COV-2 positive	19/341 (5.6)	18/334 (5.4)
Related** medically attended adverse events	122/15184 (0.8)	73/15165 (0.5)
Baseline SARS-COV-2 negative	118/14316 (0.8)	68/14366 (0.5)
Baseline SARS-COV-2 positive	0/341	5/334 (1.5)
Serious adverse event	82/15184 (0.5)	86/15165 (0.6)
Baseline SARS-COV-2 negative	79/14316 (0.6)	82/14366 (0.6)
Baseline SARS-COV-2 positive	0/341	3/334 (0.9)
Related** serious adverse event	5/15184 (<0.1)	4/15165 (<0.1)
Baseline SARS-COV-2 negative	5/14316 (<0.1)	4/14366 (<0.1)
Baseline SARS-COV-2 positive	0/341	0/334
Death*	4/15184 (<0.1)	4/15165 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	41/15184 (0.3)	71/15165 (0.5)
Baseline SARS-COV-2 negative	34/14316 (0.2)	68/14366 (0.5)
Baseline SARS-COV-2 positive	4/341 (1.2)	3/334 (0.9)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7
* There were no reports of Grade 4 injection site adverse reactions
[a] EUA request (interim analysis)-November 11, 2020
**Related as assessed by investigator

In subgroup analyses of adults ≥65 years of age, rates of solicited reactions (any, Grade 3 or higher) and all other unsolicited adverse events (AEs) (all and related) were comparable to those observed in all participants. Table 20 below summarizes AEs in participants ≥65 years of age, irrespective of baseline serostatus (as less than 1% of ≥65-year-olds were seropositive at baseline).

Table 20. Adverse Events Among Adults ≥65 Years of Age (Safety Set)[a]

Participants Reporting at Least One	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set		
Solicited adverse reactions after any injection	3497/3766 (92.9)	2010/3750 (53.6)
Solicited local adverse reaction	3337/3766 (88.6)	859/3750 (22.9)
Grade 3 solicited local adverse reaction	279/3766 (7.4)	66/3750 (1.8)
Solicited systemic adverse reaction	2922/3766 (77.6)	1754/3750 (46.8)
Grade 3 or 4 solicited systemic adverse reaction	444/3766 (11.8)	119/3750 (3.2)
Safety Set		
Unsolicited Adverse Event up to 28 days after any	872/3770 (23.1)	734/3750 (19.6)
Related** unsolicited adverse events	261/3770 (6.9)	138/3750 (3.7)
Medically Attended Adverse Event	336/3770 (8.9)	376/3750 (10.0)
Related** medically attended adverse events	22/3770 (0.6)	13/3750 (0.3)
Serious Adverse Event	36/3770 (1.0)	42/3750 (1.1)
Related** serious adverse event	2/3770 (<0.1)	1/3750 (<0.1)
Death	1/3768 (<0.1)	2/3752 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	12/3770 (0.3)	17/3750 (0.5)
Related** AE leading to discontinuation of the vaccine	3/3370 (<0.1)	4/3750 (0.1)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7. [a] EUA request (interim analysis)-November 11 2020. Data provided in response to Information Request (IR),- received December 7 2020
**Related as assessed by investigator

Solicited Adverse Reactions

Solicited local and systemic adverse reactions with onset within 7 days after each dose were assessed across groups and are presented in the tables below stratified by age (18 to 64 years; ≥65 years) for all participants. Solicited adverse reactions (AR) were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling, and lymphadenopathy) and systemic reactions (fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting).

Local Adverse Reactions

Solicited local AR were reported by the majority of vaccine recipients and at higher rates than placebo recipients. Vaccine recipients reported higher rates of local reactions after dose 1 than dose 2. The proportions of participants reporting any local AR were 84.2% and 88.8% after dose 1 and dose 2 in vaccine recipients, compared to 19.8% and 18.8% after dose 1 and dose 2 in placebo recipients, respectively. The proportions reporting at least one grade 3 local AR were 3.5% and 7.0% after dose 1 and dose 2, respectively in vaccine recipients and 0.5% after any dose in placebo recipients. There were no reports of Grade 4 local reactions after any dose across groups. The majority of vaccine recipients (57.6%) reported onset of local AR on Day 1 while at home, and the median duration was 2 days after dose and 3 days after dose 2.

Overall across both age cohorts, the most frequently reported local AR was pain, reported by 83.7% vs 19.8% of vaccine/placebo recipients after the first dose (2.8% vs 0.4% reported as Grade 3) and 88.4% vs 17.0% of vaccine/placebo recipients after dose 2 (4.1% vs 0.3% reported as Grade 3). The median durations for pain were 2 days and 3 days after dose 1 and dose 2, respectively. The highest rates of pain were in participants 18 to <64 years after dose 2, with 90.1% reporting any pain and 4.6% reporting Grade 3 pain.

Axillary lymphadenopathy (vaccination arm) was the second most frequently reported local AR overall. It was reported in 10.2% vs 4.8% of vaccine/placebo recipients after dose 1 and 14.0% vs 3.9% of vaccine/placebo recipients after dose 2 respectively. Grade 3 axillary lymphadenopathy was reported in 0.3% vs 0.2% vaccine/placebo recipients after dose 1 and in 0.5% vs 0.1% of vaccine/placebo recipients after dose 2. The median duration after dose 1 was 1 day and after dose 2 was 2 days. The highest rates of axillary lymphadenopathy were reported by participants 18 to 64 years of age after dose 2, with 16.0% reporting any severity lymphadenopathy and 0.4% reporting Grade 3 lymphadenopathy.

Local reactions that persisted beyond 7 days after any dose were reported by both vaccine recipients and placebo recipients. Local reactions that persisted were reported by 3.7% of vaccine recipients and 1.3% of placebo recipients across both age cohorts. In the younger age cohort, 4.2% of vaccine recipients and 1.4% of placebo recipients reported a local reaction that persisted beyond 7 days, of which 0.6% of vaccine recipients and <0.1% of placebo recipients reported a Grade 3 reaction that persisted. In the older age cohort, 2.3% of vaccine recipients compared to 1.1% of placebo recipients reported a local reaction that persisted, including 0.5% of vaccine recipients, and <0.1% of placebo recipients reporting Grade 3 local reactions. Frequently reported local reactions persisting beyond 7 days in the younger age cohort in vaccine/placebo recipients were pain (1.5%/0.6%) and axillary lymphadenopathy (2.5%/0.7%), and in the older age cohort pain (1.2%/0.6%) and erythema (0.7%/<0.1%).

Table 21. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18 to <64 years, Solicited Safety Set[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	9960/11401 (87.4)	2432/11404 (21.3)	9371/10357 (90.5)	2134/10317 (20.7)
Grade 3	452/11401 (4.0)	39/11404 (0.3)	766/10357 (7.4)	41/10317 (0.4)
Pain[a]	9908/11401 (86.9)	2179/11404 (19.1)	9335/10357 (90.1)	1942/10317 (18.8)
Grade 3	367/11401 (3.2)	23/11404 (0.2)	479/10357 (4.6)	21/10317 (0.2)
Erythema[b] (Redness)	345/11401 (3.0)	46/11404 (0.4)	928/10357 (9.0)	42/10317 (0.4)
Grade 3	34/11401 (0.3)	11/11404 (<0.1)	206/10357 (2.0)	12/10317 (0.1)
Swelling[b] (Hardness)	768/11401 (6.7)	33/11404 (0.3)	1309/10357 (12.6)	35/10317 (0.3)
Grade 3	62/11401 (0.5)	3/11404 (<0.1)	176/10357 (1.7)	4/10317 (<0.1)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Lymphadenopathy[c]	1322/11401 (11.6)	567/11404 (5.0)	1654/10357 (16.0)	444/10317 (4.3)
Grade 3	36/11401 (0.3)	13/11404 (0.1)	45/10357 (0.4)	10/10317 (<0.1)

Source: Sponsor's Table 14.3.1.1.4, Table 14.3.1.1.5
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose
[a] EUA request (interim analysis)-November 11 2020
Note: Adverse reaction data were collected on the electronic diary (eDiary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
c: Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e. lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
Note: No grade 4 solicited local adverse reactions were reported.

Table 22. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	2805/3762 (74.6)	566/3746 (15.1)	3010/3587 (83.9)	473/3549 (13.3)
Grade 3	77/3762 (2.0)	39/3746 (1.0)	212/3587 (5.9)	29/3549 (0.8)
Pain[a]	2782/3762 (74.0)	481/3746 (12.8)	2990/3587 (83.4)	421/3549 (11.9)
Grade 3	50/3762 (1.3)	32/3746 (0.9)	96/3587 (2.7)	17/3549 (0.5)
Erythema[b] (Redness)	86/3761 (2.3)	19/3746 (0.5)	265/3587 (7.4)	13/3549 (0.4)
Grade 3	8/3761 (0.2)	2/3746 (<0.1)	75/3587 (2.1)	3/3549 (<0.1)
Swelling[b] (Hardness)	166/3761 (4.4)	19/3746 (0.5)	386/3587 (10.8)	13/3549 (0.4)
Grade 3	20/3761 (0.5)	3/3746 (<0.1)	69/3587 (1.9)	7/3549 (0.2)
Lymphadenopathy[c]	231/3761 (6.1)	155/3746 (4.1)	302/3587 (8.4)	90/3549 (2.5)
Grade 3	12/3761 (0.3)	14/3746 (0.4)	21/3587 (0.6)	8/3549 (0.2)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5]
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
[a] EUA request (interim analysis)-November 11 2020.
Note: Adverse reaction data were collected on the electronic diary by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
c: Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e. lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
Note: No grade 4 solicited local adverse reactions were reported.

Systemic Adverse Reactions

Solicited systemic AR were reported for the majority of vaccine recipients and at higher rates than for placebo recipients. Vaccine recipients had higher rates of systemic reactions after the second dose than the first dose. The proportions of vaccine and placebo participants reporting systemic AR were as follows: reporting any grade was 54.9% vs 42.2% after dose 1 and 79.3% vs 36.5% after dose 2, and reporting Grade 3 was 2.9% vs. 2.0% after dose 1 and 15.7% vs. 2.0% after dose 2, respectively. Across groups and doses <0.1% reported a Grade 4 systemic reaction (mainly fever > 104 °F). The majority of vaccine recipients reported onset of systemic AR while at home either on Day 1 (33.7%) or on Day 2 (37.0%), and the median duration after any dose was 2 days.

Overall, the most frequently reported systemic AR was fatigue, reported by 68.5% of vaccine recipients and 36.1% of placebo recipients. After any dose, Grade 3 fatigue was reported by 9.6% of vaccine participants and 1.3% of placebo recipients. Grade 4 fatigue was reported by 1 participant in the vaccine group and none in the placebo group. After dose 1, any/Grade 3 fatigue was reported by 37.2%/1.0% of vaccine recipients and after dose 2 any/Grade 3 fatigue was reported by 65.2%/9.7% of vaccine recipients. The median duration for fatigue in vaccine recipients was 2 days after any dose. The highest rates of fatigue were reported by participants 18 to 64 years after the 2nd dose, with 67.6% reporting any fatigue, 10.6% reporting Grade 3, and 1 participant reporting Grade 4 (after Dose 1).

Rates of other solicited systemic AR were: headache 63.0% vaccine group vs. 36.5% placebo group; myalgia 59.6% vaccine group vs. 20.1% placebo group; arthralgia 44.8% vaccine group vs. 17.2% placebo group; and chills 43.4% vaccine group vs. 9.5% placebo group. The rates of Grade 3 AR were: headache 5.5% vaccine group vs. 2.2% placebo group; myalgia 8.6% vaccine group vs. 0.6% placebo group; arthralgia 5.1% vaccine group vs. 0.5% placebo group; and chills 1.3% vaccine group vs. 0.2% of placebo group. The median duration was 1 day after dose 1 and 1 to 2 days after dose 2. The highest rates of solicited reactions were observed in participants 18 to 64 years after dose 2 and included the following: headache 62.8% (5.0% reported Grade 3), myalgia 61.3% (10.0% Grade 3), arthralgia 45.2% (5.8% Grade 3), and chills 45.8% (1.5% Grade 3). There was one vaccine recipient in the younger age cohort who also reported Grade 4 arthralgia after dose 1.

Fever was reported after any dose by 14.8% of vaccine participant and 0.6% of placebo recipients. Fever was reported after dose 1 in 0.8% of vaccine recipients and 15.6% of vaccine recipients after dose 2. Grade 3 (≥102.1 °F) was reported by <0.1% (11 participants) of vaccine recipients after Dose 1 and 1.3% (186 participants) of vaccine recipients after dose 2. Grade 4 (≥104.0 °F) fever were reported by 4 vaccine recipients after dose 1 and 11 vaccine recipients after dose 2. In participants 18 to 64 years after dose 2, any fever, Grade 3 fever, and Grade 4 fever were reported in 1,806 participants (17.4%), 168 participants (1.6%), and 10 participants (<0.1%), respectively.

Systemic reactions persisting longer than 7 days were reported in both age cohorts of vaccine and placebo recipients after any dose. In the vaccine group, 11.9% of participants reported a solicited reaction that persisted beyond 7 days compared to 9.5% of placebo participants. In the younger age cohort, 9.8% of vaccine recipients and 8.9% of placebo recipients reported a systemic reaction that persisted beyond 7 days; and 2.0% of vaccine recipients and 1.2% of placebo recipients reported Grade 3 or 4 systemic reaction that persisted beyond 7 days. In the older age cohort, 9.4% of vaccine recipients and 8.1% of placebo recipients reported a systemic reaction that persisted; 1.7% of vaccine recipients (63 participants) and 0.8% of placebo

recipients (31 participants) reported a Grade 3 or 4 reaction that persisted. The most frequently reported systemic reactions that persisted beyond 7 days in vaccine recipients/placebo recipients 18 to 64 years were fatigue (5.7%/5.0%), headache (4.8%/4.0%), myalgia (2.7%/2.7%), and arthralgia (2.6%/2.8%); in the older cohort were fatigue (5.8%/4.5%), arthralgia (3.7%/3.8%), myalgia (2.9%/2.7%), and headache (2.8%/2.7%).

Fever persisted beyond 7 days in 7 vaccine recipients and 4 placebo recipients, all of whom were in the younger age cohort. There were 2 vaccine recipients who reported grade 3 fever that persisted, and none in the placebo group.

Table 23. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18-64 years, Solicited Safety Set[*a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	6503/11405 (57.0)	5063/11406 (44.4)	8484/10358 (81.9)	3967/10320 (38.4)
Grade 3	363/11405 (3.2)	248/11406 (2.2)	1801/10358 (17.4)	215/10320 (2.1)
Grade 4	5/11405 (<0.1)	4/11406 (<0.1)	10/10358 (<0.1)	2/10320 (<0.1)
Fever	105/11403 (0.9)	39/11404 (0.3)	1806/10352 (17.4)	38/10315 (0.4)
Grade 3	10/11403 (<0.1)	1/11404 (<0.1)	168/10352 (1.6)	1/10315 (<0.1)
Grade 4	4/11403 (<0.1)	4/11404 (<0.1)	10/10352 (<0.1)	2/10315 (<0.1)
Headache	4031/11401 (35.4)	3303/11404 (29.0)	6500/10357 (62.8)	2617/10317 (25.4)
Grade 3	219/11401 (1.9)	162/11404 (1.4)	515/10357 (5.0)	124/10317 (1.2)
Fatigue	4384/11401 (38.5)	3282/11404 (28.8)	7002/10357 (67.6)	2530/10315 (24.5)
Grade 3	120/11401 (1.1)	83/11404 (0.7)	1099/10357 (10.6)	81/10315 (0.8)
Grade 4	1/11401 (<0.1)	0	0	0
Myalgia	2698/11401 (23.7)	1626/11404 (14.3)	6353/10357 (6.1)	1312/10316 (12.7)
Grade 3	73/11401 (0.6)	38/11404 (0.3)	1032/10357 (10.0)	39/10316 (0.4)
Arthralgia	1892/11401 (16.6)	1327/11404 (11.6)	4685/10357 (45.2)	1087/10315 (10.5)
Grade 3	47/11401 (0.4)	29/11404 (0.3)	603/10357 (5.8)	36/10315 (0.3)
Grade 4	1/11401 (<0.1)	0	0	0
Nausea/Vomiting	1069/11401 (9.4)	908/11404 (8.0)	2209/10357 (21.3)	754/10315 (7.3)
Grade 3	6/11401 (<0.1)	8/11404 (<0.1)	8/10357 (<0.1)	8/10315 (<0.1)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Chills	1051/11401 (9.2)	730/11404 (6.4)	5001/10357 (48.3)	611/10315 (5.9)
Grade 3	17/11401 (0.1)	8/11404 (<0.1)	151/10357 (1.5)	14/10315 (0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis)-November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ≥39.0 – ≤40.0°C or ≥102.1 – ≤104.0° F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Table 24. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 Years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	1818/3761 (48.3)	1335/3748 (35.6)	2580/3589 (71.9)	1102/3549 (31.1)
Grade 3	84/3761 (2.2)	63/3748 (1.7)	387/3589 (10.8)	58/3549 (1.6)
Grade 4	0	0	2/3589 (<0.1)	1/3549 (<0.1)
Fever	10/3760 (0.3)	7/3748 (0.2)	366/3587 (10.2)	5/3549 (0.1)
Grade 3	1/3760 (<0.1)	1/3748 (<0.1)	18/3587 (0.5)	0
Grade 4	0	2/3748 (<0.1)	1/3587 (<0.1)	1/3549 (<0.1)
Headache	921/3761 (24.5)	724/3745 (19.3)	1665/3587 (46.4)	635/3549 (17.9)
Grade 3	52/3761 (1.4)	34/3745 (0.9)	107/3587 (3.0)	32/3549 (0.9)
Fatigue	1251/3761 (33.3)	851/3745 (22.7)	2094/3587 (58.4)	695/3549 (19.6)
Grade 3	30/3761 (0.8)	23/3745 (0.6)	248/3587 (6.9)	20/3549 (0.6)
Myalgia	743/3761 (19.8)	443/3745 (11.8)	1683/3587 (46.9)	385/3549 (10.8)
Grade 3	17/3761 (0.5)	9/3745 (0.2)	201/3587 (5.6)	10/3549 (0.3)
Arthralgia	618/3761 (16.4)	456/3745 (12.2)	1252/3587 (34.9)	381/3549 (10.7)
Grade 3	13/3761 (0.3)	8/3745 (0.2)	122/3587 (3.4)	7/3549 (0.2)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Nausea/Vomiting	194/3761 (5.2)	166/3745 (4.4)	425/3587 (11.8)	129/3549 (3.6)
Grade 3	4/3761 (0.1)	4/3745 (0.1)	10/3587 (0.3)	3/3549 (<0.1)
Grade 4	0	0	1/3587 (<0.1)	0
Chills	202/3761 (5.4)	148/3745 (4.0)	1099/3587 (30.6)	144/3549 (4.1)
Grade 3	7/3761 (0.2)	6/3745 (0.2)	27/3587 (0.8)	2/3549 (<0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (Interim analysis) November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ≥39.0 – ≤40.0°C or ≥102.1 – ≤104.0°F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Unsolicited AEs

Unsolicited AEs from the November 11, 2020 data cutoff include safety data from participants who had at least 1 month of follow-up after dose 2 (76.7% of all participants) those who had at least 2 months of follow-up after dose 2 (25.3% of all participants). The median study duration following dose 2 was 7 weeks across study groups. Table 25 below shows unsolicited AEs reported through the first data cutoff. Treatment emergent adverse events (AEs) were defined as any event that occurred during the study and was not present before exposure (study vaccine or placebo), any event that occurred during the study and was not present before exposure, or any event already present that worsened after exposure. The following unsolicited adverse events were specified in the protocol:

- Unsolicited AEs observed or reported during the 28 days following each vaccine or placebo dose
- AEs leading to discontinuation from vaccination and/or study participation through Day 759 (study completion) or withdrawal from the study
- Serious adverse events and medically attended adverse events through Day 759 (study completion) or withdrawal from study

Determination of severity for all unsolicited AE were made by the investigators based on medical judgement and definitions of severity as mild, moderate, or severe.

The overall proportions of participants who reported an unsolicited adverse event were generally similar, with numerically slightly higher rates of unsolicited AEs in the vaccine group compared to placebo group for some categories of unsolicited nonserious AEs.

Table 25. Summary of Unsolicited AEs Regardless of Relationship to the Investigational Vaccine, Through 28 Days After Any Vaccination, Study 301, Safety Set

Event Type	Nov 11 Dataset[a] mRNA-1273 (N=15184) n (%)	Nov 11 Dataset[a] Placebo (N=15165) n (%)	Nov 25 Dataset[b] mRNA-1273 (N=15185) n (%)	Nov 25 Dataset[b] Placebo (N=15166) n (%)
All unsolicited AEs	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Medically-attended	1215 (8.0)	1276 (8.4)	1372 (9.0)	1465 (9.7)
Severe unsolicited AEs	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)	50 (0.3)	80 (0.5)
Serious	82 (0.5)	86 (0.6)	93 (0.6)	89 (0.6)
Death	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)

Source:
Abbreviation: AE = adverse event.
Note: An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages were based on the number of safety participants.
[a] EUA request (interim analysis)-November 11 2020
[b] Primary efficacy analysis-November 25, 2020

Unsolicited Adverse Events

The table below shows rates of unsolicited AEs that occurred within 28 days of any vaccination and at rates of ≥1% in the vaccine group through the November 11, 2020 data cutoff. The proportion of vaccine recipients who reported an unsolicited AE was 21.9% (3325 participants) compared to 19.4% of placebo participants. A higher frequency of unsolicited adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local and systemic reactogenicity following vaccination.

Table 26. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants, by MedDRA Primary System Organ Class and Preferred Term (Safety Analysis Set)[a]

System Organ Class Preferred Term	Vaccine N=15184 n (%) Any	Vaccine N=15184 n (%) Severe	Placebo N=15165 n (%) Any	Placebo N=15165 n (%) Severe
Infections and infestations	521 (3.4)	13 (<0.1)	621 (4.1)	25 (0.2)
Vascular disorders	149 (1.0)	28 (0.2)	138 (0.9)	39 (0.3)
Nervous system disorders	624 (4.1)	27 (0.2)	552 (3.6)	21 (0.1)
Headache	435 (2.9)	19 (0.1)	409 (2.7)	13 (<0.1)
Respiratory, thoracic and mediastinal disorders	480 (3.2)	8 (<0.1)	522 (3.4)	9 (<0.1)
Cough	148 (1.0)	1 (<0.1)	143 (0.9)	1 (<0.1)
Oropharyngeal pain	137 (0.9)	1 (<0.1)	184 (1.2)	3 (<0.1)
Gastrointestinal disorders	426 (2.8)	14 (<0.1)	387 (2.6)	16 (0.1)
Diarrhea	178 (1.2)	2 (<0.1)	147 (1.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	213 (1.4)	4 (<0.1)	158 (1.0)	2 (<0.1)
Musculoskeletal and connective tissue disorders	586 (3.9)	24 (0.2)	521 (3.4)	18 (0.1)
Arthralgia	174 (1.1)	10 (<0.1)	152 (1.0)	2 (<0.1)
Myalgia	172 (1.1)	11 (<0.1)	138 (0.9)	0

System Organ Class Preferred Term	Vaccine N=15184 n (%)	Vaccine N=15184 n (%)	Placebo N=15165 n (%)	Placebo N=15165 n (%)
General disorders and administration site	894 (5.9)	43 (0.3)	560 (3.7)	13 (<0.1)
Fatigue	344 (2.3)	12 (<0.1)	307 (2.0)	7 (<0.1)
Injection site pain	147 (1.0)	6 (<0.1)	49 (0.3)	1 (<0.1)
Injury, poisoning and procedural complications	238 (1.6)	16 (0.1)	262 (1.7)	13 (<0.1)

Source: Sponsor's Tables 14.3.1.8.1 and 14.3.1.17.1
n (%)=number (percentage) of participants reporting the adverse event at least once
[a] EUA request (interim analysis): November 11, 2020 data cutoff.

Unsolicited AEs considered related by the investigator to study vaccination were reported by 7.4% of vaccine recipients and 4.0% of placebo recipients. The proportion of participants who reported severe unsolicited AEs was 1.4% following any vaccine dose (275 participants) and 1.3% following any placebo dose (225 participants). The most frequently reported severe AEs that occurred in greater numbers of vaccine than placebo recipients were headache, myalgia, arthralgia, injection site erythema, and injection site pain (Table 26).

Medically attended adverse events (MAAE) from dose 1 through 28 day following any dose were reported for 8.0% of participants in the vaccine group (1,839 events in 1,215 participants) and 8.4% of those in the placebo group (1,837 events in 1,276 participants). The majority of these events were considered not related to study vaccinations and were primarily attributed to local and systemic reactogenicity following vaccinations.

FDA conducted standard MedDRA queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited adverse events with onset following dose 1 through the November 11, 2020 cutoff. The SMQs were conducted on adverse event Preferred Terms that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune disorders. FDA assessment of additional safety data accrued through the November 25, 2020 cutoff is ongoing, though specific SMQ of adverse events of clinical interest were assessed.

A SMQ evaluating lymphadenopathy-related events (including injection site lymphadenopathy, lymph node pain, and lymphadenitis) through the November 25, 2020 data cut demonstrated a numerical imbalance across study groups, with 1.1% of vaccine recipients (191 events in 173 vaccine recipients) compared to 0.63% of placebo recipients (109 events in 95 participants) reporting such events in the Safety Set. The rates reported in the older cohort (≥65 years) were 0.74% (28 events in 28 participants) in vaccine recipients compared to 0.35% (16 events in 13 participants) in placebo recipients. The rates reported in the younger cohort (18-64 years) were 1.3% (163 events in 145 participants) in vaccine recipients and 0.72% (93 events in 82 participants) in placebo recipients. These events support a plausible relationship to study vaccination and were also reported in the evaluation of solicited local adverse reactions. Local axillary swelling/tenderness was reported in approximately 19% of participants during the 7 days following any dose in the Solicited Safety Set. The median duration following any dose was 1 to 2 days, and <1% reported Grade 3 axillary swelling/tenderness.

A SMQ evaluating hypersensitivity-related adverse events through the November 25, 2020 data cutoff demonstrated a numerical imbalance across study groups, with 1.5% of vaccine recipients (258 events in 233 participants) and 1.1% of placebo recipients (185 events in 166 participants) reporting such events in the Safety Set. In the older cohort (age ≥65 years) which

comprised 24.8% of the Safety Set, the rates of hypersensitivity were 1.8% (74 events in 68 participants) in vaccine recipients and 1% (45 events in 38 participants) in placebo recipients. In the younger age cohort (18-64 years), the rates were 1.5% (184 events in 165 participants) in vaccine recipients compared to 1.1% (140 events in 128 participants). Overall, the most frequently reported AEs in the hypersensitivity SMQ were injection site rash (0.24% vaccine, 0.01% placebo), injection site urticaria (0.1% vaccine, 0% placebo), and rash maculo-papular (0.07% vaccine, 0.01% placebo). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

A query of specific adverse events of clinical interest in the Safety Set through November 25, 2020 demonstrated a small imbalance in the number of participants reporting Bell's palsy (facial paralysis), with 3 vaccine recipients and 1 placebo recipient reporting this MAAE. One case of Bell's palsy in the vaccine group was considered a SAE; a 67-year-old female with diabetes was hospitalized for stroke due to new facial paralysis 32 days after vaccination. This case was reported as resolving. Another Bell's palsy case in the vaccine group occurred 28 days after vaccination in a 30-year-old female who reported an upper respiratory infection 27 days prior to onset of her facial paralysis. This case was reported as resolved. An additional case of Bell's palsy in the vaccine group was reported with the primary analysis safety data (November 25, 2020 data cutoff) and occurred 22 days after vaccination in a 72-year-old female; this event was still ongoing at the time of safety report. The case in the placebo group, reported as resolving, occurred 17 days post injection in a 52-year-old-male. Causality assessment is confounded by predisposing factors in these participants. However, considering the temporal association and biological plausibility, a potential contribution of the vaccine to the manifestations of these events of facial palsy cannot be ruled out. FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to the Moderna COVID-19 vaccine.

Immediate Adverse Events

Immediate solicited reactions occurring within 30 minutes of vaccination were infrequent and there does not appear to be an imbalance between the treatment groups. Review of unsolicited AEs that occurred within 30 minutes of vaccination demonstrated comparable rates across study groups (0.6% vaccine, 0.6% placebo), and none of the events reported in the vaccine group were considered serious.

Study Withdrawals due to an Adverse Event (Safety Set)

Adverse events that led to discontinuation of vaccination were reported in 0.3% in the vaccine group and 0.5% in the placebo group. Following the November 25, 2020 cutoff, 4 participants were withdrawn from the study due to an adverse event (2 vaccine recipients and 2 placebo recipients). The two AEs reported in the vaccine group were acute pancreatitis and road traffic accident, and the two AEs reported in the placebo group were incarcerated hernia and duodenal ulcer hemorrhage. FDA's review of data through this latter time point is ongoing.

Serious Adverse Events

Deaths

As of December 3, 2020, 13 deaths were reported (6 vaccine, 7 placebo). Two deaths in the vaccine group were in participants >75 years of age with pre-existing cardiac disease; one

participant died of cardiopulmonary arrest 21 days after dose 1, and one participant died of myocardial infarction 45 days after dose 2. Another two vaccine recipients were found deceased at home, and the cause of these deaths is uncertain: a 70-year-old participant with cardiac disease was found deceased 57 days after dose 2, and a 56-year-old participant with hypertension, chronic back pain being treated with opioid medication died 37 days after dose 1 (The official cause of death was listed as head trauma). One case was a 72-year-old vaccine recipient with Crohn's disease and short bowel syndrome who was hospitalized for thrombocytopenia and acute kidney failure due to obstructive nephrolithiasis 40 days after dose 2 and developed complications resulting in multiorgan failure and death. One vaccine recipient died of suicide 21 days after dose 1. The placebo recipients died from myocardial infarction (n=3), intra-abdominal perforation (n=1), systemic inflammatory response syndrome in the setting of known malignancy (n=1), COVID-19 (n=1), and unknown cause (n=1). These deaths represent events and rates that occur in the general population of individuals in these age groups.

Non-fatal Serious Adverse Events

Among participants who received at least one dose of vaccine or placebo (N=30,351), the proportion of participants who reported at least one SAE from dose 1 to the primary analysis cutoff date (November 25, 2020) was 1% in the mRNA-1273 group and 1% in the placebo group. The most common SAEs occurring at higher rates in the vaccine group than the placebo group were myocardial infarction (0.03% in vaccine group, 5 cases vs. 3 cases in placebo group), cholecystitis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group), and nephrolithiasis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group). The small numbers of cases of these events do not suggest a causal relationship. The most common SAEs occurring at higher rates in the placebo arm than the vaccine arm, aside from COVID-19 (0.1% in placebo group), were pneumonia (0.05% in placebo group) and pulmonary embolism (0.03% in placebo group). Occurrence of other SAEs, including cardiovascular SAEs, were otherwise balanced between treatment groups.

As of November 25, 2020, 7 SAEs (4.8%) in the mRNA-1273 group and 5 (3.3%) in the placebo group were assessed by the investigator as related to study vaccination (Table 27). Of the 7 SAEs in the mRNA-1273 group, the Sponsor assessed 4 as related and 3 as unrelated to the vaccine.

Table 27. SAEs Considered Related by Investigator

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Intractable nausea and vomiting	1	65 F; history of headaches and severe nausea requiring hospitalization	Resolved	Yes/Yes
mRNA-1273	Facial swelling	1	46 F; dermal filler cosmetic injection 6 months prior	Resolved	Yes/Yes
mRNA-1273	Facial swelling	2	51 F; dermal filler cosmetic injection 2 weeks prior	Resolved	Yes/Yes
mRNA-1273	Rheumatoid arthritis	14	57 M; hypothyroid	Unresolved	Yes/Yes
mRNA-1273	Dyspnea with exertion, peripheral edema	8	66 F; diabetes, hypertension	Resolving	Yes/No

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Autonomic dysfunction	24	46 F; hypothyroid; possible sinus infection	Unresolved	Yes/No
mRNA-1273	B-cell lymphocytic lymphoma	31	75 F; history of metastatic lung cancer, breast cancer	Unresolved	Yes/No
Placebo	Polymyalgia rheumatica	15	83 M; chronic low back pain	Resolving	Yes/Yes
Placebo	Facial swelling, paresthesia, anxiety	7	41 F; dental procedure 2 weeks prior	Resolved	Yes/No
Placebo	Procedural hemorrhage	16	52 M; aortic stenosis, hyperlipidemia; aspirin intake	Resolved	Yes/No
Placebo	Pulmonary embolism	24	59 M; smoking	Unresolved	Yes/No
Placebo	Pneumonia and myocardial infarction	29	70 M; coronary artery disease, chronic kidney disease, diabetes	Resolved	Yes/No

There was one event of lip angioedema 2 days after vaccination in a 29-year-old female participant in the vaccine group which was classified as medically significant but not considered an SAE. The participant has a history of dermal filler injection in the lips (unknown how long prior to vaccination). She reported having a similar reaction after receipt of an influenza vaccine in the past. Taken in context with the SAEs of facial swelling which occurred in 2 participants who had previous history of cosmetic filler injections, it is possible the localized swelling in these cases is due to an inflammatory reaction from interaction between the immune response after vaccination and the dermal filler. This phenomenon has been reported after natural infection (e.g., after an influenza-like illness).

In FDA's opinion following review of the narratives, 3 SAEs are considered likely related, including the one report of intractable nausea/vomiting and 2 reports of facial swelling. The possibility that the vaccine contributed to the SAE reports of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction cannot be excluded. The vaccine was unlikely to have contributed to the other SAEs assessed by the investigator as related. As described in detail in a previous section, there was one report of Bell's palsy in the vaccine arm which occurred 32 days after vaccination; both the investigator and the Sponsor assessed this event as unrelated to the study vaccine, but in FDA's assessment a causal relationship cannot be definitively excluded.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or

before vaccination and not detected by pre-vaccination screening tests. Thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (2 vaccine, 3 placebo), within 30 days after LMP in 5 participants (2 vaccine, 3 placebo), >30 days after LMP in 2 participants (1 vaccine, 1 placebo), and date of LMP not known in 1 participant (1 vaccine, 0 placebo). Unsolicited AEs related to pregnancy include a case of spontaneous abortion and a case of elective abortion, both in the placebo group. One participant in the placebo group is lost to follow-up. Pregnancy outcomes are otherwise unknown at this time.

A combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats was submitted to FDA on December 4, 2020. FDA review of this study concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of the mRNA-1273 vaccine in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 3 safety population (N=30,350; 15,184 vaccine,15,165 placebo) meets the expectations described in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The initial EUA request was based on data from the pre-specified interim analysis (November 11, 2020 data cutoff) with a median follow-up duration of 7 weeks after dose 2; this interim analysis data is the primary basis of this EUA review and conclusions. Data and analyses from a November 25, 2020 data cut with a median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series was submitted as an amendment to the EUA request on December 7, 2020. The FDA has not independently verified the complete safety data from the primary analysis, aside from all new deaths (including those reported through December 3, 2020) and SAEs. No new safety concerns have been identified. The rates and types of solicited adverse reactions and unsolicited adverse events are unlikely to change significantly with an additional 2 weeks of follow-up. The totality of the data package submitted in the EUA request meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); 0.2% to 9.7% were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in adults ≥65 years of age as compared to younger participants. Among adverse events of clinical interest, lymphadenopathy was reported in 173 participants (1.14%) in the vaccine group and 95 participants (0.63%) in the placebo group. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the Safety Set. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there has been three reports of Bell's palsy in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-

1273.

As of December 3, 2020, there were a total of 13 deaths reported in the study (6 vaccine, 7 placebo). These deaths represent events and rates that occur in the general population of individuals in these age groups. The frequency of non-fatal serious adverse events was low and without meaningful imbalances between study arms (1% in the mRNA-1273 group and 1% in the placebo group). The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

ModernaTX expects that participants, including approximately 25% who are healthcare workers, may request unblinding to receive mRNA-1273 or another vaccine potentially available under EUA external to the trial. More extensive participant-driven crossover would be expected to alter the composition of the trial population, with greatly increased participant dropout due to a large proportion of participants belonging to priority vaccination groups desiring to be vaccinated with vaccine made available under EUA. ModernaTX is evaluating the opportunity to amend the protocol to proactively reconsent participants who received placebo to be offered mRNA-1273 vaccination and to remain in the trial, enabling ModernaTX to continue to collect the relevant safety and effectiveness data over the entire two years of follow-up while increasing the likelihood of retaining participants on trial. Adverse events among those vaccinated within the trial will be captured, regardless of the treatment group to which the participants were originally allocated, over the entire follow-up period of 24 months.

7. Pharmacovigilance Activities

The Sponsor submitted a Pharmacovigilance Plan to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease (which includes but is not limited to vaccine-associated enhanced respiratory disease) and anaphylactic reactions (including anaphylaxis) as important potential risks. Use in the pediatric population, use in pregnant and breast-feeding women, immunogenicity in participants with immunosuppression, concomitant administration with non-COVID vaccines, long-term safety and long-term effectiveness are areas the Sponsor identified as missing information.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and proposed to submit periodic safety reports at quarterly intervals, or at another interval specified by FDA. FDA has

requested that periodic reports be submitted monthly. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following three planned surveillance studies.

- Pregnancy Cohort: The Sponsor plans to establish a passive pregnancy registry to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA, and to submit a protocol for FDA review and approval.

- Active Follow-up for Safety: This study is an active safety surveillance activity conducting retrospective analyses of medical and pharmacy claims data to address three objectives; estimation of background rates of 23 prespecified adverse events of special interest (AESI), descriptive analyses of observed versus expected rates, and self-controlled risk interval analyses that will be conducted if certain criteria are met from the descriptive analyses. The planned study duration is through December 2022.

- Real World Effectiveness Study: This study is a prospective cohort study to be conducted at Kaiser Permanente Southern California to evaluate vaccine effectiveness in preventing the following outcomes: laboratory confirmed and clinical COVID-19 infection, hospitalization, and mortality for COVID-19. Vaccinated participants will receive Moderna COVID-19 Vaccine between January 1, 2021 and December 31, 2021, and the comparator group will be age matched, unvaccinated KPSC members. The planned study duration is through December 31, 2023.

FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

Reporting to VAERS and ModernaTX, Inc.

Providers administering the Moderna COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to ModernaTX the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports

medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1 Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 14 days after the second dose of vaccine
- Reduction in the risk of confirmed severe COVID-19 occurring at least 14 days after the second dose of vaccine

The 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 14 days after receipt of the second dose. Secondary efficacy analyses showed consistency with outcomes in the primary efficacy analysis; the vaccine was effective in preventing COVID-19 using a less restrictive definition of the disease and considering all cases starting 14 days after the first injection. Efficacy findings in the interim analysis were also consistent across various subgroups, including racial and ethnic minorities, participants ages 65 years and older, and those at risk for severe COVID-19 disease due to obesity, diabetes, cardiac disease, liver disease, chronic lung disease, mild to severe asthma, and infection with HIV, although the efficacy estimate in participants ages 65 years and older was slightly lower in the primary efficacy analysis.

8.2 Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) are too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

Limited data suggest that individuals with prior SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination. Regarding the benefit of the mRNA-1273 for individuals with prior infection with SARS-CoV2, participants with a known history of SARS-CoV-2 infection were excluded from the Phase 3 study, and there was only one case of COVID-19 among study participants with positive SARS-COV-2 infection status at baseline. Thus, the study was not designed to assess the benefit in individuals with prior SARS-CoV-2 infection.

Effectiveness in pediatric populations

No efficacy data are available from participants ages 17 years and younger.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27, 2020 to November 21, 2020, in sites across the United States. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine in preventing asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[13-16] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3 Known Risks

The vaccine elicited increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were pain at injection site (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). Adverse reactions characterized as reactogenicity were generally mild to moderate; 0.2% to 9.7% of these events were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in older adults (≥65 years of age) as compared to younger participants. Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination. The number of participants reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (258 events in 233 participants [1.5%] vs. 185 events in 166 participants [1.1%]). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

Serious adverse events, while uncommon (1.0% in both treatment groups), represented medical events that occur in the general population at similar frequency as observed in the study. Of the 7 SAEs in the mRNA-1273 group that were considered as related by the investigator, FDA considered 3 as related: intractable nausea and vomiting (n=1), facial swelling (n=2). For the serious adverse events of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction, a possibility of vaccine contribution cannot be excluded. For the event of B-cell lymphoma, an alternative etiology is more likely. An SAE of Bell's palsy occurred in a vaccine recipient, for which a causal relationship to vaccination cannot be concluded at this time.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

8.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 18 years of age, pregnant and lactating individuals, and immunocompromised individuals.

FDA review of a combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in female rats concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of approximately 30,000 participants over the period of follow-up at this time. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Although the safety database revealed an imbalance of cases of Bell's palsy (3 in the vaccine group and 1 in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

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10. Appendix A. Phase 1 and 2 Studies

Study DMID Protocol 20-0003

Study Design
DMID Protocol 20-0003 is an ongoing Phase 1, open-label, first-in-human, dose-ranging study to evaluate the safety and immunogenicity of mRNA-1273 in healthy adults 18 years of age and older. A total of 120 participants without risk factors for progression to severe COVID-19 were enrolled into one of 10 age and dose cohorts to receive 2 injections of 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273 given 28 days apart. The study included 60 participants 18 through 55 years of age, 30 participants 56 through 70 years of age, and 30 participants 71 years and older. Participants will be followed safety and immunogenicity for 12 months after last vaccination.

Study Objectives/Endpoints Relevant to the EUA
The immunogenicity objectives are to evaluate the binding antibody (bAb) concentrations for spike IgG as measured by ELISA and neutralizing antibody (nAb) titers as measured by PsVNA for all dose levels at baseline and at various time points after vaccination. The study also evaluated T-cell responses elicited by the mRNA-1273 vaccine as assessed by an intracellular cytokine stimulation assay. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study, and all results were descriptive.

Study Results

The study showed a dose response in participants across all age groups as measured by both binding and neutralizing antibodies after 2 doses. There was a comparable response between the 100-µg and 250-µg dose groups, and both were greater compared to the 25-µg group. The bAb and nAb levels seen after 2 doses of 100 µg or 250 µg of mRNA-1273 were similar in magnitude compared to those seen in pooled convalescent sera from patients recovered from COVID-19. All dose levels elicited CD4+ T-cell responses that were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. This Th1-dominant profile was clinically reassuring in terms of risk of developing vaccine-induced disease. These results, along with the interim safety data showing a lower incidence of reactogenicity in the 100ug group compared to the 250ug group, led to the selection of the 100ug dose to advance to Phase 2 and 3. Preliminary safety data from this Phase 1 study show a similar profile to that observed in the Phase 3 study. No SAEs or severe COVID-19 cases have been reported from this study as of November 16, 2020.

Study mRNA-1273-P201

Study Design
Study mRNA-1273-P201 is an ongoing phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in healthy adults 18 years and older. The study enrolled 600 participants, consisting of 300 participants 18 to <55 years old and 300 participants 55 years and older, who

were randomized equally to receive either 2 doses of 50ug of mRNA-1273, 100ug of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months post last vaccination.

Study Objectives/Endpoints Relevant to the EUA
The immunogenicity objectives are to evaluate the immunogenicity of 2 doses of mRNA-1273 at the 2 dose levels (50 µg and 100 µg) administered 28 days apart as assessed by level of bAb and by nAb titers at baseline and at various time points after vaccination. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study and all results were descriptive.

Study Results

The immune response as assessed by bAb and nAb after 2 doses were comparable in the 50-µg and 100-µg dose groups, with an overall geometric mean fold rise (GMFR)>20-fold in bAB as measured by ELISA and >50-fold in nAb as measured by microneutralization assay at 28 days post-dose 2. In the 100-µg dose group, the older age cohort (≥55 years) had slightly lower bAb response when compared to the younger age cohort (18 to <55 years) at 28 days post-dose 2, but the nAb response was similar between both age groups

Safety profile was similar to that reported in the Phase 3 study. Laboratory evaluations (including complete blood count, liver function tests, kidney functions tests, and coagulation studies) were conducted for participants ≥55 years of age (N=100) at baseline and at 1 month after the second dose (Day 29, Day 57). According to narratives that the Sponsor provided to FDA on December 6, 2020, there were 2 participants in the 100-µg group who experienced Grade 3 decreases in hemoglobin (Grade 0 reported at baseline), but both Grade 3 values were within normal range and not clinically significant. The overall event rates were not provided.

As of December 6, 2020, there were 3 SAEs reported in the vaccine group: a 65-year-old participant with community acquired pneumonia 25 days after vaccination, a 72-year-old participant with arrhythmia after being struck by lightning 28 days after vaccination, and an 87-year-old participant with worsening of chronic bradycardia 45 days after vaccination. On FDA review of the narratives, none of these SAEs are assessed as related. There were no cases of severe COVID-19 reported in the study.

This is Exhibit " T " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

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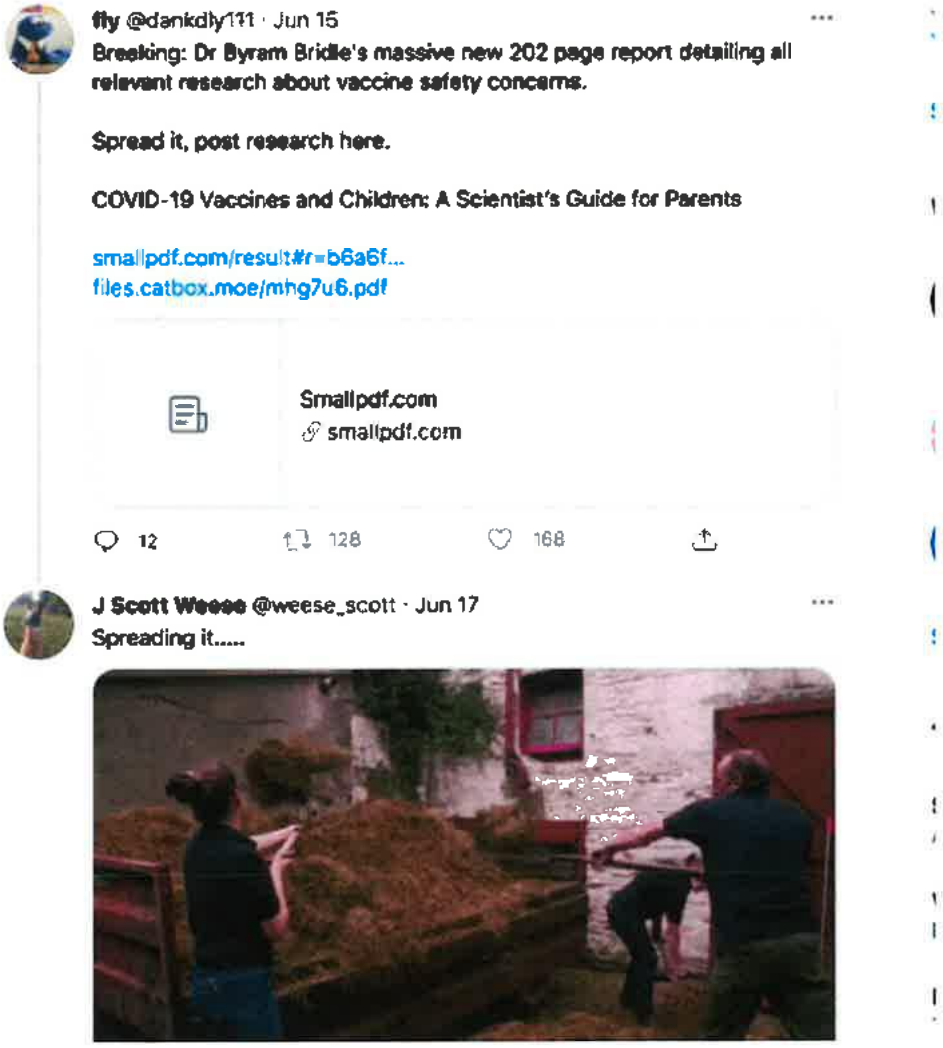

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Breaking: Dr Byram Bridle's massive new 202 page report detailing all relevant research about vaccine safety concerns.

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COVID-19 Vaccines and Children: A Scientist's Guide for Parents

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J Scott Weese @weese_scott · Jun 17

Spreading it.....

This is Exhibit " U " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

RW Malone MD, MS
Consulting and Analytics for Biopharma
434-979-0090
357 Hebron Valley Rd, Madison, VA 22727

www.rwmalonemd.com
Your World is
Our World

June 19, 2021

From: Robert W. Malone, MD, MS
357 Hebron Valley Rd,
Madison, VA 22727

To: Whom it may Concern

I am writing this letter to support Dr. Bridle's good character and his right to freely express his scientific opinion, which is backed up by the literature and well informed deductive reasoning.

I am a US-based physician and scientist with an extensive record of successful innovation in basic and applied science, pathology, molecular virology, immunology, vaccine development, biodefense, project management, clinical development, regulatory affairs, and bioethics. I have been working in this area since 1984, and have been through multiple outbreaks – usually supporting either pharmaceutical clients or the US Department of Defense. I have been granted "secret" clearance for the DoD. I played a key role in advancing the PHAC rVSV-ZEBOV Ebola vaccine candidate and engaging Merck in development, which resulted in the eventual licensure of this very important product of Canadian PHAC research.

I am also the original inventor of mRNA vaccines and DNA vaccines. This claim is substantiated by academic publications as well a large suite of US and worldwide patents with a filing date of 1989.

I have independently assessed most of the data which serves as the basis for Dr. Bridle's communications regarding safety risks associated with the COVID-19 genetic vaccines, concur with his findings, and have independently raised my concerns with the US FDA including speaking directly with CBER director Peter Marks.

I am particularly alarmed and surprised by the bioethical positions being taken by the government of Canada regarding these experimental – stage vaccines, and very surprised. I have always considered the government and people of Canada to be eminently reasonable, almost to a fault. These policies appear contrary to what I have been trained as the bedrock principles of clinical research/human subjects bioethics.

And then there is the censorship of legitimate academic discourse, which brings us back to the specific case of Dr. Bridle. In short, do his accusers have no shame? I am truly shocked. Again, this is contrary to everything I had ever believed about the people and culture of Canada. I guess I will need to re-think my assumptions about Canadian fundamental reasonableness – ey?

Furthermore, these attacks on him will make him a global martyr and amplify his message. Is that really good public policy?

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Please stop. Think about what is going on here. This is not fair. This is not right. This is not proper. Dr. Bridle has examined the data available to him and has drawn reasonable conclusions about the meaning of that data in toto. He is not profiting from this. There are no financial conflicts of interests. He is not someone seeking fame and fortune. He is doing what he can, in good faith, to help protect the people of Canada and the world – and particularly the adolescents and children.

In sum, in regards to COVID-19, I find the general censorship of the government of Canada, the bioethical lapses, and this specific example involving Dr. Bridle to be particularly egregious, and inconsistent with all I had previously believed regarding the fundamental reasonableness and commitment to fairness of Canadian political and social culture.

Please stop politicizing science. The scientific process requires dissent and discussion to arrive at truth. This is a central tenant. Dr. Bridle has spoken truth as he sees it. Others may interpret the data differently. My assessment is very much aligned with that of Dr. Bridle. That does not make it right or wrong. Time will sort this out. But I am quite sure that the attempts to silence Dr. Bridle and damage his career and reputation are fundamentally wrong.

Regardless of your or my individual assessments and opinions, please let science and the scientific process resolve this. These attacks on the credibility of Dr. Bridle and his good faith efforts to provide an alert concerning safety signals associated with these vaccines are highly inappropriate and counterproductive. I suspect that history will not look back on this kindly. Canadians have not always been on the right side of history – witness the indigenous peoples. But in my experience they do try to do the right and proper thing.

So do the right thing here.

Sincerely

Robert W Malone, MD, MS

This is Exhibit " V " to the Affidavit of

Byram Bridle, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

From: J. Scott Weese
To: Glen Pyle
Subject: Re: Byram
Date: Sunday, May 30, 2021 11:23:25 AM

Not surprising, unfortunately. I should ramp up what I'm saying so he can come after me at the same time.

If you need any support...moral, letter writing, sending the same statements...let me know. I'll be more than happy to do it.

Scott

J. Scott Weese DVM DVSc DACVIM FCAHS
Professor, Ontario Veterinary College
Director, Centre for Public Health and Zoonoses
University of Guelph
http://www.wormsandgermsblog.com
Twitter: @Weese_scott

From: Glen Pyle <gpyle@uoguelph.ca>
Date: Sunday, May 30, 2021 at 11:02 AM
To: J. Scott Weese <jsweese@uoguelph.ca>
Subject: RE: Byram

Thanks Scott.

I received an email from him this morning that he will call the police to visit me on Monday, so I guess that is some drama.

Glen.

W. Glen Pyle, PhD
Senior Career Investigator
Improving the Heart & Brain Health for Women in Canada, Heart & Stroke Foundation
Distinguished Professor, Innovation in Teaching
Co-Lead, COVID-19 Resources Canada Science Explained
Professor & Assistant Chair, Department of Biomedical Sciences
Ontario Veterinary College, University of Guelph
Associate Member, IMPART, Dalhousie University
LinkedIn: www.linkedin.com/in/glenpyle
Twitter: @glenpyle
"By a divine paradox, wherever there is one slave there are two. So in the wonderful reciprocities of

being, we can never reach the higher levels until all our fellows ascend with us."
-- Edwin Markham

-------- Original message --------
From: "J. Scott Weese" <jsweese@uoguelph.ca>
Date: 2021-05-30 8:39 AM (GMT-05:00)
To: Glen Pyle <gpyle@uoguelph.ca>
Subject: Byram

Glen

Thanks for the nice synopses of that misinformation. I've been dealing with damage control from the crap that he's been spewing for months, since I get a lot of questions from vets or the general population because I'm active in the area and on the Science Table. It's great to have someone with your immunological expertise critique the comments.

Byram aggressively accused me of threatening him earlier simply by saying generically at a dept meeting something like ("I'd just ask everyone to remember that words matter. People are scared and confused, and we need to think about how we communicate"). Hopefully he doesn't add drama for you, but I'm happy to back you up whenever I can. I've raised the issue before with the University to at least stop amplifying his messages by tweeting his interviews or putting things in the OVC Newsletter (but some things still get out. Academic freedom is different from the University needing to promote someone's views).

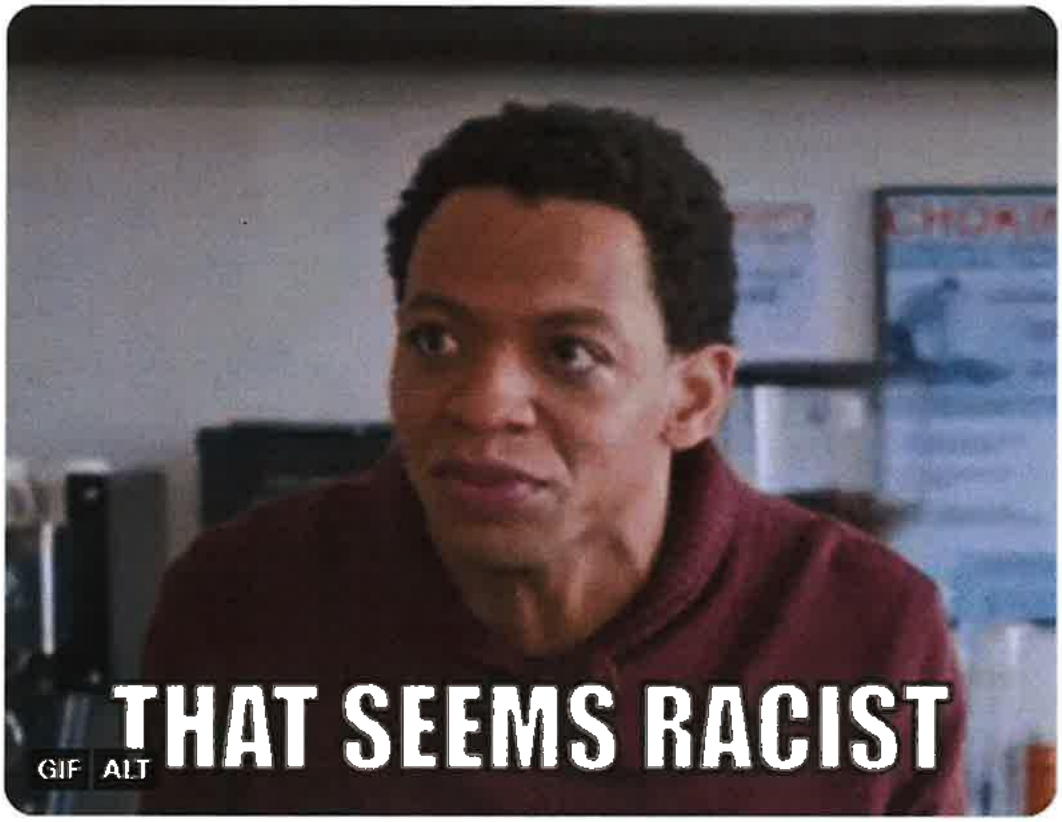
Scott

J. Scott Weese DVM DVSc DACVIM FCAHS
Professor, Ontario Veterinary College
Director, Centre for Public Health and Zoonoses
University of Guelph
http://www.wormsandgermsblog.com
Twitter: @Weese_scott

← **Thread**

Glen Pyle | #GetVaccinated @glenpyle · Apr 30

Scratch an anti-vaxxer, find a racist.



3

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Toronto Superior Court of Justice / Cour supérieure de justice

More name-calling and accusing me of killing people.

J Scott Weese @weese_scott · Aug 6

Yeah...blame the vaccine for variants

Pseudoscientific babble at its best. The problem is, people like this frame it with enough science-talk that their receptive audience eats it up.

These idiots are killing people.

> **Osler** @osler78 · Aug 6
> Dr. Byram Bridle on The Ingraham Angle about new variants

1 3 16

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This statement is likely directed largely at me.

← **J Scott Weese**
1,486 Tweets

Follow

J Scott Weese Retweeted

David Fisman @DFisman · Aug 19
Replying to @imgrund @Moms_a_fan and 2 others
@uofg administration has been absolutely bizarre for months now.

They've coddled spreaders of vaccine misinformation on campus, even as they've created safety issues (not just related to vaccination) for others in the @uofg university community.

6 17 73

J Scott Weese Retweeted

Lamb @TheQuiltLamb · Aug 19
Am I the only one who is more than a little pissed that we are essentially organizing our society around people who refuse to get vaccinated?!

103 444 3.1K

J Scott Weese @weese_scott · Aug 19
Exactly the same here. Abuse and threats from the fans of the misinformation crowd. Horrible management of the pandemic by this institution. Pissing people off because leaders won't lead.

Drained is the generous description.

Fatima Tokhmafshan (she/elle) @DeNovo_Fati · Aug 19
I'm frigging exhausted!
Between tackling #misinformation peddled by antivaxx & anti-science grifters, and trying to convince a world-class institution of higher learning & one of 's top research universities to follow the advice of scientists on #VaccineMandate I'm tuckered out

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← **J Scott Weese**
1,406 Tweets

Follow

J Scott Weese @weese_scott · Aug 21
Yes, many imbeciles have been empowered by interviewing them like this.

Bridle spreading more paranoia and misinformation. Trying to scare athletes. Even suggesting students can sue and make a lot of money. (Who's going to make money from that? Just the lawyers, I assume).

> **ClausR2020** @ClausR2020 · Aug 21
> Dr. Byram Bridle Voices His Concerns Over Vaccine Mandates at Universities And Colleges rumble.com/v1h6gn-dr.-byr... Interviewer Pastor Michael Thiessen: "We've empowered the imbeciles..."

20

J Scott Weese @weese_scott · Aug 21
Dear Universities..

Use your critical assessment skills and ignore the crap. Do what's right. You know what it is.

Don't be intimidated by misinformation and grift. Ignore petitions like this: libertycoalitioncanada.com/open-letter-to... (and the associated false info filled interview with Bridle).

Open Letter to Universities and Colleges
TO: Presidents of Universities and Colleges in Ontario that are mandating COVID vaccines. RE: Demand to cease the use of unlawful ...
libertycoalitioncanada.com

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Pushing for the U of G to silence people like me.

J Scott Weese @weese_scott · Aug 24

People and organizations that are able to counter misinformation but won't are complicit and share blame for the damage that is caused.

With privilege comes responsibility. Ignoring misinformation and hoping it will go away isn't effective or ethical.

@uofg

> **Timothy Caulfield** @CaulfieldTim · Aug 24
> It can get worse? Yep.
>
> "WHO says #Covid #misinformation is a major factor driving pandemic around the world" cnb.cx/3jcloBS by @RichMendezCNBC
>
> @mvankerkhove: "In the last four weeks or so, the amount of misinformation that is out there seems to be getting worse.."
>
> 6 21

J Scott Weese Retweeted

Timothy Caulfield @CaulfieldTim · Aug 24

It can get worse? Yep.

"WHO says #Covid #misinformation is a major factor driving pandemic around the world" cnb.cx/3jcloBS by @RichMendezCNBC

@mvankerkhove: "In the last four weeks or so, the amount of misinformation that is out there seems to be getting worse.."

J Scott Weese Retweeted

Glen Pyle | #GetVaccinated @glenpyle · Aug 25

If I publish fraudulent data from my lab, that is academic misconduct.

If I give interviews spreading misinformation & am criticized by the scientists who did the research, that is academic freedom.

Those are the rules, apparently.

5 32 119

This is in reference to me. The criticizing scientists who did the research are the ones that 'fact-checked' me.

This is in reference to the Canadian COVID Care Alliance, of which I am a member.

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I am the 'anti-vaxxer' being referred to here.

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T. Ryan Gregory
@TRyanGregory

Huh. So an institution *can* take a public stance where a member makes inaccurate claims that are harmful to society. How about that, @glenpyle and @weese_scott?

UofT Dept of Surgery @UofTSurgery · Aug 31
Please see response from the Department of Surgery, University of Toronto @UofTSurgery in regard to a recent editorial by a UofT faculty member

Surgery
UNIVERSITY OF TORONTO

Recently an editorial written by Dr. Lawrence Klotz, a urologist at the University of Toronto, was published in the European Journal of Urology. The editorial has received a lot of attention through social media due to the opinions expressed about gender and surgery, garnished through "reverberacy". We would like to make it clear that the opinions expressed in this editorial do not represent those of the Department of Surgery at the University of Toronto.

Our Department seeks to promote an environment where equity and diversity are core values, where gender, ethnic, and racial diversity shape the culture, academic mission, and policies. We believe that equity and diversity drive high quality patient care, education, and innovation in research. One does not grow at the expense of the other; we can simultaneously raise our standards for both inclusion and clinical productivity. Promoting gender equity, and academic excellence are rather synergistic than mutually exclusive. While we support the right to academic freedom of speech, we do feel it is necessary to establish that these sentiments are in direct contrast to the mission and value system

6:47 PM · Aug 31, 2021 · Twitter for Android

3 Retweets 1 Quote Tweet 9 Likes

Tweet your reply

Reply

@TRyanGregory and @weese_scott
n not just a public statement saying we can agree to disagree. A emen that exp icitly says the views expressed are in direct contrast to lue

I guess it helps to have a mission & values against which to measure things.

10

They are talking about me in this thread. They have been trying very hard to get the U of G to make a public statement that they do not condone my messaging.

J Scott Weese @weese_scott · Aug 31
It's a matter of will (and ethics). That's all there is to it.

Good on UofT Surgery for addressing this. It's easier to ignore it and hope if goes away, but it's not right.

University's need to stop using the easy button.

T. Ryan Gregory @TRyanGregory · Aug 31
Huh. So an institution *can* take a public stance where a member makes inaccurate claims that are harmful to society. How about that, @glenpyle and @weese_scott? twitter.com/UofTSurgery/st...

5

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1,456 Tweets

Follow

J Scott Weese Retweeted

@imgrund @Moms_a_fan and 2 others

@uofg

They've coddled spreaders of vaccine misinformation on campus, even as they've created safety issues (not just related to vaccination) for others in the @uofg university community.

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Drained is the generous description.

> **Fatima Tokhmafshan (she/elle)** @DeNovo_Fati... · Aug 19
> I'm frigging exhausted!
> Between tackling #misinformation peddled by antivaxx & anti-science grifters, and trying to convince a world-class institution of higher learning & one of 🇨🇦's top research universities to follow the advice of scientists on #VaccineMandate I'm tuckered out

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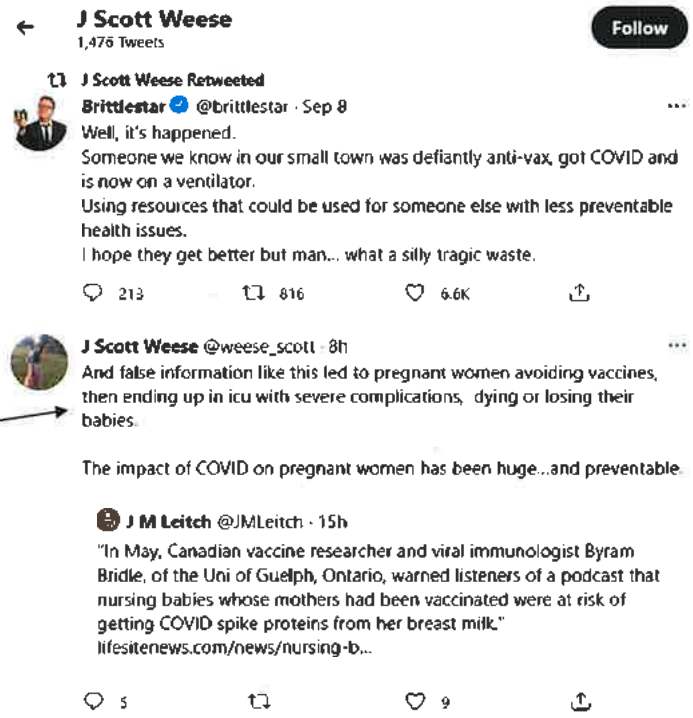
Scott accused me of being the indirect cause of deaths of pregnant women and babies.



J Scott Weese
1,475 Tweets

Follow

J Scott Weese Retweeted

Brittlestar @brittlestar · Sep 8

Well, it's happened.
Someone we know in our small town was defiantly anti-vax, got COVID and is now on a ventilator.
Using resources that could be used for someone else with less preventable health issues.
I hope they get better but man... what a silly tragic waste.

213 816 6.6K

J Scott Weese @weese_scott · 8h

And false information like this led to pregnant women avoiding vaccines, then ending up in icu with severe complications, dying or losing their babies.

The impact of COVID on pregnant women has been huge...and preventable.

J M Leitch @JMLeitch · 15h

"In May, Canadian vaccine researcher and viral immunologist Byram Bridle, of the Uni of Guelph, Ontario, warned listeners of a podcast that nursing babies whose mothers had been vaccinated were at risk of getting COVID spike proteins from her breast milk."
lifesitenews.com/news/nursing-b...

5 9

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Dr. Scott Weese has ignored the official police warning to cease and desist in his ongoing public harassment of me. This also follows prior receipt of a letter from lawyer Rocco Galati that also requested that he cease and desist.

First, Dr. Weese Retweeted an old Tweet from Dr. Fisman to tell the public to link 'antivaxxers' to neo-Nazi white supremacists; he routinely tells the public that I am an 'antivaxxer' (despite the fact that I am a vaccinologist who has continued to publish pro-vaccine papers throughout the declared pandemic). Then he sent a public message that I am continuing to promote various conspiracies yet failed to provide any evidence against what I talked about. Note that he suggested that others could do the fact checking; he wasn't willing to any fact checking himself. There was no question that he aimed this libelous message that lacked any scientific backing at me since the link goes directly to my picture and name. He does this all the time; the essence of his messages are 'Dr. Bridle is lying and/or does not know what he is talking about; believe this because I [Dr. Weese] said so'. He constantly picks on my oral off-the-cuff messaging to lay audiences where I cannot show my references. Never does he tackle my written documentation that is packed with scientific data and references. I submitted an affidavit about COVID-19 issues this past week; it was 593 pages long and contained original data and 387 references. I do know what I am talking about and can back it up with a profound quantity of scientific data. Remarkably, Dr. Weese's messaging is in text and on-line where he has every opportunity to show people peer-reviewed scientific studies to back-up his messages. I have never publicly released Dr. Weese's name. I focus on debating the science and leave the people behind the science out of the discussions. This is how academic conduct is to be practiced. Of additional concern, Dr. Weese then posted a Tweet that confirms his knowledge of potential action against him. This series of Tweets demonstrate that he is challenging the warnings issued against him. There has been no change is his harassing behaviour. As this continues to progress, I am becoming increasingly more concerned about my safety. Dr. Weese is clearly trying to make a public link between me, lies, and white supremist neo-Nazis. This has the potential to incite public violence against me. I have talk about COVID-19 issues yesterday to an audience of ~800 people. It was at this event that the series of Tweets shown here were brought to my attention. Members of the public and fellow scientists are expressing a lot of concern about my safety as Dr. Weese's behaviours continue to go unchecked. If needed, I can call upon a huge number of members of the public and fellow scientists to testify to this fact in a court of law. I will not feel safe unless Dr. Weese's harassment of me is stopped. To be clear, it is my opinion that Dr. Weese should feel free to discuss science; but he needs to start showing the evidence himself. He is free to attack science with science; but needs to stop attacking the people who are serving as messengers of scientific evidence.

← **J Scott Weese**
2,013 Tweets

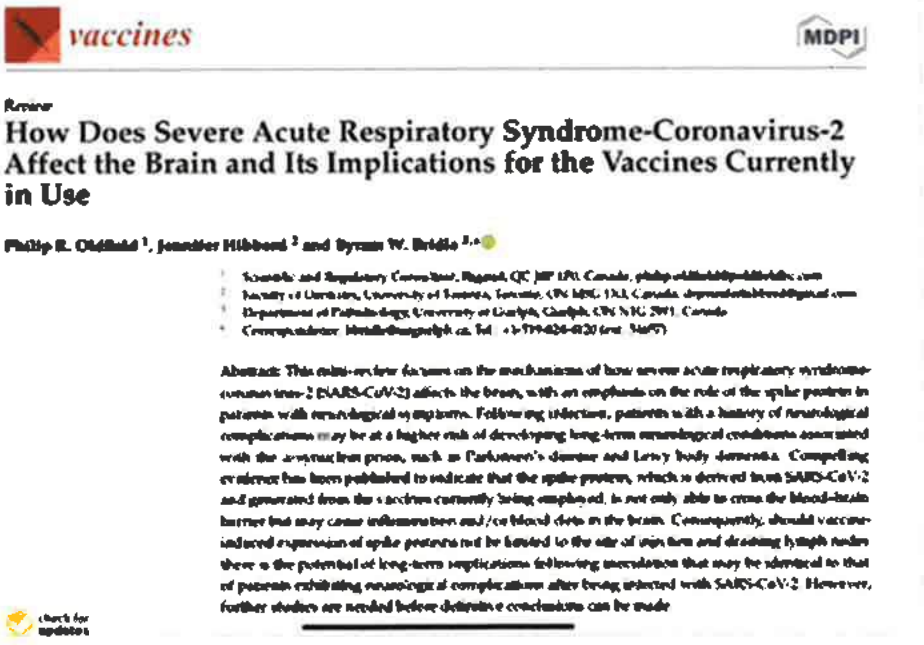
Follow

2 4

J Scott Weese @weese_scott · Dec 23, 2021
"Until such definitive studies are carried out and results substantiated, it lends consideration for caution when deciding whether to administer the COVID-19 vaccines to the younger age groups."

I know MDPI journals are crap but do they even review?

> **Angelus Iustitiae** @Alustitiae · Dec 23, 2021
> 📍 Important new scientific paper highlighting the potential for the spike protein produced in our bodies by the covid vaxxines to cause prion disease.
>
> mdpi-res.com/d_attachment/v...



vaccines MDPI

Review

How Does Severe Acute Respiratory Syndrome-Coronavirus-2 Affect the Brain and Its Implications for the Vaccines Currently in Use

Philip R. Oldfield [1], Jennifer Hibbert [2] and Byram W. Bridle [3,*]

3 1 10

J Scott Weese @weese_scott · Dec 23, 2021
Or does MDPI have a special submission process for anti-vaxxers with no expertise (neuro disease, public health...) in the topic of the paper?

1 8

This is Exhibit " W " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

ROCCO GALATI LAW FIRM
PROFESSIONAL CORPORATION
1062 College Street, Lower Level
Toronto, Canada M6H 1A9

Direct Line (416) 530-9684 Fax (416) 530-8129

September 30th, 2021

RE: Tortious and Criminal Harassment of My Client

TO: Scott J. Weese <jsweese@uoguelph.ca>

CC: Dean Wichtel <jwichtel@uoguelph.ca>

Dear Mr. Weese,

I represent Professor Bryam Bridle. It's come to my attention that at least since May 29th, 2021, when my client first became aware, up to the present, you have and continue to post derogatory and hateful messages with respect to my client on social media and elsewhere, which constitute not only defamation and online harassment but moreover, criminal conduct.

My client, by two separate emails, on May 31st, 2021, notified you that your remarks were disparaging, harmful and constituted harassment. He emphatically requested that the "harassment in the workplace needs to stop." You failed to do so. On the contrary, since then your harassment of my client has escalated in tone, tenor, and frequency.

Ironically, since your frivolous, vexatious defamatory allegations against my client, made to Dean Wichtel in your complaint, dated July 21st, 2021, you have posted nearly **daily** provocative and harassing comments undercutting and undermining your own allegations. My client has not had **any** in-person encounters with you in more than one year. Yet, you continually and repeatedly make false provocatory and abusive comments about my client inciting harassment and hate against him.

The University has been placed on notice, as of September 7th, 2021 (but even prior to that on June 2nd, 2021), by my client that your harassment of him must cease immediately. It has not. Therefore, this serves as your final notice to immediately cease and desist any direct or indirect reference to my client, in any form or forum, whatsoever.

This also serves as notice that my client will be initiating proceeding, both civil **and criminal** against your past and most recent and ongoing harassment unless you issue a public and clean apology forthwith.

.../ 2

Yours very truly,
ROCCO GALATI LAW FIRM PROFESSIONAL CORPORATION
Per:

Rocco Galati, B.A., LL.B, LL.M.
RG*sc

Subject: Letter
Date: Thu, September 30, 2021 1:58 pm
To: jsweese@uoguelph.ca
Cc: jwichtel@uoguelph.ca,rocco@idirect.com,amina@constitutionalrightscentre.ca

Dear Mr. Weese,

I represent Professor Bryam Bridle, please find attached, a two-page letter that is self-explanatory.

Rocco Galati

ROCCO GALATI LAW FIRM
PROFESSIONAL CORPORATION
Rocco Galati, B.A., LL.B., LL.M.
1062 College Street, Lower Level
Toronto ON M6H 1A9

TEL: 416-530-9684
FAX: 416-530-8129

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"Oh why, oh why, does the wind never blow backwards?"---Woody Guthrie

Attachments:

letter- scott weese.pdf	
Size:	82 k
Type:	application/pdf

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Meeting Request

Jeffrey Wichtel <jwichtel@uoguelph.ca>
Sun 6/20/2021 2:44 PM

To: Byram Bridle <bbridle@uoguelph.ca>
Cc: Laurie Arnott <l.arnott@exec.uoguelph.ca>

Dear Byram,

I am in receipt of the workplace harassment complaint you submitted.

I have had an opportunity to review the complaint and the attached evidence submitted in support of it. As I understand it, the complaint involves comments attributed to the Drs. Scott Weese and Glen Pyle, faculty members at the University, that occurred on a third-party social media platform (Twitter). There is also reference to a website with your name as the domain name, the creator of which is unknown but is not alleged to be one of the Respondents, though you indicate that Dr. Pyle knows its creator.

I have also had an opportunity to consult with Faculty and Academic Staff Relations regarding the workplace harassment process and its definition, I have also had an opportunity to consult with Faculty and Academic Staff Relations regarding the workplace harassment process, its definition and the behaviour that constitutes harassment thereunder.

Can we schedule a meeting to discuss your complaint? I'm available between 2 and 4pm tomorrow (Monday) – so feel free to get back to me and choose a 30-minute timeslot between 2 and 4. Laurie Arnott will join me on the meeting. If that time does not work, please get back to me and we will find another. If it works, I'll send a Teams invitation for the elected time.

You mention impact on your mental and physical health as a result of the issue you bring forward in your complaint. We've spoken about EAP, but I want to remind you about this service as it can be very helpful. At our meeting we can also discuss the challenges that you indicate you are experiencing completing work.

Sincerely,

Jeff

Jeffrey J. Wichtel | Professor and Dean
Ontario Veterinary College | University of Guelph
OVC Main Building | 50 Stone Road East | Guelph, ON | N1G 2W1
jwichtel@uoguelph.ca
Website, Facebook, Twitter, and Instagram ***@OntVetCollege***

Y

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

Bird, Jeff

From: Larry O'Connell <larryo@uoguelph.ca>
Sent: Wednesday, November 17, 2021 11:18 AM
To: Bird, Jeff
Subject: Fwd: Point of contact at U of G

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Hey Jeff

Please read below.If you have any concerns or questions about the Bridle incident the University of Guelph contact is Laurie Arnott. Thanks Larry

Get Outlook for iOS

From: Garry Male <maleg@uoguelph.ca>
Sent: Wednesday, November 17, 2021 11:14 AM
To: Larry O'Connell
Subject: Point of contact at U of G

Hi Larry,

I spoke with Mary Murphy today about the email from Detective Jeff Bird and her directive was that he should be referred directly to Laurie Arnott, VP of Faculty Staff relations from this point on as Laurie has been dealing with this situation from the start. Laurie's email is as follows: l.arnott@exec.uoguelph.ca

G

Garry Male
Operations Manager
Campus Safety Office
University of Guelph
50 Stone Rd E, Guelph, ON, N1G 2W1
519-824-4120, Ext. 56482
maleg@uoguelph.ca
www.uoguelph.ca

UNIVERSITY of GUELPH

IMPROVE LIFE.

Sent: Tuesday, November 16, 2021
To: Garry Male <maleg@uoguelph.ca>; David Lee <dlee@uoguelph.ca>; David Pringle <dpringle@uoguelph.ca>; Bird, Jeff <Jeff.Bird@peelpolice.ca>
Subject: Re: Harassment

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No to Peel police. It appears HR is not interested in doing anything for him so he retained a lawyer. He is wondering how a university employee is able to
Post freely breaching university policies.

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From: Garry Male <maleg@uoguelph.ca>
Sent: Tuesday, November 16, 2021 2:28:55 PM
To: Larry O'Connell <larryo@uoguelph.ca>; David Lee <dlee@uoguelph.ca>; David Pringle <dpringle@uoguelph.ca>; Bird, Jeff <Jeff.Bird@peelpolice.ca>
Subject: RE: Harassment

Larry,

Did Professor Bridle forwarded this to HR?

From: Larry O'Connell <larryo@uoguelph.ca>
Sent: Tuesday, November 16, 2021 2:22 PM
To: Garry Male <maleg@uoguelph.ca>; David Lee <dlee@uoguelph.ca>; David Pringle <dpringle@uoguelph.ca>; Bird, Jeff <Jeff.Bird@peelpolice.ca>
Subject: Fwd: Harassment

As you can see Scott Weese an employee of the university continues to tweet about bridle. It appears the university of Guelph is not interested in doing anything to stop his behaviour. Can you please pass this on to Human resources who will be receiving some attention in the near future. Scott Weese who uses social media and identifies himself as a university employee needs to read the definition of criminal harassment and save himself and the university sone embarrassment. To refer to
Bridle as anti vaxxer and white supremacy is crossing the line. Again Weese has never responded to my email about a safety plan. Larry

Get Outlook for iOS

From: Bird, Jeff <Jeff.Bird@peelpolice.ca>
Sent: Tuesday, November 16, 2021 1:56:34 PM
To: Larry O'Connell <larryo@uoguelph.ca>
Subject: FW: Harassment

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See attached

From: Dr. Byram Bridle <viralimmunologist@protonmail.com>
Sent: Sunday, November 14, 2021 12:28 PM
To: Bird, Jeff <Jeff.Bird@peelpolice.ca>
Subject: Harassment

CAUTION: This email originated from outside the organization. Do not click on links or open attachments you do not trust.

Dear Cst. Bird,

I gave a talk about COVID-19-related matters to ~800 people at an in-person event yesterday. At that event, it was revealed to me that Dr. Scott Weese is continuing his harassment of me in an uninterrupted fashion, despite the repeated warnings (both from Rocco and the police). Members of the public are perceiving his harassment as escalating. In this case, they felt that he had designed his recent thread of Tweets to intentionally start trying to link me to white supremist neo-Nazi's. Having reviewed the Tweets myself, I tend to agree. Based on both public feedback and my own assessments, I am growing progressively more fearful about the potential for Scott's ongoing and uninterrupted public harassment of me to incite some kind of retribution against me. The specific nature of this current complaint is in the attached Powerpoint file. Can you please help put an end to this?

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)

University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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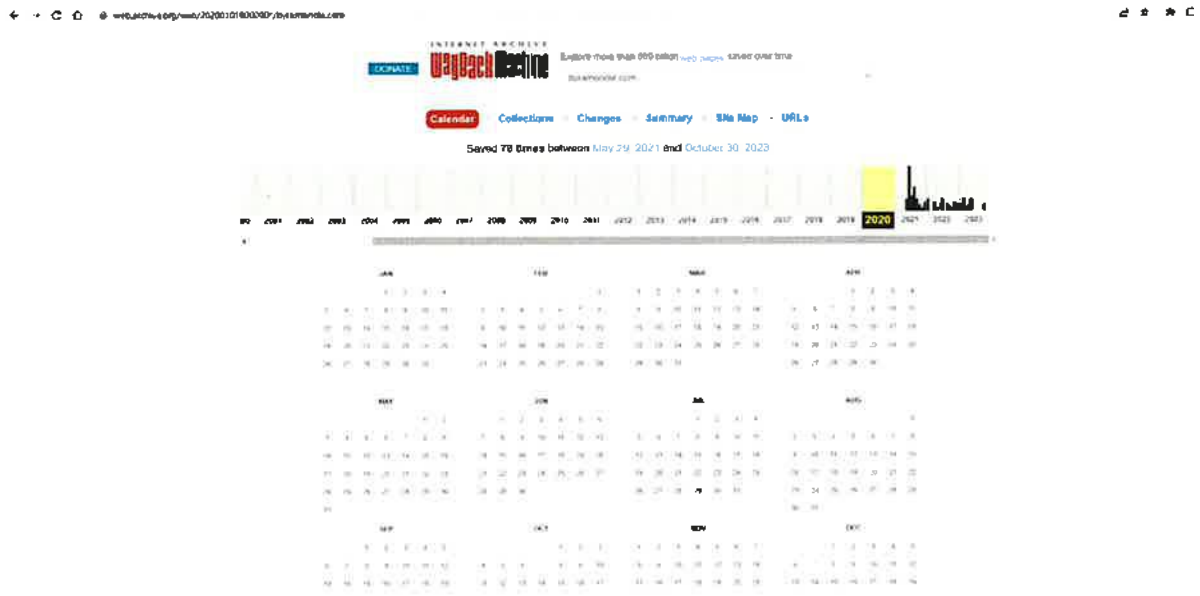
Peel Regional Police

2

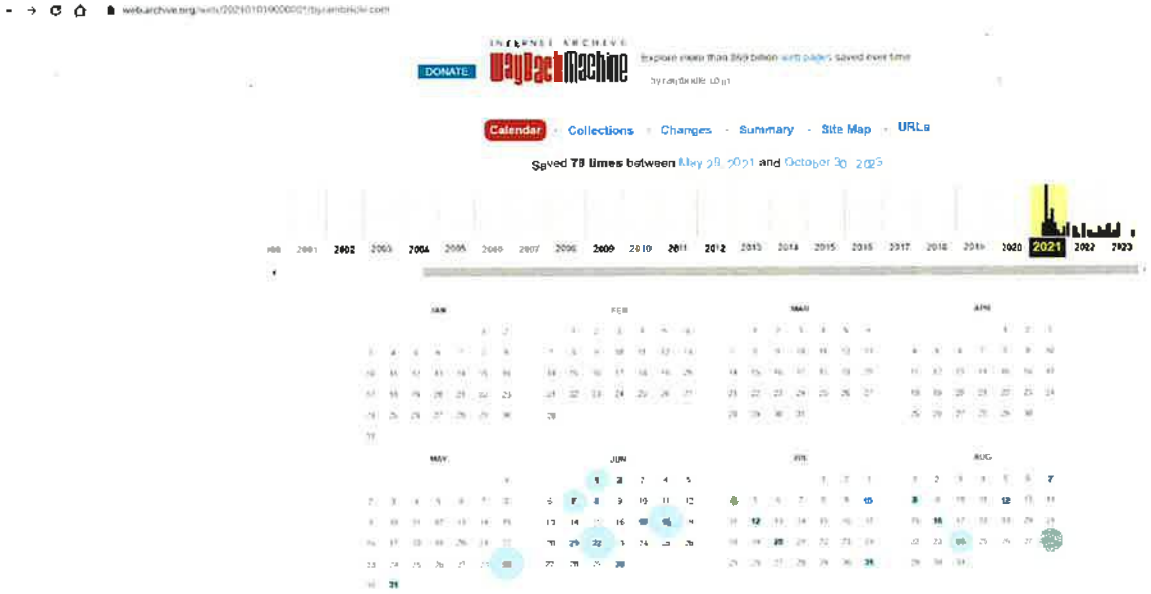
A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

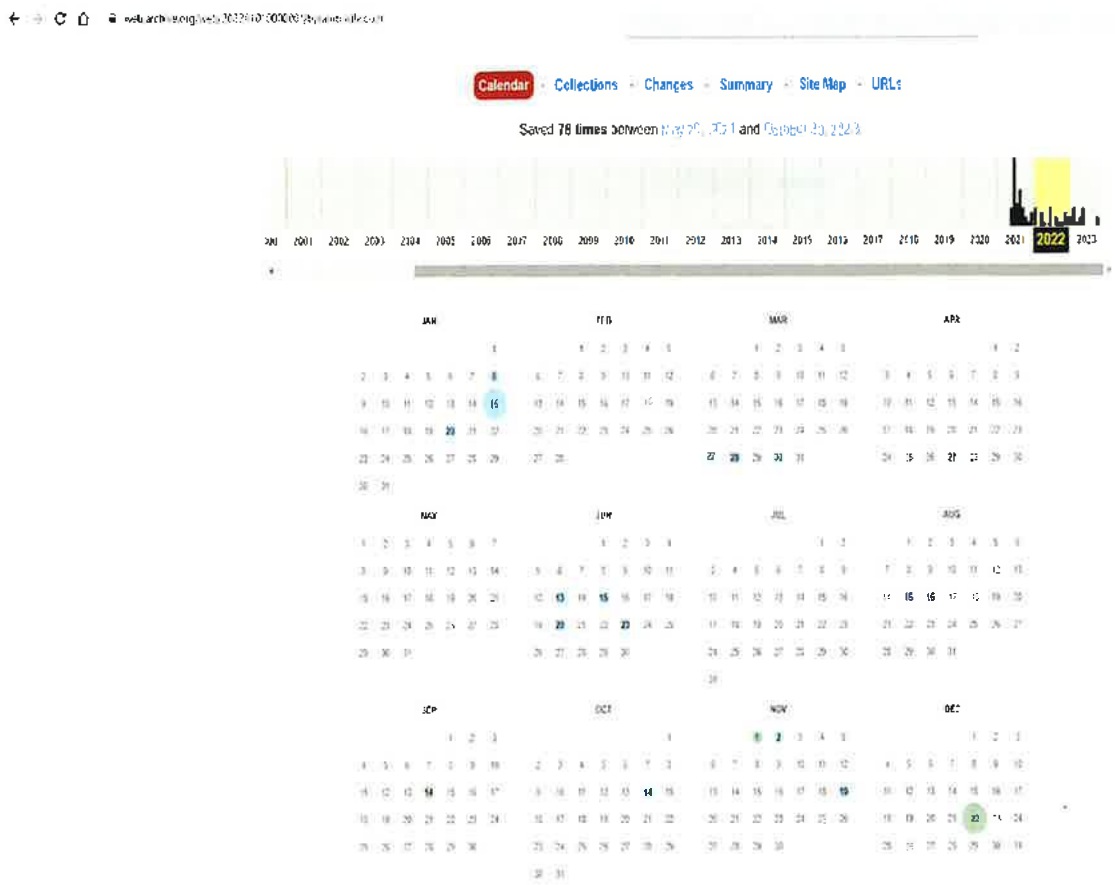
Search for Byrambridle.com shows no hit in 2020



Blue mark indicates website formation on May 29th 2021



Search indicates multiple hits and editations for 2022 (blue/green marker)



Don't Leave Your Dating Life To Chance

It's A Good Idea To Make Plans

Say No When It Doesn't Feel Right

Pay For At Least Part Of The Date

In Conclusion

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What is a Tantric Escort?

The Importance Of Planning In Your Dating Journey

In the fast-paced world of dating, where apps and online connections have become the norm, it's easy to get caught up in the excitement of meeting new people and overlook the importance of planning your dating journey. However, approaching your dating journey with a sense of purpose and preparation can greatly enhance the experience, providing direction and clarity. It helps you set realistic expectations, manage your time effectively, and increase the likelihood of finding a meaningful connection. In this article, we will explore why planning is a crucial element in navigating the complex world of dating and how it can help you make the most out of your dating journey.

Understanding Your Dating Goals

Before you start swiping right or left, it's important to take some time to reflect on what you're looking for in a partner and what you want to achieve through dating. Are you looking for a long-term relationship, casual dating, or simply to have fun and meet new people? Understanding your dating goals will help you narrow down your options and focus on individuals who align with your objectives. It will also help you communicate your intentions clearly to potential partners, avoiding misunderstandings and wasted time.

Quality Over Quantity

In the age of online dating, it's easy to fall into the trap of mindlessly swiping through countless profiles in search of the perfect match. However, this approach often leads to superficial connections and burnout. Instead of aiming for quantity, focus on quality. Take the time to carefully review profiles, read between the lines, and look for genuine compatibility. By investing more time and effort into each potential connection, you increase the chances of finding someone who truly aligns with your values and interests.

Time Management

Dating can be a time-consuming endeavor, especially if you're actively engaging with multiple matches and attending numerous dates. Without proper planning, it can easily become overwhelming and interfere with other aspects of your life, such as work, hobbies, and spending time with friends and family. By setting aside dedicated time for dating activities and establishing boundaries, you can maintain a healthy balance and prevent dating from taking over your entire schedule.

Preparation and Research

Before going on a date, it's essential to do some preparation and research. This can help you feel more confident and knowledgeable during the interaction. Take the time to learn about your date's interests, hobbies, and recent activities. This information can serve as conversation starters and help you find common ground. Additionally, researching potential date ideas in advance can ensure that you have a memorable and enjoyable experience.

Planning can turn a simple meeting into a memorable experience. Choosing activities that interest both parties, such as attending a cooking class, hiking, or visiting an art exhibit, can lead to richer interactions. Shared experiences often foster a deeper connection than traditional dinner dates and can be a refreshing change from the norm.

Safety Considerations

Safety is paramount in the dating world. Planning ahead allows you to take necessary precautions, such as meeting in public places, informing a friend about your whereabouts, and setting boundaries. A considered approach to [illegible] ensures a safer experience, allowing you to relax and enjoy the date.

Budgeting for Dating

[illegible] Planning your dating budget in advance helps you avoid overspending and ensures that you can enjoy dates without financial stress. Whether you're treating yourself to a fancy dinner or opting for a budget-friendly activity, setting aside a portion of your income for dating purposes demonstrates responsibility and respect for your financial well-being.

Emotional Preparedness

Dating can be an emotional rollercoaster, and it's important to be prepared for the highs and lows. Planning ahead helps you manage your expectations, reduce anxiety, and approach each date with a clear mind. It allows you to focus on building genuine connections rather than getting caught up in the pressure of the moment.

Long-Term Perspective

[illegible] Planning your dating journey with a long-term perspective in mind can help you avoid impulsive decisions and stay true to your values. Planning allows you to identify your relationship goals and make choices that align with those goals, increasing the likelihood of finding a fulfilling and lasting partnership.

Reflecting and Adjusting

A planned dating journey includes reflection and adjustment. After each date or interaction, take time to consider what went well and what didn't. This evaluation allows you to refine your approach, learn from mistakes, and [illegible] your goals and values.

In Conclusion

[illegible] Planning your dating journey can [illegible] to [illegible] a partner who complements and enhances your life. Planning [illegible] about setting the stage for success. We're successful dates are not [illegible] but by enjoying the journey, learning as we go, and making [illegible] connections that could lead to lasting [illegible]

Search

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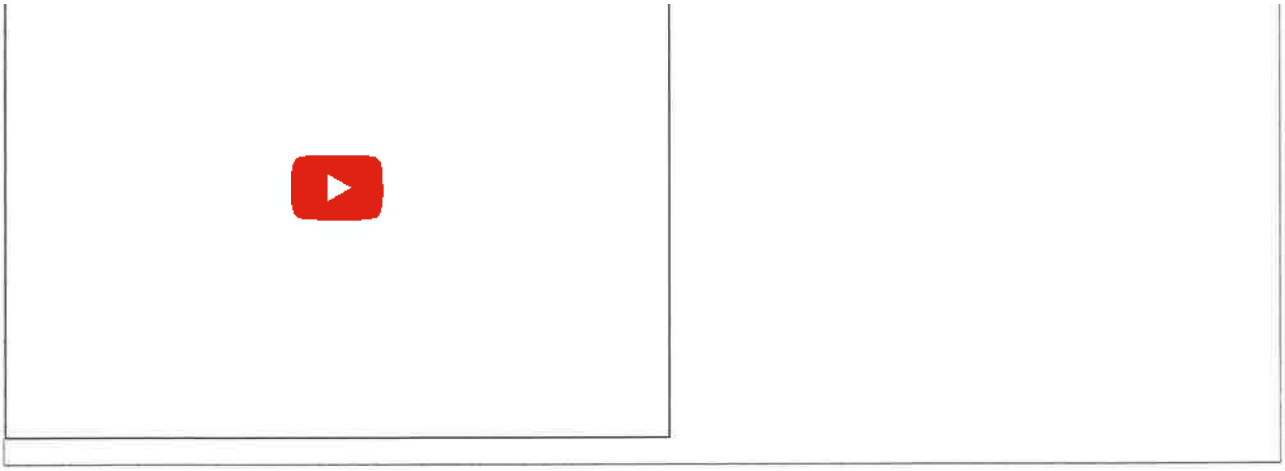
[illegible]

[illegible]



Putting Your Foot Down In Dating

establish boundaries in dating

1. Boundaries as Foundations

2. The Dangers of Over-Accommodation

3. Communication is Key

4. Non-Negotiables

Putting your foot down can [illegible] behaviors, or values misalignment. Addressing these elements by reinforcing your boundaries can prevent deeper entanglement in potentially [illegible]

6. The Role of Self-Respect

The ability to put your foot down is deeply tied to self-respect. It requires recognizing your worth and understanding that you deserve a relationship that brings happiness and fulfillment, not discomfort or pain. It's about honoring your needs as much as you respect the needs of others.

7. The Empowerment of Choice

[illegible]

8. Avoiding the Pitfalls of People-Pleasing

People-pleasing behaviors often stem from a fear of losing agency and attachment. But by setting boundaries, you're not pushing people away; you're [illegible]

9. The Art of Saying No

Learning [illegible] is a powerful act of setting boundaries. It's not about being [illegible] respecting your own limits and ensuring that your relationships are [illegible]

10. Resilience in the Face of Pushback

When you put your foot down, you might face pushback or attempts to negotiate your boundaries. Resilience in maintaining your stance, even when pressured, is crucial. It sends a clear message that your boundaries are not a matter of convenience but [illegible]

11. Respect for Mutual Boundaries

Just as you assert your boundaries, it's important to respect those of the person you're dating. This mutual respect [illegible] creates a healthy environment where both partners can feel safe and heard.

12. The Path to a Healthier Relationship

[illegible]

Conclusion

Putting your foot down in dating [illegible] complexities of human connection. [illegible] walking away from a situation [illegible] not just enduring, but also enriching.

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[illegible]

[illegible]

WordPress.org

What is a Tantric Escort?

This is Exhibit " AA " to the Affidavit of
Byram Bridle, sworn before me on
this 15th day of December 2023

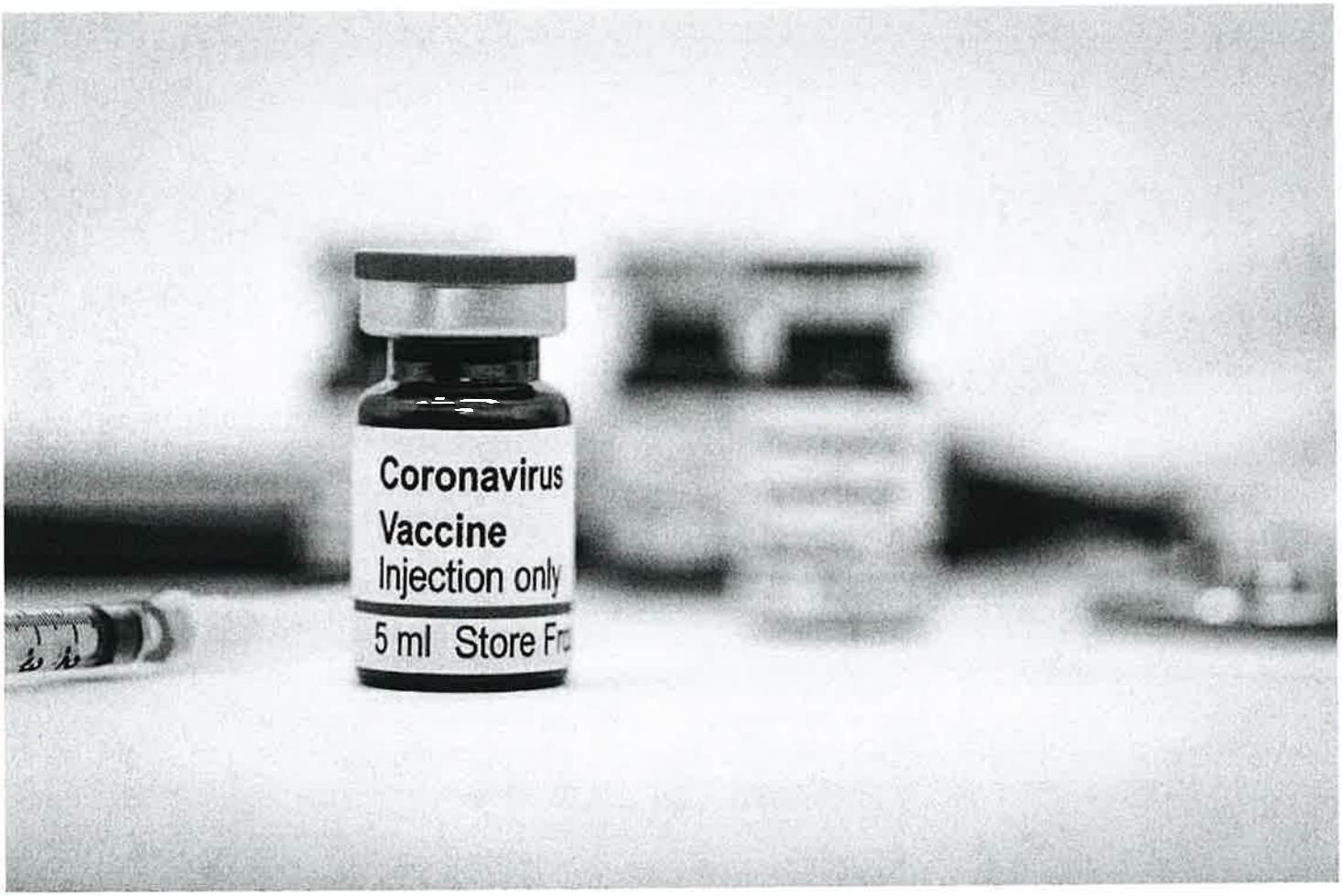
A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

GUELPHTODAY.com

Lack of reviews of COVID vaccine raises concern with U of G expert

Anam Khan
Dec 15, 2020 7:00 AM



Stock photo

While the vaccine has arrived, some experts still have concerns.

The lack of scientific peer review raises some concerns, says Byram Bridle, a viral immunologist at the University of Guelph currently doing research to help prepare a vaccine for the next highly pathogenic coronavirus.

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immunology and I teach all of my students that good quality vaccines that have been vetted by the scientific community are, in my opinion, the best tool that we have in our medical toolbox and the most efficient ways to save a huge number of lives and a great form of preventative medicine," said Bridle.

The problem, he says, is we just don't know the long-term effects of this vaccine regardless of the new technology used.

"These vaccines have only been in people at most for half a year. And that's probably a bit liberal," says Bridle.

"That means that we can really only have absolute confidence in the safety of the vaccine up to about six months."

He says even when a vaccine takes years to develop, safety is still monitored when it goes out to the general public. But in this case, companies will be monitoring the results for at least the next two years once everyone gets vaccinated in order to collect safety data.

"This has never happened before. To collect that long term data. To know whether it continues to be safe a year after vaccination, two years after vaccination. We always had that data previously. We don't have it now and we will only get it as we monitor the rollout," says Bridle.

Bridle says many companies were developing a vaccine for MERS and were able to quickly switch over when COVID-19 came along.

Although these were made at a record-shattering pace, it's not quite the same as historical vaccines that had to start from scratch, says Bridle giving the example of the Ebola vaccine, which had several years of accumulated safety data before it was distributed to the public.

He says although the vaccines have met the milestones required for them to be approved by governing healthcare bodies, they are being rolled out without the phase 3 clinical trials being 100 per cent completed.

"I'm not judging the vaccines in any way, shape, or form. I'm just trying to state the facts," says Bridle.

"I have been asked many times personally would I take the vaccine right now? Personally, I don't feel 100 percent comfortable with it," says Bridle, adding that historically there have been side effects from vaccines despite taking some time to manifest.

"If there are any chronic issues with this, we're not going to be aware."

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it needs to be approved by Health Canada, and second, the results from the phase 3 clinical trials need to be available – which really tells how the vaccine is working and what the safety profile looks like.

"I want to see that (phase 3 clinical trials) published and to go through rigorous scientific peer review."

On Dec. 9 Health Canada approved the Pfizer vaccine and stated that along with the Public Health Agency of Canada, it will closely monitor the safety vaccine once it hits the market, and also take necessary steps if there are safety concerns.

It also published documents about the vaccine ingredients, allergies, and possible side effects.

Regardless, Bridle gives the analogy of two toys priced the same but from different companies sitting on a shelf. One has a high-quality control system in place while the other has little to no quality control.

"When it comes to science, our quality control is the peer review process," says Bridle.

He says to publish the data, first of all, it has to go through the hands of reviewers to ensure the science is good and when it gets published, the entire scientific community has access to that data including scientists around the world who have no connection to that research and who have nothing to gain from that vaccine being marketed.

"Right now the phase 3 clinical trials have only been seen by the regulatory agencies. I trust they're doing their job. I also imagine that they're probably under the most enormous pressures that they've ever been in their careers in terms of trying to get a vaccine developed as soon as possible," says Bridle.

Nevertheless, he says decisions are being made by a relatively limited number of scientists.

"Yes, they have lots of expertise in the area but again, that's what I want to see personally and that's how it's happened in the past," says Bridle.

Bridle also talks about potential rare side effects which are normally not a big concern, however, because the goal is to roll the vaccine out on a global scale, Bridle says even very rare side effects could end up affecting a large number of people.

He gives the example of the two individuals who suffered an anaphylactic reaction in the UK the very first day the Pfizer vaccine rolled out.

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that once the vaccine is administered across the globe, it's possible hundreds of thousands of people have an anaphylactic reaction or something else.

After those allergic reactions, those with allergies were immediately told not to receive the vaccine.

"And then you can start asking the question, how many people with these allergies were enrolled in these trials? Well, because the data is not published, we don't know this," says Bridle adding that the vaccine is to only be administered in centers that have the equipment and expertise available to resuscitate people.

"The fact of the matter is, not everybody with a pre-existing condition could be tested in the phase 3 trials. Scientists have not been able to evaluate it and we've just simply had a very limited number of months in which this vaccine could be assessed and that only by those looking at the clinical trials."

"I personally cannot assure anybody 100 per cent that there are going to be no issues."

Comments (23)

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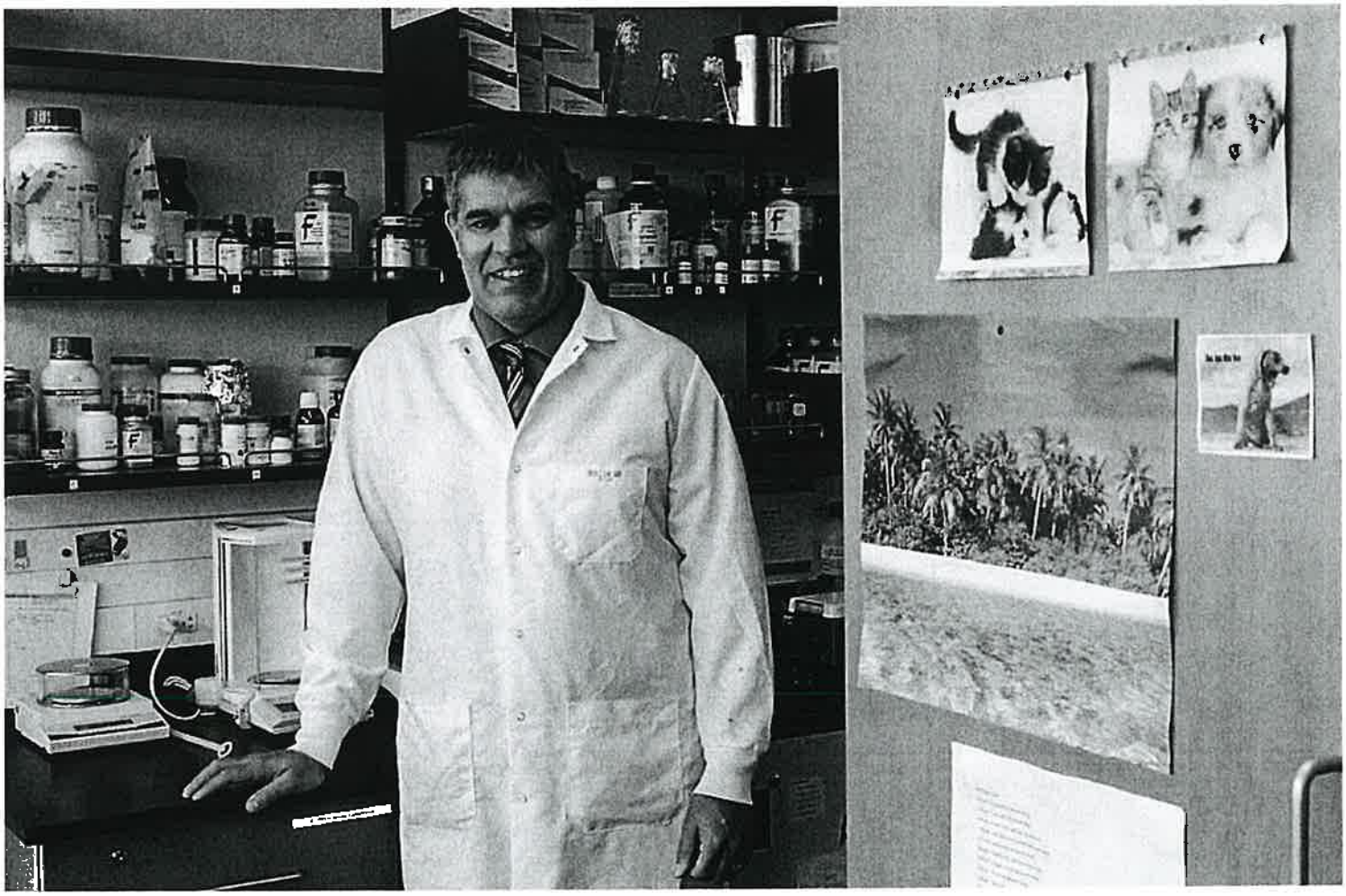
GUELPHTODAY.com

Controversial U of G prof criticizes school's vaccine mandate

Daniel Caudle
Sep 27, 2021 7:00 AM



Byram Bridle, professor in U of G's Department of Pathobiology. Kenneth Armstrong/GuelphToday | Kenneth Armstrong/GuelphToday file photo

Listen to this article
00:03:00

Controversial University of Guelph associate professor Byram Bridle has penned an open letter to U of G president Charlotte Yates calling for an end to the vaccine mandate.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

requested the 'favour of a reply' from Yates, asking that the response not be deferred to public health officials or a committee.

"Instead, a reply with the scientific rigour expected from a scholarly colleague rebutting each of my comments and addressing each question. Surely, you know the science underpinning COVID-19 vaccines inside and out by now," Bridle's letter stated.

U of G spokesperson Deirdre Healey confirmed the letter from Bridle, which was also published online, was received by Yates, and an appropriate response would be issued in a timely manner.

Bridle's letter states he could not be in stronger disagreement with Yates for forcing the current COVID-19 vaccines upon everyone who is part of the campus community.

He outlines those with naturally-acquired immunity don't need to be vaccinated and are at greater risk of harm if vaccinated and how testing for naturally-acquired immunity was a viable option but ignored.

The U of G was reporting recently that of those who submitted information, 99 per cent are partially or fully vaccinated and one per cent have requested or been granted an exemption.

The university said of the nearly 20,000 students who have provided information, 94 per cent are fully vaccinated and five per cent are partially vaccinated.

As well, 97 per cent of the faculty and staff who provided information are fully vaccinated and two per cent are partially vaccinated.

Bridle said in his letter: "My concern is not primarily for myself. I am using my case to highlight how wrong your vaccine mandate is.

"I am more concerned for the more vulnerable on our campus. I hold tenure, and if ever there was a time when this was important, it is now."

Bridle has spoken publicly about his concerns with the vaccine, which he says has caused harassment at the workplace.

Going against the university's mandate which requires all faculty to have both doses of a COVID-19 vaccine or a medical exemption, Bridle said he has been "banned" from campus for at least the next year.

"I can show proof of immunity against SARS-CoV-2 but you will not allow me to enter buildings. But someone else can show a receipt saying that someone saw two needles go into their arm and you

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The letter reads: "I have found it necessary to write this so you can fully understand my perspective. With my life and that of my family, many friends and treasured colleagues being destroyed under your watch, I figure the least you can do is read and consider this very carefully. It is incredible to note that many, if not most, of my on-campus detractors have judged me without reading any of my scientific arguments or talking to me about them."

Attempts to reach Bridle for comment were unsuccessful.

Comments (13)

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GUELPHTODAY.com

Controversial U of G prof called as vaccine 'expert' in family court fight

GuelphToday Staff
Nov 11, 2022 8:00 AM

Byram Bridle, associate professor in U of G's Department of Pathobiology. | Kenneth Armstrong/GuelphToday file photo

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00:03:26

A Toronto mother chose a controversial University of Guelph professor as her expert witness in a battle with the father over who should should have the final say in their son's vaccinations.

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peak of the pandemic and has been criticized by much of the scientific and medical community, was called as an expert by a mother fighting with the father of their 11-year-old son over who would control if and what vaccines the boy would receive.

The father wanted the boy to receive standard vaccinations and the COVID vaccine. The mother did not.

The court ruling determined the father, who does not have custody of the child, was best to make those decisions.

"In deciding this issue, the court must determine which parent is best capable of making vaccination decisions in their child's best interests," said Justice Sheilagh O'Connell in her written decision granting control to the father.

The child had COVID last February, reinforcing the father's quest to get him vaccinated for COVID.

The father's expert witness was Dr. Abdu Sharkawy, an internal medicine and infectious diseases specialist at the University Health Network. He testified that the 11 year old should receive the COVID vaccine at the appropriate time.

"Dr. Sharkawy also discussed the concerns raised by some, including the mother's proposed expert, about the MRNA technology used to create the vaccine. He explained that this technology is not new and that it has been around for many years," said the written judgment.

"Dr. Sharkawy's medical practice is at Toronto Western Hospital, where he has worked on the Covid ward and the Intensive Care Unit (ICU) attending Covid patients since the beginning of the pandemic. He is trained in pediatric infectious diseases. He has had extensive first-hand, front line "real world" experience treating Covid patients throughout the pandemic."

The judge noted that Sharkawy's opinions regarding vaccines for children are shared by numerous health organizations around the world.

While acknowledging that Bridle is an expert in his research field, she ruled he was not qualified to give expert opinion on this case.

"However ... the court does not accept that Dr. Bridle is qualified to give opinion evidence with respect to the safety and efficacy of the Covid-19 vaccine for children," the ruling states.

"Dr. Bridle acknowledged that he is not a medical doctor. He has never vaccinated a child, he has never treated a child or an adult suffering from a reaction to a vaccine, nor has he ever treated a child or an adult who is suffering from an infectious disease."

and death, regardless of the shorter duration of immunity, Bridle would not acknowledge that receiving the vaccine prevented severe or serious illness and death. In fact, he stated that vaccinated people are at greater risk than unvaccinated people given his interpretation of hospital admissions.

"Respectfully, this is so far removed from the mainstream and widely accepted views of the Canadian and international medical and scientific community that the court cannot accept Dr. Bridle's evidence on the Covid vaccine as reliable," the judge ruled.

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Report a mistake **Ask a question**

This is Exhibit " BB " to the Affidavit of

Byram Bridle, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

David Fisman
@DFisman

Professor, interested in plagues, pestilences and politics. I am, literally, a Fish who needs a bicycle.

Chelm
dlsph.utoronto.ca/faculty-profil
Joined February 2019
1,459 Photos and videos

27.4K 38.4K

Tweets Tweets & replies Media

Pinned Tweet

David Fisman @DFisman 5 Apr 2020

Replying to @bikehounds

Thank you for taking time out of your busy day to explain infectious disease epidemiology to me.

109 108 1.9K

4. COVID sceptical 14%

Now compare to🇨🇦.

Overall 82% would take the shot immediately (Angus Reid 5/17/21)

@JaneBrownNews @DFisman @drlynnwilson @ASPphysician

5 min read:

Tweets 30.6K | Following 9,520 | Followers 83.6K | Likes 42.1K | Lists 1

David Fisman
@DFisman

Professor, interested in plagues, and politics. The devil's child, per fanboy. George Soros may, or may not, have me on speed-dial.

Chelm
dlsph.utoronto.ca/faculty-profil...
Joined February 2019

Tweets | Tweets & replies | Media

Pinned Twee

David Fisman @DFisman · 5 Apr 2020

Replying to @bikehounds

Thank you for taking time out of your busy day to explain infectious disease epidemiology to me.

David Fisman Retweeted

David Elfstrom @DavidElfstrom · 20h

JULY 26, 2021—Ontario Society of Professional Engineers @O_S_P_E calls upon @sflecce & @ONgov to immediately consult with subject matter experts and address #airborne transmission in schools before more outbreaks occur ospe.on.ca/advocacy/engin... /1

Dec 31st 2021


Tweets 38.4K
Following 10.9K
Followers 105K
Likes 49.5K
Lists 1
David Fisman
@DFisman
Air: it's the new poop "An alarmist seeking the spotlight"
Cheim
Joined February 2019
Tweets
Tweets & replies
Media
Pinned Tweet
David Fisman @DFisman Dec 2
HelenH @heinrichs_helen
Replying to @PennyDaflos @DFisman @CTVVancouver
Is this person's opinion credible? Have seen much negative press on him
David Fisman Retweeted
Dr. Dick Zoutman @DickZoutman 6h
Opinion We're in the 'you're on your own' stage of the pandemic - The Globe and Mail
New to Twitter?
Sign up now to get your own personalized timeline!
Sign up

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Messages
Grok
Lists
Communities
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Profile
More
Post

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David Fisman
@DFisman

Notoriously unfair to viruses, bacteria, fungi, anti-vaxxers, and the Toronto Star. Roasting marshmallows over Elon's trash-fire, but with declining frequency.

Chelm · dlsph.utoronto.ca/faculty-profil... · Joined February 2019

13.4K Following **128.4K** Followers

Followed by John Cena

Posts Replies Media Likes

Pinned
David Fisman @DFisman · May 30
I spend less and less time on twitter. For good info on infectious disease risk recommended follows include

Please email directly with requests, ideas for collaboration, threats etc.

37 115 696 234K

David Fisman reposted
Deonandan @deonandan · Dec 6
Yes, your COVID rapid tests should still work. Remember that with a lot of vaccination, symptoms will precede high viral load. You might have mild symptoms but test negative, since your immunity is keeping viral load under detection threshold. Test daily for 2-3 days to be sure.

67 354 933 36K

David Fisman reposted
Kimberly Prather, Ph.D. @kprather88 · Dec 5
Only one other mask...Also using Israel nasal spray...and air blowing down hard. CO2 levels = 700...not too bad.

1.1K 192 1.4K 161K

David Fisman reposted

Live on X

Phil Kerpen is listening
FCC Commissioner Brendan Carr talks Elon Musk and Starlink +1.1K

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Michael Warner @drmwarner — Follow
Isaac Bogoch @BogochIsaac — Follow

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Barstool
5,128 posts

Trending in Canada
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What Ontario hospitals pay private staffing agencies for a nurse: $100/hr (& up)
--
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David Fisman reposted

Bryce Nickels @Bryce_Nickels · Dec 6

NO HONEST SCIENTIST WOULD ALLOW THEIR NAME TO BE ON A PAPER THAT CONTAINS THE LAST SENTENCE OF THIS PARAGRAPH.

#StrongEvidence
#RetractProximalOrigins

"While the analyses above suggest that SARS-CoV-2 may bind human ACE2 with high affinity, computational analyses predict that...
Show more

14 72 195 29K

Who to follow

Diego Bassani, PhD
@DGBassani
Follow
Senior Scientist/Epidemiologist. Not here anymore. @dgbassani.bsky.social

Court File No.: **CV-22-0069-1880-0000**

Dr. BYRAM BRIDLE -and- David Fisman et al

Plaintiffs Defendants

.

ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDING COMMENCED AT TORONTO

AFFIDAVIT OF DR. BYRAM BRIDLE

Name: ROCCO GALATI LAW FIRM

PROFESSIONAL CORPORATION
Rocco Galati, B.A., LL.B., LL.M.
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Address: 1062 College Street
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Telephone No.: 416-530-9684
Fax No.: 416-530-8129

Lawyer for the Plaintiff

TAB 5

Court File #: CV-22-0069-1880-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

AFFIDAVIT OF DR. BONNIE MALLARD

I, Dr. Bonnie Mallard, of the City of Guelph, in the Province of Ontario, MAKE OATH AND SAY:

1. I am a professor of Immunology and Immunogenetics in the Department of Pathobiology at the University of Guelph. I have worked with Dr. Bridle since he became faculty in my department at the University of Guelph in 2012, and prior to that, when he was a student at the university. As such, I have knowledge of the matters contained in this Affidavit.

A. My Professional Background

2. I am a tenured faculty member, professor and researcher, in immunology and genetics since 1990 at the University of Guelph. I have an excellent understanding of both of those disciplines, and specifically, where the two interact. I have taught the main immunology courses, from the undergraduate to the most advanced, for over 30 years. My research focuses on genetic regulation of the immune system and implications to disease resistance.

3. My understanding of the science in the areas of mammalian immunology and genetics includes the development of vaccines. I have held and still hold a number of patents in this area.
4. I have had the distinction of receiving many awards recognizing my expertise in immunology over the course of my career, including many industry awards from what is described as "big pharma", including the Pfizer Award for Research Excellence, Zoetis Research Award in immunogenetics, and Semex Alliance.
5. I won the YMCA Lifetime Achievement Award, the University of Guelph Innovation Award and the Governor General's Award for Innovation.
6. In 2021, I won the prestigious National Sciences and Engineering Research Council of Canada, (NSERC) Synergy Prize for my work in immunogenetics. https://news.uoguelph.ca/2021/11/u-of-g-prof-wins-prestigious-award-for-innovation-in-livestock-disease-resistance/
7. I am the first and only Canadian scientist to win both the Governor General's Innovation Award and the NSERC Award and have had the honour of being recognized as one of Canada's "greatest scientists". Attached as **Exhibit A** to this affidavit is my Curriculum Vitae.

B. Expertise in Immunology required to understand vaccines

8. Vaccines have the ability to provide protection to infectious diseases because they are designed to elicit robust protective immune responses by exposing the host to non-harmful components of the infectious agent so that upon subsequent exposure to the actual pathogen, they are able to mount protective memory responses. Since vaccine development relies essentially on a sound understanding of the immune system the discipline of

vaccinology has always been within the discipline of immunology. If, for example, the vaccine is against a viral or bacterial pathogen then the expertise of virologists or bacteriologists, respectively, also plays a pivotal role. To gain the level of expertise required to develop effective vaccines generally requires training at the PhD level. The immunology training at the MD or DVM level is rudimentary and generally not sufficient to design efficacious vaccines.

C. Dr. Bridle's expertise on COVID-19 vaccines

9. Dr. Bridle has PhD training in immunology, post-doctoral training in viral immunology and, as a faculty member, developed a well-funded and respected research program in the area of viral immunology. He has worked on vaccines and cancer therapies related to various species, including humans and other mammals. Dr. Bridle holds a number of patents in this area.

10. Dr. Bridle is not a veterinarian and nor would that training be required for this work. I also am not a veterinarian, but rather hold advanced degrees in immunology and genetics. This level of knowledge and expertise of the mammalian immune system is transferable and readily qualifies for work on human and animal vaccines. In fact, vaccines are often tested in various non-human species prior to being deemed safe and effective for use in humans.

11. I have published 10 peer-reviewed research papers with Dr. Bridle that can be found on PubMed, along with various other reports, letters, and book chapters. He is an outstanding reviewer of scientific research. His scientific knowledge and the rigor of his research is remarkable, attached as **Exhibit B** is a list of my publications with Dr. Bridle. Dr. Bridle is also highly published. The impact of Dr. Bridle's peer-reviewed publications in high-quality scientific journals far exceeds that of most of our colleagues at the University of

Guelph. His publications rank in the top 5-10% of the scientific literature, in terms of their importance.

12. I am one of the long-term and the highly funded scientific researchers at the University of Guelph, having held an NSERC Discovery Grant since 1991, along with grants from numerous other agencies. Dr. Bridle's research lab ***was*** also highly successful as evidenced by his funding, training and publication record, which would be described in his resume. Dr. Bridle was also the only applicant from our department to successfully obtain funding to develop a COVID-19 vaccine.
13. In my opinion, Dr. Bridle is one of the top viral immunologists in Canada and he is highly qualified to speak with integrity and accuracy about vaccines.

D. Duty to provide expert information to members of the public

14. One of the duties of a university professor is to be able to provide their expert opinion without the fear of reprisal. Thus, tenure is earned and granted to those who are proven experts in their field so they can speak to the public about the scientific evidence related to their particular discipline. This is an important way for scientists to provide the public with information regarding their expertise.
15. It is critical that all the ideas of the experts are heard and openly discussed in various public forums to extend and advance knowledge. Transparency is important in building public confidence. This is particularly critical when the health of the public is at stake even when some of the evidence and ideas go against the government or public health narrative. At this time, when knowledge is advancing at an unprecedented rate it is acutely critical to

carefully debate the scientific knowledge and ideas in order to prevent problems when new technologies quickly emerge for public utility.

16. Therefore, it is my expert opinion that the views of all experts in the field of immunology and vaccinology should have been welcomed and openly debated and countervailing views should not have been silenced as "misinformation" either prior to, during, or after the roll out of the novel genetic vaccines against SARS-CoV-2. Dr. Fisman's opinion is that criticisms of Public Health's position on the science and vaccines against COVID-19 will undermine public confidence in taking these vaccines; however, this is a false premise since rigorous science is based on debate and consideration after viewing the relevant facts from all sides. Rarely, is there total agreement within the scientific literature. Rather transparent scientific debate and discussion are required to reach consensus. This takes time and should allow the public to see the issues from all sides. These debates are not to be personal attacks but rather to be limited to the scientific facts at hand.

17. Dr. Fisman's false, malicious-sounding, and adverse labelling of Dr. Bridle's views, a leading scientist and vaccinologist, as "disinformation", "misinformation", and then personally attacking him does nothing to safeguard any "confidence" in the public. Furthermore, not only does this damage the career of Dr. Bridle, but also the entire scientific method which relies on differing opinions, thereby eroding public trust in science itself.

18. After the COVID19 pandemic was declared, Dr. Bridle was sought out by media to provide his scientific expertise on research and science related to COVID-19 and public health policies. Dr. Bridle's media interviews and speaking engagements on COVID-19-related

issues gained popularity because he is authoritative on the topic and very articulate. The University posted Dr. Bridle's interviews on its website, attached as **Exhibit C**.

19. I co-authored several open letters with Dr. Bridle and my virology and immunology colleagues at the university. Given our collective expertise in immunology, we closely followed the scientific literature on COVID-19 vaccines and collaborated in expressing concerns about them to the public. Our letters were widely circulated, nationally and internationally. Attached as **Exhibit D** are the Open Letters co-authored by us, dated, March 3, 2021; March 5, 2021; March 11, 2021, and March 16, 2021 and March 23,2021

E. Efforts to censor and deplatform Dr. Bridle at the University

20. Dr. Scott Weese is a veterinary internist in the Department of Pathobiology at the University of Guelph. He is not a virologist or immunologist. He does not hold a PhD degree but a Doctor of Veterinary Science (DVSc), which is more clinically- than research-oriented. Dr. Weese was a member of the Ontario Science Table. Dr. Fisman was also a member of the Ontario Science Table until his resignation, which he announced on August 23, 2021.

21. On April 15, 2021, Dr. Weese criticized me and Dr. Bridle for making public statements at the monthly Pathobiology Department meeting. He told us to curtail our "messaging to the public" so they were not contrary to public health. I was shocked to hear a faculty member warn another faculty to not express views within their expertise to the public. This was a first for me in over 30 years in academia. It is common for scientists to disagree and confront one another with difference of opinions, and, to disagree with government policies, to engage in scientific inquiry.

22. Dr. Weese is also very public about his views and his media appearances are also posted by the University, thus, I was surprised by Dr. Weese's intolerance of our views and his bold attempt to censor Dr. Bridle and myself. I was also surprised and disappointed that the Dean of our department, Dr. Jeff Wichtel, shut down the conversation quickly between Dr. Bridle, Dr. Weese and myself, rather than letting the discussion go on until all points of view had been thoroughly discussed as was the norm, even though the banter was robust.
23. One of the reasons we are granted tenure as academic scientists is to inform the public without censorship, or fear of loss of career or reputation. I believe the public have the right to hear opinions presented by experts in their respective fields equally from Dr. Weese, Dr. Bridle, myself and others, regardless of, and especially if, it contradicts official, dominant government mandates. This is all the more important if the public is being asked to receive an injection with a foreign substance by the government through Public Health mandates.

F. Fisman's claims about majority of scientific opinion is false

24. Dr. Bridle's scientific opinions on COVID-19 vaccine are shared by many immunologists and virologists. He is not the only viral immunologist to have insights on COVID-19 vaccines and his views are shared by world-renowned immunologists and experts in infectious diseases.
25. **Dr. Luc Montagnier** (Nobel Laureate in virology, now deceased) expressed numerous concerns about SARS-CoV-2 and COVID-19 vaccines, for which there was overlap with issues raised by Dr. Bridle. Dr. Montagnier was among the first people to express concern that SARS-CoV-2 could be the result of gain-of-function research.[1]This concern has been

[1] https://www.livemint.com/news/world/nobel-winning-scientist-claims-covid-19-virus-was-man-made-in-wuhan-lab-11587303649821.html

openly acknowledged as a legitimate one in top-tier science journals.[2] Dr. Montagnier also shared concerns that mass rollouts of the COVID-19 vaccines had the possibility of potentiating the emergence of SARS-CoV-2 variants, and that antibody-dependent enhancement of disease could be an unwanted adverse effect of COVID-19 vaccines. Indeed, mass vaccination is known to be an efficient prophylactic strategy to protect against outbreaks, assuming a vaccine is an ideal one. However, mass vaccination is not considered to be an ideal therapeutic strategy, especially if the vaccine(s) being used are less than ideal. "Less than ideal" means being unable to prevent disease and unable to prevent transmission of the causative agent, which aptly describes the genetic COVID-19 vaccines. This is based on the well-established biological principle that applying sub-lethal selection pressures on biological entities that are prone to mutation is a classical recipe for driving the emergence of variants that can escape the pressure. This is how treatment-resistant cancers and antibiotic-resistant bacteria emerge. It is also a risk when a virus like SARS-CoV-2, which is prone to incorporating random mutations into its genome, infects hosts that fail to apply lethal immunological pressure on the virus.[3] When it came to concerns about the potential for antibody-dependent enhancement of disease, it came to light in government-issued summary documents that these same concerns were shared by the manufacturer's of the genetic COVID-19 vaccines when both Pfizer and Moderna stated, "*risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains*

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[2] Gostin LO, Gronvall GK. The Origins of Covid-19 - Why It Matters (and Why It Doesn't). N Engl J Med. 2023 Jun 22;388(25):2305-2308. doi: 10.1056/NEJMp2305081. Epub 2023 Jun 7. PMID: 37285549.
Dance A. The shifting sands of 'gain-of-function' research. Nature. 2021 Oct;598(7882):554-557. doi: 10.1038/d41586-021-02903-x. PMID: 34707307.

[3] Riddell AC, Cutino-Moguel T. The origins of new SARS-COV-2 variants in immunocompromised individuals. Curr Opin HIV AIDS. 2023 May 1;18(3):148-156. doi: 10.1097/COH.0000000000000794. Epub 2023 Mar 28. PMID: 36977190.

unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure".[4]

26. **Dr. Geert Vanden Bossche** (DVM, PhD.) He held adjunct faculty appointments at universities in Belgium and Germany. Dr. Vanden Bossche joined several vaccine companies, GSK Biologicals, Novartis Vaccines, Solvay Biologicals, to serve various roles in vaccine research and development, as well as in late vaccine development. He also worked with the Bill and Melinda Gates Foundation's Global Health Discovery team in Seattle (USA) as Senior Program Officer. He also worked with the Global Alliance for Vaccines and Immunization (GAVI) in Geneva as Senior Ebola Program Manager and subsequently joined the German Center for Infection Research in Cologne as Head of the Vaccine Development Office. Like Drs. Montagnier and Bridle, Dr. Vanden Bossche shared a concern about mass vaccination during a pandemic having the potential to drive the emergence of new variants[5], although Dr. Vanden Bossche arrived at this conclusion using slightly different immunological principles than Dr. Bridle. Notably, Dr. Bridle accurately predicted that SARS-CoV-2 would become more contagious but less dangerous over time, whereas Dr. Vanden Bossche has hypothesized that the emergence of more dangerous variants is a possibility. Dr. Vanden Bossche also shares concerns that Dr. Bridle holds with respect to the importance of open debate about complex scientific problems for

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[4] **Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020, FDA Briefing Document, Pfizer-BioNTech COVID-19 Vaccine (first document in the list of meeting materials on this site: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-10-2020-meeting-announcement); Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020, FDA Briefing Document, Moderna COVID-19 Vaccine (first document in the list of meeting materials on this site: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-17-2020-meeting-announcement)**

[5] https://www.youtube.com/watch?v=BNyAovuUxro&t=8s

which many questions are outstanding, as well as the potential negative impact on immunological health caused by prolonged isolation of young people from the microbial world[6].

27. Numerous highly credentialed scientists that signed the Great Barrington Declaration (https://gbdeclaration.org/) also raise the same inquires and have the same insights as Dr. Bridle. That declaration has close to a million signatories showing the validity of alternative points of view to the dominant public health and government narrative on the topic of COVID-19. This would include, but is not limited to, the following:

    - **Dr. Ariel Munitz**, professor of clinical microbiology and immunology, Tel Aviv University, Israel;
    - **Dr. David Livermore**, microbiologist, infectious disease epidemiologist and professor, University of East Anglia, England;
    - **Dr. Gerhard Krönke**, physician and professor of translational immunology, University of Erlangen-Nuremberg, Germany;
    - **Dr. Motti Gerlic**, professor of clinical microbiology and immunology, Tel Aviv University, Israel;
    - **Dr. Rodney Sturdivant**, infectious disease scientist and associate professor of biostatistics, Baylor University, USA;
    - **Dr. Udi Qimron**, professor of clinical microbiology and immunology, Tel Aviv University, Israel;
    - **Dr. Ulrike Kämmerer**, professor and expert in virology, immunology and cell biology, University of Würzburg, Germany;

[6] https://sciencebasedmedicine.org/countering-geert-vanden-bossches-dubious-viral-open-letter-warning-against-mass-covid-19-vaccination/

- **Dr. Sunetra Gupta,** professor at Oxford University, an epidemiologist with expertise in immunology, vaccine development, and mathematical modeling of infectious diseases.

28. There is also an extensive list of scientists from around the whole that are part of the World Council for Health that share similar views to Dr. Bridle because of their expertise (https://worldcouncilforhealth.org/), including Dr. Tess Lawrie, the director of the Evidence-based Medicine Consultancy in Bath, UK.

29. The point here is that alternative views to government public health mandates are shared by thousands of researchers, physicians and scientists from all disciplines, so there is no need to try to silence or ostracize Dr. Bridle by claiming he is "spreading misinformation" for expressing scientific opinions in his field of expertise. It is far better to encourage the debate and let the best ideas float to the top rather than being dictated in a top-down fashion on the pretext that contradicting public health is "dangerous" or with unspecified and unsubstantiated claims of "public harm".

30. Such irresponsible and high-handed claims being made by a medical doctor and an academic, such as Dr. Fisman, cause ostracization and censorship. It sends a message to other scientists to not express their countervailing views. This is what happened to Dr. Bridle because of Dr. Fisman's allegations of misinformation against Dr. Bridle, which occurred in late May 2021. Since then, Dr. Bridle's public speaking engagements and media interviews regarding his expertise in COVID-19 vaccines were not announced, or posted, by the University https://www.uoguelph.ca/research/covid-research-stories/ovc.

G. Dr. Bridle's scientific predictions were accurate and not "misinformation"

31. I have read the affidavit of Dr. David Fisman filed in this motion. His claims that Dr. Bridle's opinions regarding COVID-19 vaccines are:

    a. "not scientifically sound";

    b. "implausible";

    c. "not evidence based" and "not data-based",

    d. Or that Dr. Bridle "posed a risk to the public";

    e. and is "spreading misinformation". These are all false and unjustified.

32. As a senior immunologist, I can confirm that Dr. Bridle's public communication on COVID-19 vaccines was, and is, not only based on scientific evidence and data, but his insights and predictions proved to be true and accurate, and are beneficial for public health because open discussion and criticism by experts inform better public policy decision making.

33. Dr. Fisman's allegations are unjustified and improper because for more than one year since the declaration of the pandemic in March 2020, Dr. Bridle accurately identified issues with COVID-19 vaccines, which were later admitted by government.

34. On August 17, 2020, at the *COVID-19 Science and Policy Symposium*, Dr. Bridle raised concerns about blood clots related to the Health Canada-authorized AstraZeneca COVID-19 vaccine. His presentation is available here: https://www.youtube.com/watch?v=HndetYzK8gU. Seven months later, on March 29, 2021, Health Canada discontinued its use for ages 55 and under, for concerns over blood clots: https://www.canada.ca/en/public-health/news/2021/03/use-of-astrazeneca-covid-19-vaccine.html

35. On February 10, 2021, Dr. Bridle published an article in The Conversation, in which he discussed the duration of immunity, where, if protection conferred by the vaccination did not have a sufficient duration, that the populations who were vaccinated first would lose their immunity while other populations were still being vaccinated, and therefore there would be insufficient immunity, leading to the virus spreading again through the initially vaccinated people.[8] These concerns are true, as the COVID-19 vaccines are now understood to start losing their effectiveness within one month and they become ineffective within only six months[9].

36. On June 15, 2020, in another article published in The Conversation, Dr. Bridle expressed concerns about the short research timelines in the development of the COVID-19 vaccines[10]. On March 24, 2021, Dr. Bridle expressed concern about lack of data on long-term adverse effects and efficacy. On November 16, 2023, Health Canada acknowledged that efficacy and potential long-term adverse effects of the COVID-19 vaccines were unknown at the time of the public rollout.[11]

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[8] https://theconversation.com/5-factors-that-could-dictate-the-success-or-failure-of-the-covid-19-vaccine-rollout-152856

[9] Addo IY, Dadzie FA, Okeke SR, Boadi C, Boadu EF. Duration of immunity following full vaccination against SARS-CoV-2: a systematic review. Arch Public Health. 2022 Sep 2;80(1):200. doi: 10.1186/s13690-022-00935-x. PMID: 36050781; PMCID: PMC9436729.

[10] https://theconversation.com/fast-covid-19-vaccine-timelines-are-unrealistic-and-put-the-integrity-of-scientists-at-risk-139824

[11] It should be noted that in the original purchase agreement between Pfizer and the Minister of Public Works and Government Services dated October 26, 2020, in Section 5.5 "Purchaser Acknowledgement" (page 18), the Government of Canada acknowledged that "the long-term effects and efficacy of the Vaccine are not currently known and there may be adverse effects of the Vaccine that are not currently known. Further, to the extent applicable, Purchaser acknowledges that the Product shall not be serialized." [(2020) Manufacturing and supply agreement between Pfizer Canada ULC and her Majesty the Queen in Right of Canada, represented by the Minister of Public Works and Government Services Canada dated October 26, 2020. X. Retrieved from https://twitter.com/canindependent/status/1724438683963515231]
In other words, Health Canada would not be able to track any particular Pfizer COVID-19 vaccine batches for efficacy and safety. By the beginning of December 2020, the Canadian government had 154 million COVID-19 vaccines doses for its 38 million population, which works out to 4 doses for every person in Canada. [Rastello, S., Bolongaro, K. (2020) Canada has reserved more vaccine doses per person than anywhere. BNN Bloomberg News. Retrieved

37. On May 27, 2021, Dr. Bridle was interviewed on the program "ON Point" with Alex Pierson on Global[12]. All Dr. Bridle's claims are now accepted principles in the peer-reviewed scientific literature. Specifically, Dr. Bridle stated there could potentially be a link between the mRNA vaccines and cases of myocarditis that were being diagnosed in young males shortly after immunization. He also stated that a preclinical study submitted to the Japanese health regulatory agency showed that the lipid nanoparticles used to deliver mRNAs in Pfizer's COVID-19 vaccine got widely distributed throughout the body, which agreed with the long historical understanding of this technology but contradicted public health messaging about the vaccines remaining at the injection site. With respect to concerning data showing the lipid nanoparticles accumulating in the ovaries, Dr. Bridle questioned whether this could have any impact on fertility. This was clearly posed as a scientific question, not a statement of fact. Finally, Dr. Bridle expressed concerns, based on his assessment of pathogenesis studies of natural infections with SARS-CoV-2, that the spike protein was a bioactive molecule that had the potential to cause harm in the body (*i.e.*, have toxic effects) if it got systemically distributed.

H. Dr. Fisman's claims are irresponsible, unjustified and malicious

38. On May 30 and 31st, 2021, I was forwared and copied on emails from Dr. Bridle attaching posts on Twitter by Dr. Fisman and Dr. Glen Pyle, and Weese, attached as **Exhibit E.**

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from https://www.bnnbloomberg.ca/canada-has-reserved-more-vaccine-doses-per-person-than-anywhere-1.1533041] In short, Health Canada could not, with any degree of certainty, comment on safety and efficacy of this Pfizer product.

3. The Alex Pierson Show: New peer reviewed study on COVID-19 vaccines suggests why heart inflammation, blood clots and other dangerous side effects occur on Apple Podcasts [hereinafter "On Point interview"]

39. Dr. Fisman's post dated May 29th, 2021 reads:

> "I've had questions over the past 48h about vaccine safety concerns aired Dr Bryam Bridle at @UofGuelphOAC in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here: byrambridle.com"

40. Dr. Fisman does not identify any claims which are not "data based" in his May 29th, 2021, post for the public to understand what exactly constituted "misinformation". It is unfair to allege an expert is making false claims without specifying what those are. It is also unjustified and high-handed for Dr. Fisman to claim that Dr. Bridle's answers are "not data-based". As an academic and scientist, he owed Dr. Bridle the courtesy of notifying him, and members of the public, about *which* claims were not data-based and an opportunity for Dr. Bridle to respond. In fact, Dr. Bridle stated in his interview with Alex Pierson that he was in the process of assembling the scientific basis for his concerns. So, Dr. Fisman should have known that Dr. Bridle had data that could be shared. After all, it is not possible to 'show data' in the context of a radio interview intended for a lay audience. Dr. Bridle followed through on this by publishing "COVID-19 vaccines and Children: A Scientist's Guide for Parents" is attached as "**Exhibit F**", along with two briefing documents which Dr. Fisman never referenced.

41. Dr. Fisman directs the public to a website which he states provides responses to the unidentified claims "***from Dr. Bridle's colleagues***"[15]. First, referring the public to a website he knows is not authorised by Dr. Bridle, and was set up to impersonate him, is malicious. Second, Dr. Pyle has denied any connection with the website that impersonates him.

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[15] Affidavit of Dr. Fisman at paragraph 21.

42. In his email to *USA Today* reporter Daniel Funke, Dr. Fisman states Dr. Bridle relied on an "odd document" during the ON Point interview[16]. Dr. Bridle based his comments on the Pfizer biodistribution study of where lipid nanoparticles go in the body. It is not an "odd document", as asserted by Dr. Fisman[17]. It is a scientific study that was conducted by Acuitas Therapeutics Inc. which is attached as "**Exhibit G**". The Acuitas study was confirmed by a study conducted by Pfizer and submitted to the Japanese Health regulatory agency. It was made publicly available via their website. Tables on page 6 and 7 are in English. Tables and figures should stand alone and a good scientist should be able to read and interpret the tables without reading the text. Attached as "**Exhibit H**", is a copy of the Japanese study. Subsequently, a court in the United States compelled the Food and Drug Administration to publicly release their version of the study. Dr. Fisman's referral to it as an "odd" document to an international journalist, is deceptive, shows a lack of understanding of the health regulatory process, and only acts as a smear.[18]

43. Dr. Fisman's only reason for objecting to Dr. Bridle's public comments seems to be that he was ***contradicting*** public health messaging. However, that in itself is not grounds for an accusation of misinformation.

44. The post by Dr. Fisman dated May 30, 2021, reads:

> "An excellent follow for good ***immune science from @UofGuelphOAC*** is Dr. @glenplye, who has addressed some of the misinformation in these interviews on his own tweets" (emphasis added)

45. I am one of Dr. Bridle's ***immunology*** colleagues. I was not contacted by Dr. Fisman to respond to concerns about claims which may be "misinformation". There are other

[16] Affidavit of Dr. Fisman at paragraph 30, Exhibit "N", page 184
[17] Ibid
[18] Affidavit of Dr. Fisman, Defendants Motion Record, page 183

immunologists at the University of Guelph or elsewhere, Dr. Fisman could have referred the public to for "good immune science". Dr. Pyle is neither an immunologist nor a virologist; he is however one of the faculty members seeking to censor and smear Dr. Bridle at our university. Dr. Fisman's referral to Dr. Pyle for "good immune science" on COVID-19 vaccines is disingenuous.

46. Dr. Fisman's subsequent Twitter post, again refers the public to and promotes the website impersonating Dr. Bridle:

> "The website debunking Dr. Bridle's covid-19 vaccine claims has been updated with lots of peer-reviewed science that attests to the safety of vaccines.
>
> Byrambridle.com
>
> And for those who think I made or organized this website: nope. But grateful to the scientists who did."

47. On February 22, 2021, I was interviewed by a detective in the Fraud Bureau of Municipal Regional Police Service. I was advised by the detective and do verily believe that the website is being investigated for "criminal harassment" and "identity fraud"[19].

48. The website is not a credible or knowledgeable source for scientific resource. It is improper and unethical for Dr. Fisman, a medical doctor, and tenured professor, to repeatedly direct members of the public to a website that impersonates a viral immunologist and an academic colleague with the intent to defame and discredit him.

49. Dr. Fisman's reference to Dr. Pyle from June 17th, to June 23rd, 2021 and his messages intertwining with Dr. Weese do not constitute scientific discussion. On June 23, 2021, I received an email from a research associate at the University of Guelph (who fears reprisal

[19] sections 403.1 & s.264(2)(b) of the Criminal Code

from Weese and Pyle) with screenshots of Twitter posts by Dr. Weese and Dr. Pyle in response to Dr. Bridle's research report titled "COVID-19 vaccines and Children: A Scientist's Guide for Parents" Dr. Weese posted a picture of a farmer shovelling manure, and another post, in response to a press conference on Parliament Hill, he called Dr. Bridle an "anti-vaxxer", attached as **Exhibit I.**

50. It became apparent to me that Dr. Bridle, was referred to as an "anti-vaxxer" and disseminator of "misinformation", to tarnish his stellar reputation as a vaccinologist, and discredit him so that the public would not listen to his expert opinion. The allegations otherwise are nonsensical because Dr. Bridle is a career vaccinologist who develops and researches vaccine. It is absurd and irrational to allege that a viral immunologist with a speciality in vaccinology and multiple patent holder for vaccines is "anti vax".

51. I another post Dr. Fisman's combined social media posts, with Dr. Weese, re-tweeting an old Tweet from Dr. Fisman, dated May 10, 2021, links "anti-vaxxers" to "neo-Nazi white supremacist" with a link that goes directly to Dr. Bridle's picture, name and place of work. Dr. Weese makes a link between Dr. Bridle, lies, white supremacist and neo-Nazis through Dr. Fisman's posts. There is no discussion of science and Dr. Fisman does nothing to denounce the reckless and vindictive re-posting of his tweet.

I. University's complicity in smear campaign and online harassment against Dr. Bridle

52. On June 7, 2021, July 7, 2021, and September 9, 2021, I emailed the Dean of our department, Dr. Jeff Wichtel, and others, with concerns, regarding the combined Tweets of Drs. Fisman, Pyle and Weese attached as **Exhibit J**:

"I wanted to let you know that I find it very disappointing that after Byram's interview last week the "Fact Checkers" and others on social media etc called this false news when in fact he reported on two important findings: 1 - the Pfizer report to the Japanese government (linked below, see tables on page 6-7) showing that their LNP formulation carrying mRNA is distributed within 15 minutes to most organs and tissues and remains for at least 48 hours. This bio-distribution study was done in rats which is appropriate and another study in primates showed similar results.

In addition, he spoke about an accepted peer reviewed paper by Ogata et al (authors from U of Montreal and Harvard, linked below) that showed the presence of viral spike protein in the circulation of 11 out of 12 health care workers following immunization with the mRNA 1273 vaccine. This substantiates the idea that the mRNA is being translated into spike protein in large enough quantities and finding its way from the local site/draining nodes into the circulation where it can bind to platelets and endothelial cells potentially causing damage.

This is in no way false information. In fact, it is right here in black and white along with a large number of other reports and manuscripts (I attached just a smattering) describing various concerns associated with these nucleic acid vaccines, particularly for use in children.

Why is it all of a sudden a crime or false news when a group of credible scientists offer up their valid concerns to the public, particularly about vaccinating children?

It is inappropriate in my view to let Byram be slandered by all types of false claims and say nothing. I hope you can offer some suggestions to support our colleague."

53. My email dated September 9, 2021, states, in part:

"Scott has been tweeting slanderous comments against Byram for months now and nothing has been done to stop it.
Meanwhile, Byram is the one being accused of harassment. I think the shoe is on the wrong foot here.
In my 30 years as faculty I have never seen such nonsense. To call Byram an anti-Vaxxer is completely ridiculous since his entire career revolves around vaccine production. Showing a picture of a person shovelling manure and implying this is Byram is beyond belief.
Since when do we not accept other faculty with alternative points of view rather than slandering them on social media."

54. Dean Witchel suggested that Dr. Bridle "withdraw from social media discourse", completely failing to appreciate that Dr. Bridle was not on Twitter and had no social media presence whatsoever; the attacks were one-sided.

55. On July 6, 2021, two faculty members that Dr. Fisman posted messages with on Twitter, Drs. Pyle and Weese, wrote a letter with Drs. Greer and Bienzle repeating Dr. Fisman's allegations against Dr. Bridle for "spreading misinformation" on COVID-19 vaccines, attached as **Exhibit K**.

56. As a senior viral immunologist and as a researcher and developer of vaccines, including COVID-19 vaccines, Dr. Bridle is a strong proponent of using high quality vaccines in a correct and evidence-based manner. The letter was singularly directed at Dr. Bridle and personalized to attack him. If the letter had been about the issues raised by the scientific debate on COVID-19 vaccines it would have been addressed to and involved all the senior immunologists on campus, that would have been fair comment as several of us hold the exact same views as Dr. Bridle.

57. On July 7, 2023, I wrote to the university again. Dean Witchel, replied that the university would not "referee scientific discourse in the media", which missed the point again that Dr. Bridle was not part of the Twitter discourse, but subject to one-sided attacks, and the content was not about science but vicious name-calling.

58. On July 14, 2021, I co-authored a letter in support of Dr. Bridle to address the science in the July 6, 2021, letter and unlike the letter written by Drs. Weese, Pyle, Bienzle and Greer, I did not mention any names. The letter is science-based and not a personal letter against anyone. Attached as **Exhibit L.**

J. Harms for alleging Dr. Bridle is "an immunologist spreading misinformation"

59. Dr. Bridle has conducted research and development of vaccines at the University of Guelph for over a decade. He took the time and effort to carefully develop a well-funded research program around his areas of expertise in immunology, vaccinology and cancer biology. His funding and publication record grew steadily over time. He has received various teaching and research awards. He was granted tenure as a university professor which acknowledges his expertise on a national and international level. As someone who was one of his mentors, there is no doubt that Dr. Bridle was on an upward career trajectory as a world class scientist. Dr. Bridle's vaccine development research is dependent on funding from third party donors/grantors.

60. Dr. Bridle being labelled as "spreading misinformation" by Dr. Fisman, in conjunction with Drs. Pyle and Weese, has incredibly harmed his research and reputation as a scientist. The false web-site erected under his name has cast doubt on his credibility and caused a great deal of confusion.

61. When a scientist is accused of publishing, presenting or "spreading" "misinformation" or "disinformation" it is taken by others in the scientific community to mean a fraudulent resuscitation of science which amounts to the "kiss of death" for the scientist accused, even where the accusation is false.

62. I pointed this out in my letter to Dean of our Department on June 7, 2021:

> "Byram has always been a respected and successful member of our faculty, and I am saddened to see people go after him in such a malicious manner on social media including members of our own faculty. Some have now even removed him from their grant applications. These types of slanderous posts can have a negative impact on his career and should be actively discouraged. As you point out, there is a scientific process to follow and Byram would be happy to discuss these papers with any interested parties. However, he has not been given that opportunity by the people posting against him for no valid reason."

63. Dr. Bridle has limited resources left to support his staff, students, or research. It will take him years to rebuild his research program and team of experts, as well as to reclaim his reputation. His research program required approximately $500,000 dollars to get up and running and approximately $250,000 per year in ongoing operating costs. It takes a minimum of five years to get a research program running and fully functional and to demonstrate a track-record of success that is needed to garner funding from conventional sources. This means that Dr. Bridle will require at least $1,250,000 to re-establish his program.

64. There has also been a negative impact on students and staff hearing the disparaging and insulting social media posts about Dr. Bridle. In fact, one of my own research associates was so dishearten by these posts and the situation within our department that she asked not to come into work on at least one occasion. The junior scientists on my team also expressed their concerns about the vaccines and the treatment of Dr. Bridle but didn't want to say anything for fear of harm against their future at the university or as budding immunologists. We actually put together a support group for some of the students on campus that didn't want to take the vaccine and wanted to hear what Dr Bridle had to say. They could see the evidence was rapidly going in his favour (*e.g.*, risk of myocarditis, particularly in young males).

65. These harms and attempts to silence experts, such as Dr. Bridle, has also had a chilling effect on me. It became clear very early on that to provide an opposing point of view even when backed up by the scientific evidence was going to cause alienation from my colleagues. Previously, opposing points of view were encouraged and valued to help sharpen the thinking on any given issue, but this was not the case when it came to COVID-

19 and the associated vaccinations. No one wanted to discuss the issues, even proof of naturally-acquired immunity to SARS-CoV-2 was not valued, and once those that were not vaccinated were not allowed in the building, the alienation and silencing of opposing voices was complete. Also, as a result of the smear campaign and vicious social media attacks on Dr. Bridle's character and credentials I am very cautious of Drs. Pyle and Weese. I saw the damage that they can do a colleague's career.

SWORN BEFORE ME by Bonnie)
Mallard in the City of Guelph, in the)
Province of Ontario, on this 15 day of)
December, 2023, in accordance with)
O. Reg. 431/20 Administering Oath)
Or Declaration Remotely)

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

BAMallard

Dr. Bonnie Mallard

This is Exhibit "A" to the Affidavit of
Bonnie Mallard, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Amina Sherazee Barrister and Solicitor

NSERC CRSNG

Canadian Common CV commun canadien

Protected when completed

This is a draft version only. Do not submit to any funding organization. Only the final version from the History page can be submitted.

Professor Bonnie A Mallard
Correspondence language: English

Contact Information

The primary information is denoted by (*)

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NSERC CRSNG

Canadian Common CV commun canadien

Protected when completed

This is a draft version only. Do not submit to any funding organization. Only the final version from the History page can be submitted.

Professor Bonnie Mallard

Language Skills

Language	Read	Write	Speak	Understand	Peer Review
English	Yes	Yes	Yes	Yes	Yes

Degrees

- 1987/1 — Doctorate, Immunogenetics, Focus - MHC Genetics - University of Guelph
  Supervisors: Professor Bruce Wilkie, 1983/9 - 1987/1
- 1981/10 — Master's Thesis, Quantitative Genetics and Animal Breeding, Focus - Genetic Regulation of the Immune System - University of Guelph
  Supervisors: Professor Edward Burnside, 1979/9 - 1982/10
- 1979/4 — Bachelor's, Animal BioScience, University of Guelph

Recognitions

2020/12

NSERC Synergy Award - UoG Nominee and Prize Winner
NSERC Award
Prize / Award
Recognition for innovation in immunogenetics and effective synergistic relationship with commercial partner to bring business advancement to Canada. Only Canadian to have every won both the Synergy Prize and Governor General's Award

2018/12

World Agriculture Expo Top-10 New Products Competition: Semex Elevate
World Ag Expo
Prize / Award
Recognition for genomics test for bovine immunity to advance Immunity+ technology

2018/3

Guelph Women of Distinction: Education, Training and Mentorship
YMCA Guelph
Distinction
Women of Distinction is an annual fundraiser held by the YMCA - YWCA of Guelph to recognize and celebrate the achievements of women in City of Guelph and Wellington County. The fundraiser supports programs run by the YMCA - YWCA of Guelph for women, teens, and their families. Women of Distinction supports Guelph Y programs for girls and women at all stages of life in Guelph and Wellington County, including: Power of Being a Girl - A one day conference for girls that helps build self-esteem and raises awareness about healthy relationships Teenage Parents Program (TAPPs) - A program that supports the personal growth and development of pregnant and parenting teens and their families and connects them with valuable resources Encore - A holistic program for women with breast cancer to help them build their own physical strength, as well as feel the strength and support of a community

2018/3	Guelph Women of Distinction: Lifetime Achievement Award YMCA Distinction Honoured for her groundbreaking High Immune Response technology used to breed healthier cattle, as well as for being a mentor and for co-founding the Sunrise Therapeutic Riding and Learning Centre in Puslinch, Ontario
2017/7	University of Guelph Innovation of the Year Award Catalyst Centre: Research Innovation Office UofG Prize / Award The Innovation of the Year Award has been developed to recognize and celebrate Guelph innovations that have made, or have the potential to make, significant socioeconomic impacts to Canada and beyond.
2017/5	Governor General's Innovation Award for Advancements in Immunogenetics Canada Foundation for Innovation Prize / Award In today's competitive and interconnected world, increasing productivity through the creation of new products and services, improving public sector performance, and building an inclusive, compassionate society will be the keys to Canada's success as a caring, efficient and prosperous nation. The purpose, therefore, of the Governor General's Innovation Awards is to inspire Canadians to embrace innovation and to emulate innovative, entrepreneurial risk-takers who have developed new or better ways of creating value and who are having a meaningful impact on our quality of life. As innovation and an entrepreneurial spirit are fundamentally important to all Canadians and can have a transformative, positive impact—regardless of whether it is in the private, public or not-for-profit realms—the awards encompass all sectors of Canadian society.

User Profile

Research Specialization Keywords: immunology, genetics, genomics, infectious disease, health, disease prevention

Employment

2000/6	Professor of Immunogenetics Pathobiology, University of Guelph Full-time, Professor Tenure Status: Tenure Research and Teaching Professor
2005/1 - 2010/1	Professor of Immunogenetics Biology, Science, University of Sherbrooke Part-time, Adjunct Tenure Status: Non Tenure Track
1993/11 - 2000/5	Professor of Immunogenetics Pathobiology, Ontario Veterinary College, University of Guelph Full-time, Associate Professor Tenure Status: Tenure Research and Teaching Professor
1990/1 - 1993/11	Professor of Immunogenetics Veterinary Immunology and Microbiology, Ontario Veterinary College, University of Guelph Full-time, Assistant Professor Tenure Status: Tenure Track Research and Teaching Professor

Research Funding History

Awarded [n=14]

2022/4 - 2027/3
Principal Applicant

Improving Livestock for Climate Resilience, Grant

Funding Sources:
Canada First Research Excellence Fund
Food from Thought
Total Funding ~300,000
Portion of Funding Received - 181,390
Funding Competitive?: Yes

2020/1 - 2028/1
Principal Investigator

Synergy Prize for Innovation, Grant

Funding Sources:
Natural Sciences and Engineering Research Council of Canada (NSERC)
Synergy Prize
Total Funding - 400,000
Portion of Funding Received - 200,000
Funding Competitive?: Yes

2018/10 - 2022/12
Co-applicant

Translating High Immune Response (HIR™) Genomics to Improve Beef Cattle Health and Welfare, Grant

Funding Sources:
Genome Canada
Genomic Applied Partnerships Program
Total Funding - 1,617,164
Portion of Funding Received - 800,476
Funding Competitive?: Yes

2020/5 - 2023/12
Principal Applicant

Immunity+ Colostrum: Building a State-of-the-Art Colostrum Product for Better Calf Health, Grant

Funding Sources:
Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
Gryphon's LAAIR (Leading to the Accelerated Adoption of Innovative Research)
Total Funding - 106,000
Portion of Funding Received - 106,000
Funding Competitive?: Yes

2018/10 - 2022/12
Principal Applicant

Evaluation of the High Immune Response Technology™ in beef cattle in the context of climate change, calf health and the development of a genomics test for immune response, Grant

Funding Sources:
Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
University of Guelph - OMAFRA Research Theme: Tier II
Total Funding - 48,571
Portion of Funding Received - 48,571
Funding Competitive?: Yes

2018/10 - 2022/10
Decision Maker

Translation of the HIR technology for use in beef cattle, Scholarship

Funding Sources:
Mitacs
Accelerate
Total Funding - 80,000
Portion of Funding Received - 80,000

Funding Competitive?: Yes

2021/5 - 2023/8
Principal Investigator

Maintaining Immunity+ Colostrum Bioactivity using a Unique Cold Plasma Method, Grant

Funding Sources:
Canada First Research Excellence Fund
Food from Thought - Commercialization Grant Program
Total Funding - 50,000
Portion of Funding Received - 50,000
Funding Competitive?: Yes
Semex Canada
Total Funding - 10,000
Portion of Funding Received - 10,000
Funding Competitive?: No

Co-investigator : Art Hill; Kevin Keener

2017/4 - 2022/3
Principal Applicant

Mechanisms and Genes that Shape Bovine Host Defense, Grant

Funding Sources:
Natural Sciences and Engineering Research Council of Canada (NSERC)
Discovery
Total Funding - 201,000
Portion of Funding Received - 201,000
Funding Competitive?: Yes

2020/7 - 2021/6
Co-applicant

Application of Genomics-based Methods to Select for Pig Disease Resilience, Grant

Funding Sources:
Genome Canada
Genomic Applied Partnerships Program
Total Funding - 1,026,200
Portion of Funding Received - 135,400
Funding Competitive?: Yes

2016/9 - 2021/1
Decision Maker

Canada First Research Excellence Fund - Food from Thought, Grant

Funding Sources:
Canada First Reserach Excellence Fund
Food from Thought
Total Funding - 7,660,000
Portion of Funding Received - 350,000
Funding Competitive?: Yes

Decision Maker : Bonnie Mallard; Clarence Swanton; Evan Fraser; Jan Sargeant; Jeffrey Farber; Kari Dunfield; Kevin McCann; Malcolm Campbell; Paul Hebert; Tina Widowski

2018/8 - 2024/8
Co-investigator

Use of the High Immune Response technology to access bovine immune responsivenss, Contract

Funding Sources:
The Semex Alliance Inc
Total Funding - ~955,248
Portion of Funding Received - ~815,453
Funding Competitive?: No

2019/7 - 2020/7
Co-investigator

Telemetry equipment to monitor body temperature, respiratory and heart rate in dairy cattle and other animals, Grant

Funding Sources:
University of Guelph
Research Tools and Instruments Grant Program

Total Funding - 165,000
Portion of Funding Received - 165,000
Funding Competitive?: Yes

2019/1 - 2020/1
Principal Applicant

Examining MHC Polymorphism in Holstein Dairy Sires, Grant

Funding Sources:
The Semex Alliance Inc
Total Funding - 25,000
Portion of Funding Received - 25,000
Funding Competitive?: No

2018/1 - 2020/1
Principal Applicant

Investigating the Health and Economic Benefits of Colostrum and Milk from Dairy Cattle Selected for Enhanced Immunity, Grant

Funding Sources:
The Semex Alliance Inc
Collaborative Research and Development Grant
Total Funding - 422,157
Portion of Funding Received - 422,157
Funding Competitive?: Yes
Natural Sciences and Engineering Research Council of Canada (NSERC)
Collaborative Research and Development Grant
Total Funding - 422,157
Portion of Funding Received - 188,390
Funding Competitive?: Yes

Completed [n=10]

2017/2 - 2019/1
Collaborator

Mitacs Elevate Fellowship awarded to Dr. Lauri Wagter-Lesperance in partnership with Dr. Bonnie Mallard and the Semex Alliance Inc., Fellowship

Funding Sources:
Semex Alliance Canada
Mitacs Elevate
Total Funding - 60,000
Portion of Funding Received - 60,000
Funding Competitive?: Yes

2016/6 - 2018/10
Co-applicant

Animal Models to Select for Disease Resilience: High Immune Response Technology in Swine, Grant

Funding Sources:
Ontario Research Fund (ORF)
Strategic Value Review
Total Funding - 250,000
Portion of Funding Received - 250,000
Funding Competitive?: Yes

2015/10 - 2018/10
Co-applicant

Application of Genomics to Improve Disease Resilience and Sustainability in Pork Production, Grant

Funding Sources:
Genome Canada
Large Scale Applied Research Program: Genomics and Feeding the Future
Total Funding - 9,983,836
Portion of Funding Received - 116,263
Funding Competitive?: Yes

2016/8 - 2018/8 Principal Applicant	Use of the High Immune Response technology to access bovine immune responsivenss, Contract **Funding Sources:** The Semex Alliance Inc Total Funding - 256,000 Portion of Funding Received - 256,000 Funding Competitive?: No
2015/6 - 2018/7 Principal Applicant	Genetic Selection for Disease Resistance: Adapting Immunity+ /High Immune Response (HIR) Technology for Application in the Beef Industry, Grant **Funding Sources:** Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA) Gryphon's LAAIR: Leading to Accelerated Adoption of Innovative Research Total Funding - 124,794 Portion of Funding Received - 124,794 Funding Competitive?: Yes
2016/5 - 2017/4 Principal Applicant	Investigating Mechanisms and Genes that Shape Bovine Host Defense and affect Disease Outcome in High and Low Immune Responder Phenotypes, Grant **Funding Sources:** NSERC Discovery Total Funding - 29,000 Portion of Funding Received - 29,000 Funding Competitive?: Yes
2014/1 - 2017/1 Principal Applicant	Genetic and Genomic Approaches to Improve Dairy Health, Food Quality and Farm Profitability through Enhanced Immune Response, Grant **Funding Sources:** Boviteq Inc. Total Funding - 420,200 Portion of Funding Received - 420,200 Funding Competitive?: Yes Natural Sciences and Engineering Research Council of Canada (NSERC) Total Funding - 419,000 Portion of Funding Received - 419,000 Funding Competitive?: Yes
2014/9 - 2016/9 Co-investigator	Assessing the bioactivity of immune-related microRNAs in colostrum and milk from high and low immune responder cows on human intestinal epithelial cells, Grant **Funding Sources:** Dairy Farmers of Ontario Total Funding - 112,500 Portion of Funding Received - 112,500 Funding Competitive?: Yes Natural Sciences and Engineering Research Council of Canada (NSERC) Total Funding - 112,500 Portion of Funding Received - 112,500 Funding Competitive?: Yes Principal Applicant : Niel Karrow
2013/8 - 2016/8 Principal Applicant	Transferring the High Immune Response technology to industry for testing bovine sires, Contract **Funding Sources:**

The Semex Alliance Inc
Total Funding - 384,000
Portion of Funding Received - 384,000
Funding Competitive?: No

2014/5 - 2016/5
Principal Applicant

Assessing the bioactivity of immune-related microRNA in colostrum and milk from high and low immune responder cows on intestinal epithelial cells, Grant

Funding Sources:
Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
Total Funding - 175,000
Portion of Funding Received - 175,000
Funding Competitive?: Yes

Student/Postdoctoral Supervision

Bachelor's [n=17]

2022/5 - 2022/8
Principal Supervisor

Yuqi Liang (In Progress) , University of Guelph
Thesis/Project Title: Immunity+ colostrum
Present Position: undergraduate student

2022/5 - 2022/8
Co-Supervisor

Sophie Tieu (In Progress) , University of Guelph
Thesis/Project Title: Vitamin D as an immunoceutical
Present Position: veterinary student

2021/5 - 2021/8
Principal Supervisor

Marijke Boerefyn (Completed) , University of Guelph
Thesis/Project Title: Benchmarking genetic influences on disease survivability and colostrum quality in dairy calves
Present Position: gradulate student

2021/5 - 2021/8
Principal Supervisor

Laura Willis (Completed) , University of Guelph
Thesis/Project Title: Bioactivity of colostrum after various processing methods
Present Position: veterinary student, University of Guelph

2020/5 - 2020/8
Academic Advisor

Samantha Streekstra (Completed) , University of Guelph
Thesis/Project Title: Investigation of Colostrum Quality of HIR Dairy Cattle
Present Position: Nurse, McMaster University

2020/5 - 2020/8
Academic Advisor

Connor Bryant (Completed) , University of Guelph
Thesis/Project Title: Investigation of Colostrum quality from HIR Dairy Cattle
Present Position: veterinarian, Ontario Veterinary College

2020/5 - 2020/8
Academic Advisor

Matthew Vermey (Completed) , University of Guelph
Thesis/Project Title: Translating the HIR Technology for use in Angus Beef Cattle
Present Position: Veterinary Medicine Student, Ontario Veterinary College

2019/5 - 2020/5
Principal Supervisor

Samantha Streekstra (Completed) , University of Guelph
Thesis/Project Title: Immunogenetics
Present Position: unknown

2019/5 - 2019/8
Principal Supervisor

Connor Bryant (Completed) , University of Guelph
Thesis/Project Title: immunogenetics
Present Position: Veterinary medicine student, Ontario Veterinary College

2019/5 - 2019/8
Principal Supervisor

Royan Pariappadan (Completed) , University of Guelph
Thesis/Project Title: Immunogenetics
Present Position: Medical Student

2019/5 - 2019/8 Principal Supervisor	Siobhan Mellors (Completed) , University of Guelph Thesis/Project Title: Immunogenetics Present Position: unknown
2017/5 - 2018/4 Principal Supervisor	Kiersten Hanada (Completed) , University of Guelph Thesis/Project Title: MicroRNA in bovine colostrum and milk Present Position: veterinarian
2017/5 - 2018/12 Principal Supervisor	Gabriel Laplante (Completed) , University of Guelph Thesis/Project Title: Immunogenetics Present Position: unknown
2017/5 - 2017/8 Principal Supervisor	Christine Barnes (Completed) , University of Guelph Thesis/Project Title: Assessment of HIR Technology for use in beef cattle and thoroughbred horses. Present Position: veterinarian
2016/5 - 2016/8 Principal Supervisor	Elfleda Chik (Completed) , University of Guelph Thesis/Project Title: Assessment of HIR Technology in Beef Cattle Present Position: veterinarian
2016/5 - 2017/8 Principal Supervisor	Keeley Burnside (Completed) , University of Western Ontario Thesis/Project Title: MicroRNA in bovine colostrum and milk Present Position: Physiotherapist
2016/5 - 2016/8 Principal Supervisor	Christine Barnes (Completed) , University of Guelph Thesis/Project Title: Assessment of HIR Technology for use in beef cattle and thoroughbred horses. Present Position: veterinarian

Bachelor's Equivalent [n=1]

2016/5 - 2016/12 Principal Supervisor	Nasrin Satayesh Husseini (Completed) , University of Guelph Thesis/Project Title: Assessment of HIR Technology for beef cattle Present Position: Agriculturalist

Master's non-Thesis [n=1]

2017/1 - 2017/9 Co-Supervisor	Alexandra Livernois (Completed) , University of Guelph Thesis/Project Title: Bioinformatics Present Position: Scientist

Master's Thesis [n=4]

2017/5 - 2020/8 Principal Supervisor	Nasrin Satayesh Husseini (Completed) , University of Guelph Thesis/Project Title: Assessment of the HIR Technology for beef cattle Present Position: Research Technician
2014/9 - 2017/9 Principal Supervisor	Mikayla Ross (Completed) , University of Guelph Thesis/Project Title: Assessing the bioactivity of immune-related microRNA in colostrum and milk from high and low immune responder cows Present Position: industry researcher
2014/9 - 2016/12 Academic Advisor	Adrianna Laursen (Completed) , University of Guelph Thesis/Project Title: The role of gamma-delta T-cells in immunity to Marek's Disease Present Position: unknown
2013/4 - 2016/1 Academic Advisor	Alicia Coyne (Completed) , University of Guelph Thesis/Project Title: Lactoferrin in milk of Holstein dairy cows. Present Position: unknown

Doctorate [n=10]

2018/9 - 2022/9 Principal Supervisor	Tess Altvater-Hughes (In Progress) , University of Guelph Thesis/Project Title: HIR/Immunity+ Colostrum Present Position: gradulate student
2018/9 - 2022/9 Principal Supervisor	Shannon Beard (In Progress) , Univeristy of Guelph Thesis/Project Title: HIR/Immunity+ Genomics for Angus beef Present Position: gradulate student
2017/9 - 2022/9 Principal Supervisor	Shannon Cartwright (In Progress) , University of Guelph Thesis/Project Title: Impact of Climate Variability on the Resilience of Dairy Cattle Classified as High, Average or Low Immune Responders Present Position: gradulate student
2014/9 - 2018/8 Academic Advisor	Kevin Stinton (Completed) , University of Guelph Thesis/Project Title: Immune response to Johne's Disease in cattle. Present Position: researcher
2014/9 - 2019/11 Principal Supervisor	Mehdi Emam (Completed) , University of Guelph Thesis/Project Title: Cellular Immuno-Genomics: A Systems Biology Approach to Investigate Genetic Regulation of Macrophage Function and Disease Resistance of Dairy Cattle Present Position: Post-doctoral Fellow, McGill
2014/9 - 2017/1 Academic Advisor	Alison Fleming (Completed) , University of Guelph Thesis/Project Title: Milk spectral analysis. Present Position: industry
2013/7 - 2016/7 Academic Advisor	Joshua Aleri (Completed) , University of Melbourne Thesis/Project Title: Evaluating high and low immune response in pasture-based cattle in Australia Present Position: Faculty at the University of Melbourne
2013/4 - 2016/4 Academic Advisor	Neda Barjestah (Completed) , University of Guelph Thesis/Project Title: Avian Influenza and Immune Response. Present Position: Faculty at the University of Montreal
2010/1 - 2016/10 Principal Supervisor	Lauri Wagter-Lesperance (Completed) , University of Guelph Thesis/Project Title: Genetic regulation of high and low immune responding dairy cattle Present Position: Research Associate
2009/1 - 2017/1 Principal Supervisor	Marlene Paibomesai (Completed) , University of Guelph Thesis/Project Title: Genetic and epigenetic regulation regulation of bovine immune response Present Position: Dairy Specialist for OMAFRA

Post-doctorate [n=4]

2017/9 - 2020/9 Co-Supervisor	Alexandra Livernois (Completed) , University of Guelph Thesis/Project Title: Breeding Livestock for Climate Resilience Present Position: Scientist
2017/2 - 2019/1 Principal Supervisor	Lauri Wagter-Lesperance (Completed) , University of Guelph Thesis/Project Title: High Immune Response Technology Present Position: Project Lead and Regulatory Affairs Manager, Ontario Veterinary College

2016/1 - 2017/4 Principal Supervisor	Prithy Rupa (Completed) , University of Guelph Thesis/Project Title: Examining the utility of the High Immune Response Technology for use in commercial Swine herds Present Position: industry researcher
2016/1 - 2019/9 Principal Supervisor	Saeid Tabatabaei (Completed) , University of Tehran Thesis/Project Title: Genetic regulation of high and low immune response of diary cattle Present Position: gradulate student

Research Associate [n=5]

2019/2 - 2022/12 Principal Supervisor	Lauri Wagter-Lesperance (In Progress) , Ontario Veterinary College Thesis/Project Title: High Immune Response Technology Present Position: research associate
2018/12 - 2022/12 Principal Supervisor	Douglas Hodgins (In Progress) , University of Guelph Thesis/Project Title: Genetic Selection for Disease Resistance: Adapting Immunity+ /High Immune Response (HIR) Technology for Application in the Beef Industry Present Position: research associate
2014/9 - 2022/10 Principal Supervisor	Julie Schmied (In Progress) , University of Guelph Thesis/Project Title: High Immune Response technology for use in commercial swine herds: A broad based approach to disease resistance & Translation of the HIR Technology for use in Angus Beef Cattle Present Position: research associate
2014/5 - 2019/5 Co-Supervisor	Heba Atalla (Completed) , University of Guelph Thesis/Project Title: Assessing the bioactivity of immune-related microRNA in colostrum and milk from high and low immune responder cows Present Position: Lab Manager/Technician
2009/9 - 2018/11 Co-Supervisor	Douglas Hodgins (Completed) , University of Guelph Thesis/Project Title: Genetic Selection for Disease Resistance: Adapting Immunity+ /High Immune Response (HIR) Technology for Application in the Beef Industry Present Position: research associate

Technician [n=6]

2021/2 - 2023/12 Principal Supervisor	Danielle Naylor (In Progress) , University of Guelph Thesis/Project Title: Immunological and microbiome properties of bovine colostrum Present Position: research technician, university of Guelph
2020/9 - 2022/12 Principal Supervisor	Nasrin Satayesh Husseini (In Progress) , University of Guelph Thesis/Project Title: High Immune Response Technology for Cattle Present Position: research technician, university of Guelph
2019/5 - 2023/10 Principal Supervisor	Heba Atalla (In Progress) , University of Guelph Thesis/Project Title: General lab management Present Position: Research Lab Manager, university of Guelph
2017/10 - 2019/6 Principal Supervisor	Marnie McKechnie (Completed) , University of Guelph Thesis/Project Title: Genetic regulation of bovine immunity Present Position: Nursing resident
2014/9 - 2023/9 Principal Supervisor	Natasha Gallo (In Progress) , University of Guelph Thesis/Project Title: General Lab Managment Present Position: research technician, university of Guelph

2010/1 - 2019/12 Principal Supervisor	Leah Read (Completed) , University of Guelph Thesis/Project Title: General Lab Management Present Position: unknown, unknown

Event Administration

2020/1 - 2023/1	Scientific Committee Member, International Veterinary Immunology Symposium, Conference, 2020/8 - 2023/8
2020/1 - 2022/10	Member of planning committee, International Society for Developmental Origins of Health and Disease (DOHaD), Conference, 2021/10 - 2022/10
2016/8 - 2018/7	Member of Hosting Country, International Society of Animal Genetics 2018 to be held in Canada, Conference, 2018/7 - 2018/7
2015/1 - 2018/7	Committee Member, 30th World Buiatrics Congress, Japan, Conference, 2018/7 - 2018/7
2017/1 - 2018/2	Chair for Disease Resistance, World Congress on Genetics Applied to Livestock Production: New Zealand 2018, Conference, 2018/2 - 2018/2

Editorial Activities

2012/1 - 2022/7	Editorial Board, Iranian Journal of Immunology, Journal
1990/1 - 2022/7	Editorial Board, Animal Biotechnology, Journal

Expert Witness Activities

2022/6 - 2022/12	Expert witness, Queen's Bench Alberta, Canada, Calgary Alberta Expert witness in immunology,
2021/9 - 2022/7	Expert witness, COURT OF QUEEN'S BENCH OF ALBERTA, JUSTICE CENTRE for CONSTITUTION, Canada, Edmonton Immunology expert
2021/9 - 2022/7	Expert witness, Juror Selection Case, ONTARIO SUPERIOR COURT OF JUSTICE (Toronto Region), Canada, Toronto Immunology expert

Organizational Review Activities

2014/1 - 2022/12	Ad hoc Reviewer, American Association of Dairy Science Ad hoc reviewer recognized by ADSA
2010/7 - 2020/12	Ad hoc reviewer, NSERC Ad hoc reviewer for NSERC grants as requested
2010/1 - 2020/12	Ad hoc Reviewer, Journals: Vet Immunol Immunopathol, BMC Immunol, BMC Genomics etc. Act as ad hoc reviewer for a number of journals including but not limited to Journal of Dairy Science, Canadian Journal of Vet Research. BMC Genomics and BMC Immunology
2014/1 - 2019/12	OMAFRA HQP Review Panel Member, Government of Ontario Panel Member for Reviewing and Selection of Annual OMAF HQP Graduate Scholarship Applications

International Collaboration Activities

2016/1 - 2020/12	Collaborator, Australia This is a collaboration in the area breeding disease resistant livestock based on enhanced immune responses that stemmed from earlier collaborations with this group. The PI is Dr Brad Hine at CSIRO. Other collaborators are Drs Jenny Pyrce and Andrew Fisher at University of Melbourne.
2016/3 - 2018/3	Collaborator, New Zealand This is a collaboration with Dr. Shannon Clark at AgResearch in Invermay, New Zealand. The project involves testing the High Immune Response Technology for use in NZ dairy sheep. A grant proposal has been submitted.
2013/6 - 2017/12	Collaborator, Australia Research collaboration with scientists at University of Melbourne and CSRIO in Armidale to evaluate immune response in pasture-based cattle. Activities include serving on a graduate student committee and hosting students for training in my lab as part of their training.

Committee Memberships

2020/1 - 2022/7	Committee Member, Steering and Scientific Committee, Canadian Covid Care Alliance
2015/1 - 2022/7	Co-chair, Health and Safety Committee - Department of Pathobiology and Animal Health Laboratory, University of Guelph
2014/1 - 2018/7	Committee Member, 30th World Buiatrics Congress Advisory Committee, World Buiatrics Congress

Other Memberships

1990/1 - 2022/12	Member, American Association of Veterinary Immunologists
1990/1 - 2022/12	Member, American Association of Animal Science
1990/1 - 2022/12	Member, International Society of Animal Genetics
1990/1 - 2022/12	Member, American Association of Dairy Science
1990/1 - 2022/12	Member, Canadian Society for Immunology

Presentations

1. (2022). Naturally acquired immunity. Woodbridge Science Panel, Woodbridge, Canada
   Invited?: Yes, Keynote?: No
2. (2022). Naturally acquired immunity. Parliament Hill Event, Ottawa, Canada
   Invited?: Yes, Keynote?: No
3. (2022). Immunoceuticals for Health. Canadian Covid Care Alliance RoundTable, Online, Canada
   Invited?: Yes, Keynote?: No
4. (2022). Infection and Immunity to SARS-CoV-2. Covid-19 2nd World Congress of Doctors for Life and the World Council for Health, Iguazu Falls, Brazil
   Invited?: Yes, Keynote?: No
5. (2022). Immunoceuticals for health. Canadian Centre for Learning, Online, Canada
   Invited?: Yes, Keynote?: No

6. (2022). Naturally acquired immunity. Fergus Supper Club Presentation, Fergus, Canada
Invited?: Yes, Keynote?: No

7. (2022). Naturally acquired immunity. Toronto Police Association, Online, Canada
Invited?: Yes, Keynote?: No

8. (2022). Immunoceuticals for Health. ReFound Ed, New Market, Canada
Invited?: Yes, Keynote?: No

9. (2021). Infection and Immunity to SARS-CoV-2. Covid-19 1st World Congress of Doctors for Life and the World Council for Health, Brazil
Invited?: Yes, Keynote?: No

10. (2020). HIR™/Immunity+ Technology. Private Industry Update to Semex Canada, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes

11. (2020). High Immune Response (HIR™) Technology. Private industry presentation to Canadian Angus Association, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No

12. (2020). Genetic Selection for Improving Livestock Health: HIR™ and Other Technologies. Academy of Dairy Veterinary Consultants Meeting, Portland, United States
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No

13. (2020). Genetic Selection for Improving Livestock Health: High Immune Response Technology. Feedlot Health Management Services Meeting, Okotoks, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No

14. (2020). Breeding Livestock for Resilience: The High Immune Response Technology. FarmSmart Conference, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes

15. (2020). Genetic and Genomic Selection to Improve Livestock Health, Welfare and Productivity: High Immune Response Technology. American Association of Bovine Practitioners Webinar, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No

16. (2019). Understanding Genetics, Genomics and Epigenetic regulation of the Bovine Immune System. American College of Veterinary Internal Medicine Forum, Phoenix, United States
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes

17. (2019). Immunogenetic control of calf health and bovine mammary health. Private Industry Update to Semex Canada, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes

18. (2019). Genetic and Genomic Approaches to Selecting Cattle for Improved Immunity. Private Industry Update to Semex Canada, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes

19. (2019). Genetic control of specific and natural antibody production in Canadian Holsteins. Animal Genetics and Diseases, Hinxton, United Kingdom
Main Audience: Researcher
Invited?: No, Keynote?: No

20. (2019). The High Immune Response and other Genomic Technologies for Health. American College of Veterinary Internal Medicine Forum, Phoenix, United States
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes

21. (2018). Genome-wide Association and Functional Annotation of Positional Candidate Genes for Immune Response in Canadian Dairy Cattle. World Congress of Genetics Applied to Livestock Production, Auckland, New Zealand
Main Audience: Researcher
Invited?: Yes, Keynote?: No

22. (2018). Evaluation of Milk and Colostrum Quality of HIR-Classified Cattle. Private Industry Presentation to GayLea Canada, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes

23. (2017). Genetic Regulation of Immune Response & Implications to Disease: The High Immune Response (HIR™) Technology. Spain's National Association of Bovine Specialists (ANEMBE), XXII Congress, Pamplona, Spain
Main Audience: Researcher
Invited?: Yes, Keynote?: No

24. (2017). Practical Implications of Breeding for Immunity in Dairy and Beef Cattle: A Short Summary. Spain's National Association of Bovine Specialists (ANEMBE), XXII Congress, Pamplona, Spain
Main Audience: Researcher
Invited?: Yes, Keynote?: No

25. (2017). Practical Implications of Breeding for Immunity in Dairy and Beef Cattle: A Short Summary. Guest Seminar: University of Madrid, Madrid, Spain
Main Audience: Researcher
Invited?: Yes, Keynote?: No

26. (2017). Genetic Regulation of Immune Response & Implications to Disease: The High Immune Response (HIR™) Technology. Guest Seminar: University of Madrid, Madrid, Spain
Main Audience: Researcher
Invited?: Yes, Keynote?: No

27. (2016). High Immune Response Technology and Breeding Selection. Dairy Strong Conference, Madison, Wisconsin, United States
Invited?: Yes, Keynote?: No

28. (2016). Genetic & Genomic Selection to Improve Health of Dairy Cattle: The High Immune Response (HIR™) Technology. Dairy Research and Innovation Day, Guelph, Ontario, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No

29. (2016). Immunogenetics Approaches to Improving Livestock Heath: The High Immune Response™ (HIR) Technology. University of Waikato and AgrResearch. Ruakura Campus seminar, Hamilton, New Zealand
Main Audience: Researcher
Invited?: Yes, Keynote?: No

30. (2016). Immunogenetics Approaches to Improving Livestock Heath: The High Immune Response™ (HIR) Technology. Invermay AgrResearch Centre. Main Campus seminar, Invermay, New Zealand
Invited?: Yes, Keynote?: No

31. Dr Julie Schmied (main presenter). (2016). Breeding Livestock for Disease Resistance. Livestock Research Innovation Corporation (LRIC) Annual General Meeting – Disruptive Technologies for Livestock, Guelph, Canada
Main Audience: Decision Maker
Invited?: Yes, Keynote?: No

32. (2016). Genetic & Genomic Selection to Improve Health of Dairy Cattle: The High Immune Response (HIR™) Technology. IP and Entrepreneurship Workshop. University of Guelph, Guelph, Ontario, Canada
Invited?: Yes, Keynote?: No

33. (2016). Immunogenetics Approaches to Improving Dairy Heath: The High Immune Response™ (HIR) Technology. Iowa State University Animal Science Department Seminar, Ames, Iowa, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No

34. (2016). Immunogenetics Approaches to Improving Livestock Heath: The High Immune Response™ (HIR) Technology. University of Melbourne Veterinary School seminar, Melbourne, Australia
Main Audience: Researcher
Invited?: Yes, Keynote?: No

35. (2016). Adapting the High Immune Response (HIR™) Technology to Improve Beef Cattle Health. OMAFRA Gryphon's LAAIR Showcase, Guelph, Ontario, Canada
Invited?: Yes, Keynote?: No

36. (2016). Immunogenetics Approaches to Improving Livestock Heath: The High Immune Response™ (HIR) Technology. AgrResearch Otago Campus seminar, Mosgiel, New Zealand
Main Audience: Researcher
Invited?: Yes, Keynote?: No

37. (2016). Breeding Livestock for Disease Resistance - A Scientific Journey. Iowa State University, Animal Science Graduate Student Mentor Breakfast Seminar, Ames, Iowa, United States
Invited?: Yes, Keynote?: No

38. (2016). Immunogenetics Approaches to Improving Livestock Heath: The High Immune Response™ (HIR) Technology. La Trobe University seminar, Melbourne, Australia
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Broadcast Interviews

2022/06/16 - 2022/07/27	Immunoceuticals for Health, Dr. Julie Ponesse Publications, The Democracy Fund
2022/02/12 - 2022/07/27	Naturally acquired immunity, Issues, Faytene TV
2016/01/08 - 2016/06/14	Bovine Immunity, Semex Immunity+ at Schwab Dairy, https://www.youtube.com/watch?v=KRN6r-v9mts
2013/05/07 - 2016/06/14	High Immune Response, Agri Food and Rural Link - University of Guelph, https://www.youtube.com/watch?v=bPgTokY0630
2012/12/04 - 2016/06/14	Immunity+, Youtube video by Semex Alliance, https://www.youtube.com/watch?v=skttmww8ygc

Text Interviews

2020/10/01	Helping Ontario beef producers make better herd management and breeding decisions, Ontario Beef Magazine
2018/05/22	High Immune Response technology improves genetics and herd health, M2 Magazine: Magazine for Mastitis and Milk Quality for the Dairy Professional
2017/09/28	Breeding cows with superior immune response, Dairy Global Digital Magazine

2017/07/25	Helping pigs to be better prepared for disease pressure, Pig Progress Digital Magazine
2016/06/30	Bred for Healthier Living, University of Guelph, Food Institute Webpage Article

Publications

Journal Articles

1. T. Sullivan, A. Sharma, K. Lamers, C. White, B.A. Mallard, A. Cánovas, N.A. Karrow. (2022). Dynamic changes in Holstein heifer circulatory stress biomarkers in response to lipopolysaccharide immune challenge. Veterinary Immunology and Immunopathology. 248: 110426.
   Published
   Refereed?: Yes
2. Nasrin, Husseini; C, Beard Shannon; C, Hodgins Douglas; Christy, Barnes; Elfleda, Chik; A, Mallard Bonnie. (2022). Immuno-phenotyping of Canadian beef cattle: adaptation of the high immune response methodology for utilization in beef cattle. Translational animal science. 6(1): txac006.
   Published
   Refereed?: Yes
3. Altvater-Hughes, T., Hodgins, D., Wagter-Lesperance, L., Beard, S., Cartwright, S., and Mallard. B. (2022). Concentration and heritability of immunoglobulin G and natural antibody immunoglobulin M in dairy and beef colostrum along with serum total protein in their calves. Journal of Animal Science.
   Published
   Refereed?: Yes
4. Cartwright, S. L., Schmied, J., Livernois, A. and B. A. Mallard. (2022). Effect of In-vivo Heat Challenge on Physiological Parameters and Function of Blood Mononculear Cells in Immune Phenotyped Dairy Cattle. Veterinary Immunology and Immunopathology. 246
   Published
   Refereed?: Yes
5. Shannon L. Cartwright, Marnie McKechnie, Julie Schmied, Alexandra M. Livernois & Bonnie A. Mallard. (2021). Effect of in-vitro heat stress challenge on the function of blood mononuclear cells from dairy cattle ranked as high, average and low immune responders. BMC Veterinary Research. 17: 233.
   Published
   Refereed?: Yes
6. Mikayla, Ross; Heba, Atalla; Niel, Karrow; A, Mallard Bonnie. (2021). The bioactivity of colostrum and milk exosomes of high, average, and low immune responder cows on human intestinal epithelial cells. Journal of Dairy Science. 104(3): 2499-2510.
   Published
   Refereed?: Yes
7. Naylor, D.; Sharma, A.; Li, Z.; Monteith, G.; Mallard, B. A.; Bergeron, R.; Baes, C.; Karrow, N. A. (2021). Endotoxin-induced cytokine, chemokine and white blood cell profiles of variable stress-responding sheep. Stress.
   Published
   Refereed?: Yes
8. Mehdi Emam, Saeid Tabatabaei, Mehdi Sargolzaei, and Bonnie Mallard. (2021). Response to Oxidative Burst-Induced Hypoxia Is Associated With Macrophage Inflammatory Profiles as Revealed by Cellular Genome-Wide Association. Frontiers in Immunology. 12: 688503.
   Published
   Refereed?: Yes

9. A, Karrow Niel; K, Shandilya Umesh; Steven, Pelech; Lauraine, Wagter-Lesperance; Deanna, McLeod; Byram, Bridle; A, Mallard Bonnie. (2021). Maternal COVID-19 Vaccination and Its Potential Impact on Fetal and Neonatal Development. Vaccines. 9(11)
Published
Refereed?: Yes

10. A. M. Livernois, B. A. Mallard, S. L. Cartwright & A. Cánovas. (2021). Heat stress and immune response phenotype affect DNA methylation in blood mononuclear cells from Holstein dairy cows. Scientific Reports. 11: 11371.
Published
Refereed?: Yes, Open Access?: Yes

11. Naylor, D., Sharma, A., Li, Z., Monteith, G., Sullivan, T., Canovas, A., Mallard, B.A, Baes, C., & Karrow N.A. (2020). Short communication: Characterizing ovine serum stress biomarkers during endotoxemia. J. Dairy Sci.103(6): 5501-5508.
Published
Refereed?: Yes

12. Sharma, A., Shandilya, U.K., Sullivan, T., Naylor, D., Canovas, A., Mallard, B.A,, & Karrow, N.A. (2020). Identification of Ovine Serum miRNAs Following Bacterial Lipopolysaccharide Challenge. Int. J. Mol. Sci.21(21)
Accepted
Refereed?: Yes, Open Access?: Yes

13. Emam, M., Cánovas, A., Islas-Trejo, A.D., Fonseca, P.A.S., Medrano, J.F., & Mallard, B. (2020). Transcriptomic Profiles of Monocyte-Derived Macrophages in Response to Escherichia coli is Associated with the Host Genetics. Sci. Rep.10(1): 271.
Accepted
Refereed?: Yes

14. Aleri, J. W., Hine, B. C., Pyman, M.F., Mansell, P. D., Wales, W.J., Mallard, B., Stevenson, M. A., & Fisher, A. D. (2019). Associations between immune competence, stress responsiveness, and production in Holstein-Friesian and Holstein-Friesian × Jersey heifers reared in a pasture-based production system in Australia.J. Dairy Sci.102(4): 3282-3294.
Published
Refereed?: Yes

15. Asselstine, V., Miglior, F., Suárez-Vega, A., Fonseca, P. A.S., Mallard, B., Karrow, N., Islas-Trejo, A., Medrano, J. F., & Cánovas, A. (2019). Genetic mechanisms regulating the host response during mastitis.J. Dairy Sci.102(10): 9043-9059.
Published
Refereed?: Yes

16. Emam, M., Livernois, A., Paibomesai, M., Atalla, H., & Mallard, B. (2019). Genetic and Epigenetic Regulation of Immune Response and Resistance to Infectious Diseases in Domestic Ruminants.Vet. Clin. North Am. Food Anim. Pract.35(3): 405-429.
Published
Refereed?: Yes

17. Emam, M., Tabatabaei, S., Sargolzaei, M., Sharif, S., Schenkel, F., Mallard, B. (2019). The effect of host genetics on in vitro performance of bovine monocyte-derived macrophages. J. Dairy Sci.102(10): 9107-9116.
Published
Refereed?: Yes

18. Emam, M., Livernois, A., Paibomesai, M., Atalla, H., & Mallard, B. (2019). Genetic and Epigenetic Regulation of Immune Response and Resistance to Infectious Diseases in Domestic Ruminants. Vet. Clin. North Am. Food Anim. Pract.35(3): 405-429.
Published
Refereed?: Yes

19. de Klerk, B., Emam, M., Thompson-Crispi, K., Sargolzaei, M., van der Poel, J.J., & Mallard, B. A. (2018). A genome-wide association study for natural antibodies measured in blood of Canadian Holstein cows. BMC Genomics. 19(694)
Published
Refereed?: Yes

20. Paibomesai, M. A., Sharif, S., Karrow, N., & Mallard, B.A. (2018). Type I and type II cytokine production of CD4+ T-cells in immune response biased dairy cattle around calving. Vet. Immunol. Immunopathol.199(May): 70-76.
Published
Refereed?: Yes

21. Fleming A, Schenkel FS, Malchiodi F, Ali RA, Corredig M, Mallard B, Sargolzaei M, Jamrozik, J, Johnston, J, Miglior F. (2018). Genetic correlations of mid-infrared predicted milk fatty acid groups with milk production traits. J. Dairy Sci.10(5): 4295-4306.
Published
Refereed?: Yes, Open Access?: No

22. Cartwright, S.L, Malchiodi, F, Thompson-Crispi, K, Miglior, F, Mallard, B.A. (2017). Short Communication: Prevalence of Digital Dermatitis in Canadian Dairy Cattle classified as High, Average or 23 Low Antibody and Cell-Mediated Immune Responders. J. Dairy Sci.100(10): 8409-8413.
Published
Refereed?: Yes, Open Access?: No

23. Fleming A, Schenkel FS, Chen J, Malchiodi F, Bonfatti V, Ali RA, Mallard B, Corredig M, Miglior F. (2017). Prediction of milk fatty acid content with mid-infrared spectroscopy in Canadian dairy cattle using differently distributed model development sets. J. Dairy Sci.100(6): 5073-5081.
Published
Refereed?: Yes, Open Access?: No

24. Fleming, A, Schenkel, FS, Chen, F, Malchiodi, RA, Ali, B, Mallard, B, Sargolzaei, M, Cerredig, M, Miglior, F. (2017). Variation in fat globule size in bovine milk and its prediction using mid-infrared spectroscopy. J. Dairy Sci.100(3): 1640-1649.
Published
Refereed?: Yes, Open Access?: No

25. Fleming A, Schenkel FS, Koeck A, Malchiodi F, Ali RA, Corredig M, Mallard B, Sargolzaei M, Miglior F. (2017). Heritabilities of measured and mid-infrared predicted milk fat globule size, milk fat and protein percentages, and their genetic correlations. J. Dairy Sci.100(5): 3735-3741.
Published
Refereed?: Yes, Open Access?: No

26. Martin, C.E, Paibomesai, M.A, Emam S.M, Gallienne, J, Hine B.C, Thompson-Crispi K.A, Mallard, B. A. (2016). Short Communication: Cytokine profiles from blood mononuclear cells of dairy cows classified with divergent immune response phenotypes. J. Dairy Sci.99(3): 2364-2371.
Published
Refereed?: Yes, Open Access?: No

27. Atalla, H; Mallard, B; Karrow, N. (2016). P3044 Characterization of exosomal immune-related micrornas in colostrum and milk from average, low and high immune responder cows.J. Animal. Sci.94: 74-75.
Published
Refereed?: Yes

28. Aleri, JW, Hine, BC, Pyman, MF, Mansell, PD, Wales, WJ, Mallard, B, Fisher, AD. (2016). An assessment of immune and stress responsiveness in Holstein-Friesan cows selected for high and low feed conversion efficiency. Animal Production Science.
Published
Refereed?: Yes

29. Aleri, JW., Hine, BC., Pyman, MF., Mansell, PD., Wales, WJ., Mallard, BA., Fisher, AD. (2016). Periparturient immunosupression and strategies to improve dairy cow health during the periparturient period.Res. Vet. Sci.108: 8-17.
Published
Refereed?: Yes, Open Access?: No

30. Stoop CL, Thompson-Crispi KA, Cartwright SL, Mallard BA. (2016). Short communication: Variation in production parameters among Canadian Holstein cows classified as high, average, and low immune responders. J. Dairy Sci.99(6): 4870-4874.
Published
Refereed?: Yes, Open Access?: No

31. Fleming, K, Thompson-Crispi, KA, Hodgins, DC, Miglior, F, Corredig, M, Mallard BA. (2016). Short communication: Variation of total immunoglobulin G and ?-lactoglobulin concentrations in colostrum and milk from Canadian Holsteins classified as high, average, or low immune responders.J. Dairy Sci.99(3): 2358-2363.
Published
Refereed?: Yes, Open Access?: No

Book Chapters

1. Mallard, Bonnie; Emam, Mehdi; Cartwright, Shannon; Altvater-Hughes, Tess; Livernois, Alexandra; Wagter-Lesperance, Lauri; Atalla, Heba; Hine, Brad; Aleri, Joshua; Fisher, Andrew,Douglas C. Hodgins. (2020). Advances in understanding immune response in dairy cattle. Francis Dodds et al. Improving dairy herd health. 1(1): 1.
Published, Burleigh Dodds Science Publishing
Refereed?: Yes

2. Stear, M; Mallard, B; Groth, D; Fairlie-Clarke, K; Jonsson, N. (2016). Genetic Variation in Immunity and Disease Resistance in Livestock. Webster, J.Achieving Sustainable Production of Cow's Milk. (2): 1-41.
Published, Burleigh Dodds Science Publishing
Refereed?: Yes

Reports

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1. Beard, S.C.; Hodgins, D.C.; Schmied, J.; Caswell, J.; Devani, K.; Lohuis, M.; Miller, S.; Schenkel, F.S.; Mallard, B.A. (2021). Heritability estimates of antibody- and cell-mediated immune response in North American Angus beef cattle. American Animal Science Association Annual Meeting, Louisville, United States
   Conference Date: 2021/7
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   Refereed?: No, Invited?: No

2. Altvater-Hughes, T.; Hodgins, D.; Wagter-Lesperance, L.; Mallard, B. (2020). Comparing Colostral Natural Antibody Titers in High, Average, and Low Immune Responder Dairy and Beef Cows. Conference of Research Workers in Animal Diseases, Online,
   Conference Date: 2020/12
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   Refereed?: No, Invited?: No

3. Altvater-Hughes., T; Hodgins., D; Wagter-Lesperance., L; Read., L; Gallo., N; Mallard., B. (2019). Evaluating Immunoglobulin G and Natural Antibody IgM in the Colostrum Beef and Dairy Cows and the Effect it has on Passive Transfer in Their Calves. Smart Calf Rearing Conference, Guelph, Canada
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4. Suarez-Vega, A.; Borkowski, E. A.; Dixon, S.; Karrow, N. A.; Peregrine, A. S.; Menzies, P.; Mallard, B. A.; Boareki, M. N.; Schenkel, F. S.; Canovas, A. (2019). Identification of novel transcripts associated with parasite resistance in sheep. Ontario Sheep Farmers Convention, Nottawasaga, Canada
   Conference Date: 2019/10
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   Refereed?: No, Invited?: No

5. Altvater-Hughes.T., Hodgins., D, Wagter-Lesperance., L, Read., L, Gallo., N, and Mallard., B. (2019). Evaluating Differences in Concentrations of Total Immunoglobulin G and Natural Antibody in Colostrum of Beef and Dairy Cows. Dairy Cattle Breeding and Genetics Conference, Guelph, Canada
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   Refereed?: No, Invited?: No

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7. Cartwright, S.L.; Livernois, A.; McKechnie, M; Schmied, J.; Mallard, B.A. (2019). Effect of Heat Stress on Peripheral Blood Mononuclear Cell (PBMC) Function of Dairy Cows ranked as High, Average or Low Immune Responders. International Veterinary Immunology Symposium, Seattle, United States
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10. Suarez-Vega, A.; Borkowski, E. A.; Dixon, S.; Karrow, N. A.; Peregrine, A. S.; Menzies, P.; Mallard, B. A.; Boareki, M. N.; Schenkel, F. S.; Arranz, J.J.; Tosser-Klopp, G.; Klopp, C.; Canovas, A. (2019). Identification of differentially expressed lncRNAs linked to gastrointestinal nematode infection in variable stress-responder sheep.Ontario Small Ruminant Veterinary Conference, Guelph, Canada
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11. Suarez-Vega, A.; Borkowski, E.A.; Dixon, S.; Karrow, N.A.; Peregrine, A.S.; Menzies, P.; Mallard, B.A.; Boareki, M.N.; Arranz, J.J.; Tosser-Klopp, G.; Klopp, C.; Canovas, A. (2019). Identification of lncRNAs regulating variable stress-responding sheep naturally exposed to gastrointestinal nematode parasites. Proceedings of the 37th International Conference on Animal Genetics. International Society for Animal Genetics, LLeida, Spain
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Refereed?: Yes, Invited?: No

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Conference Date: 2016/7
Abstract
Accepted
Refereed?: Yes, Invited?: No

Intellectual Property

Patents

1. BOVINE MONOCYTE-DERIVED MACROPHAGE IN CULTURE SYSTEM AND METHODS FOR MEASURING INNATE IMMUNITY.Canada. 62/878,3770. 2019/09/03.
   Patent Status: Pending
   Inventors: Mallard and Emam
   This method is being licensed to Canadian cattle breeding company. Previous patents from Mallard et al have also been licensed for use by Canada's largest dairy genetics company, the Semex Alliance. This new patent adds breadth and utility to existing patents in the area of breeding livestock for health.

Licenses

1. BOVINE MONOCYTE-DERIVED MACROPHAGE IN CULTURE SYSTEM AND METHODS FOR MEASURING INNATE IMMUNITY PCT/CA2020/050997
   Granted
   Filing Date: 2020/07/17
   A license to use this patented technology to measure nitric oxide in bovine monocytes and related trade secrets has been granted to the Canadian corporation, the Semex Alliance. Although the patent is still pending the license for use has been granted.

This is Exhibit "**B**" to the Affidavit of

Bonnie Mallard, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

1: Karrow NA, Shandilya UK, Pelech S, Wagter-Lesperance L, McLeod D, Bridle B, Mallard BA. Maternal COVID-19 Vaccination and Its Potential Impact on Fetal and Neonatal Development. Vaccines (Basel). 2021 Nov 18;9(11):1351. doi: 10.3390/vaccines9111351. Erratum in: Vaccines (Basel). 2022 Nov 14;10(11): PMID: 34835282; PMCID: PMC8617890.

2: Tieu S, Charchoglyan A, Paulsen L, Wagter-Lesperance LC, Shandilya UK, Bridle BW, Mallard BA, Karrow NA. N-Acetylcysteine and Its Immunomodulatory Properties in Humans and Domesticated Animals. Antioxidants (Basel). 2023 Oct 16;12(10):1867. doi: 10.3390/antiox12101867. PMID: 37891946; PMCID: PMC10604897.

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5: Tao W, Mallard B, Karrow N, Bridle B. Construction and application of a bovine immune-endocrine cDNA microarray. Vet Immunol Immunopathol. 2004 Sep;101(1-2):1-17. doi: 10.1016/j.vetimm.2003.10.011. PMID: 15261689.

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7: Nino-Soto MI, Jozani RJ, Bridle B, Mallard BA. Analysis of gene expression patterns by microarray hybridization in blood mononuclear cells of SLA-DRB1 defined Canadian Yorkshire pigs. BMC Res Notes. 2008 Jun 23;1:31. doi: 10.1186/1756-0500-1-31. PMID: 18710484; PMCID: PMC2529311.

8: Bridle BW, Wilkie BN, Jevnikar AM, Mallard BA. Deviation of xenogeneic immune response and bystander suppression in rats fed porcine blood mononuclear cells. Transpl Immunol. 2007 Jun;17(4):262-70. doi: 10.1016/j.trim.2007.01.010. Epub 2007 Mar 5. PMID: 17493529.

9: Nino-Soto MI, Jozani RJ, Bridle B, Mallard BA. CDNA microarray analysis of gene expression patterns in blood mononuclear cells of SLA-DRB1-defined Yorkshire pigs. Dev Biol (Basel). 2008;132:321-325. doi: 10.1159/000317177. PMID: 18817320.

10: Bridle BW, Wilkie BN, Jevnikar AM, Mallard BA. Rat genotype influences quantitative and qualitative aspects of xenogeneic immune response to pig blood mononuclear cells. Xenotransplantation. 2006 Jul;13(4):299-307. doi: 10.1111/j.1399-3089.2006.00306.x. PMID: 16768723.

This is Exhibit "C" to the Affidavit of

Bonnie Mallard, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

U of G Immunologist Has Concerns Over COVID-19 Vaccine Candidates

Prof. Byram Bridle

Two drug makers recently announced promising interim results for two COVID-19 vaccine candidates, but a University of Guelph viral immunologist says he has reservations.

Prof. Byram Bridle studies oncolytic viruses (viruses that target cancer cells) in U of G's Department of Pathobiology. He recently received provincial research funding to adapt the technology to develop a vaccine against SARS-CoV-2, the pandemic coronavirus.

Like many others, Bridle said he worries that Pfizer and Moderna released their interim test results as a press release. Without full scrutiny of the results, he said, many questions are left unanswered.

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"Not enough data has been released to know how well the vaccine prevents COVID-19, or if it can weaken symptoms," he said, "nor do we know how protective the vaccine will be for those who are most susceptible to severe cases."

For Bridle, a larger concern is the lack of data on the immune response offered by the vaccines, which are called subunit vaccines because they use a fragment of the virus to trigger an immune response.

"Subunit vaccines like these can be misinterpreted by the immune system as an extracellular pathogen," he said. "That creates the possibility that those who receive such a vaccine might have a 'bias' imprinted on their immune system that could cause them to respond sub-optimally to natural infections with future coronaviruses."

Bridle said the companies provided no data about the vaccine's effect on immunological memory, "which is the entire point of a vaccine. If the memory response is weak and wanes too quickly, those who receive the vaccine will not be protected over the long term."

He recently co-wrote a commentary on this topic for *Conversation Canada* with pathobiology professor Shayan Sharif, associate dean of research and graduate studies in U of G's Ontario Veterinary College.

Bridle is available for interviews this week.

Contact:

Prof. Byram Bridle
bbridle@uoguelph.ca

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Posted Thursday, November 19, 2020
Updated Thursday, November 19, 2020
Lead photo: Dr. Byram Bridle

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U of G Vaccine Researcher Makes Headlines

Prof Byram Bridle

Prof. Byram Bridle, with the Department of Pathobiology at U of G's Ontario Veterinary College, appeared Sunday on *Global TV's The West Block* with Mercedes Stephenson for a segment on whether hopes for a COVID-19 vaccine within the next year are misplaced.

Bridle told the show that Canadians need to come to terms with how unlikely such a time frame is.

"I'm not going to say it's impossible, but I would say it's highly improbable," he said. "...Everybody wants hope, and the reason why I'm speaking out, though, is that false hope can be really problematic."

Bridle also spoke to *The Globe and Mail* for an article about it's important for most people to get the vaccine once it's available, to build "herd immunity." Bridle noted that he is worried that rushing a vaccine out to the market could undermine public trust in that vaccine which might lead to poor uptake of the vaccine.

"As soon as you use terms like 'warp speed,' it creates the impression that corners are being cut and a lot of people will question the safety of the vaccine," he said.

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Bridle raised similar concerns in a recent *Conversation Canada* commentary he wrote with pathobiology colleague Prof. Shayan Sharif, associate dean of research and graduate studies at OVC. In that piece, they argued that it may not be possible to develop an effective COVID vaccine at "warp speed."

"We contend that a safe and effective vaccine against COVID-19 most likely cannot be made available to the public in time to make a substantial difference to the natural outcome of this pandemic," they wrote.

Bridle's team was one of 15 research teams across Ontario that recently received rapid provincial research funding to pursue research to develop a vaccine against the pandemic virus. They hope to adapt technology they developed that uses viruses to deliver cancer therapies.

Their plan is to develop avian and adenoviruses that could deliver proteins that would help humans fight off the coronavirus that causes COVID-19.

Watch the West Block segment here

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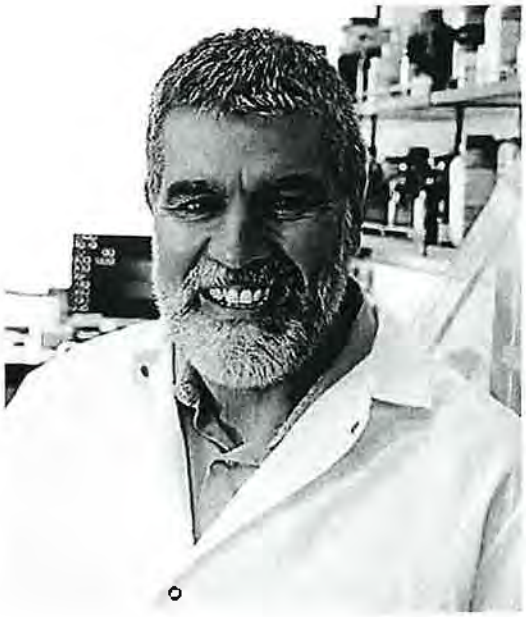
The Guardian Consults Virologist on Children's Immunity Concerns



Dr. Byram Bridle

Dr. Byram Bridle, a professor of immunology with the Department of Pathobiology at U of G's Ontario Veterinary College, spoke to *The Guardian* newspaper in the U.K. about whether extended quarantines might be harmful to children's immune systems.

Bridle said he's concerned that limiting children's exposure to the natural world, as has been done often in the last year, could lead to a rise in immunological disorders in children. He noted that the immune systems of young children go through an important period of immune system development before they reach the age of six.

Bridle studies oncolytic viruses and has received provincial research funding to adapt technology to develop a vaccine against SARS-CoV-2, the coronavirus that causes COVID-19.

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Lead photo: Dr. Byram Bridle

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Immunologist Pens Commentary on Kids' Health in COVID-19

Dr. Byram Bridle

Dr. Byram Bridle, a professor of immunology with the Department of Pathobiology at U of G's Ontario Veterinary College, provided a commentary for the *Conversation Canada* about the potential health effects for children who have remained indoors for most of the last year because of the COVID-19 pandemic.

He argued that kids who have been living largely in sanitized homes may be at greater risk of developing hypersensitivities and autoimmune diseases.

"An unfortunate and under-appreciated long-term legacy of this pandemic will likely be a cluster of 'pandemic youth' that grow up to suffer higher-than-average rates of allergies, asthma and autoimmune diseases. This will hold true for children in all countries that enacted isolation policies," Bridle wrote.

The commentary was re-posted on *Business Insider*, the *National Post*, the *Philippine Canadian Inquirer* and elsewhere. *Conversation Canada* has also translated the

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commentary into French.

Bridle studies oncolytic viruses and has received provincial research funding to adapt technology to develop a vaccine against SARS-CoV-2, the coronavirus that causes COVID-19.

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Lead photo: Dr. Byram Bridle

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Published on Office of Research (https://www.uoguelph.ca/research)

Ontario Veterinary College COVID-19 Research Stories

Date Posted	Researcher(s)	Article
March 10, 2023	Scott Weese	CNN Consults Pathobiologist on COVID-19 in Rodents [1]
October 13, 2022	Melissa MacKay	Better Crisis Communication Needed in Health Emergencies: U of G Researchers [2]
June 30, 2022	Andria Jones-Bitton	Farmer Mental Health in Canada Worsened During Pandemic, U of G Research Finds [3]
June 27, 2022	Scott Weese Dorothee Bienzle	Canadian Press Highlights OVC Research on COVID-19 and Pets [4]
June 13, 2022	Scott Weese	Cat-to-Human Coronavirus Spread a Reminder of Need for Precautions: U of G Expert [5]
April 25, 2022	Matthew Pike	PhD Candidate's Research on COVID and Community Health Makes Headlines [6]
April 5, 2022	Scott Weese	National Geographic Consults Zoonosis Researcher on COVID-19 Spread in Animals [7]
March 16, 2022	Scott Weese	Toronto Star Speaks to Zoonosis Researcher on Dogs and Diseases [8]
March 16, 2022	Andrew Papadopoulos	A Lack Of Effective Canadian COVID-19 Communications Can Impact Public Trust, Study Finds [9]
March 3, 2022	Scott Weese	CNN Consults Zoonosis Researcher on COVID-19 in Deer [10]

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February 28, 2022	Scott Weese	Possible Case of Deer Spreading COVID-19 to Humans 'Concerning,' Says Veterinary Expert [11]
February 22, 2022	Scott Weese	New York Times Consults Veterinary Infectious Disease Specialist [12]
February 10, 2022	Scott Weese	OVC Chief of Infection Control Makes International Headlines [13]
February 3, 2022	Scott Weese	OVC Chief of Infection Control Makes Headlines on COVID in Deer [14]
January 19, 2022	Scott Weese	COVID-19 in Ontario Deer Unsurprising But Vigilance Needed: U of G Expert [15]
January 17, 2022	Glen Pyle	Myocarditis: COVID-19 Is a Much Bigger Risk to the Heart Than Vaccination [16]
January 18, 2022	Andrew Papadopoulos	Health Impact Assessment Uncovers Secondary Effects of Lockdowns and Physical Distancing [17]
December 16, 2021	Scott Weese	AP Consults U of G Infectious Disease Veterinarian [18]
December 8, 2021	Amy Greer	Toronto Star Consults U of G Epidemiologist on COVID in Schools [19]
December 2, 2021	Scott Weese	Zoonosis Expert Discusses First Case of COVID-19 Found in Canadian Wildlife [20]
November 17, 2021	Amy Greer	Study Shows Pandemic Public Health Measures May Have Targeted the Wrong Groups During the Virus' Second Wave [21]
November 12, 2021	Scott Weese	Canadian Press Consults Pathobiologist on COVID-19 in Minks [22]

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September 30, 2021	Amy Greer	Epidemiologist Discusses Rapid Testing in Schools With Globe and Mail [23]
September 1, 2021	Zvonimir Poljak	Evaluating animal health surveillance practices during the pandemic [24]
July 23, 2021	Lee Niel	Animal Behaviour Researcher Discusses Pandemic Pets With HuffPost [25]
July 6, 2021	Dorothee Bienzle Scott Weese	Pets at High Risk of COVID-19 Infection From Owners, U of G Research Finds [26]
July 6, 2021	Dorothee Bienzle	The susceptibility of pets to SARS-CoV-2 [27]
June 22, 2021	Katie Clow	Vector-borne Zoonosis Researcher Makes Headlines [28]
June 21, 2021	Amy Greer	U of G Epidemiologist Makes Headlines Discussing Schools [29]
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May 26, 2021	Glen Pyle	Researcher Discusses COVID Online Seminars With CBC Radio [31]
May 19, 2021	Dorothee Bienzle	Pathobiologist Discusses Minks and COVID-19 with Global News [32]
May 17, 2021	Byram Bridle	The Guardian Consults Virologist on Children's Immunity Concerns [33]
April 27, 2021	Scott Weese	Toronto Star Consults Zoonosis Researcher on Mink Farms [34]

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April 19, 2021	Glen Pyle	U of G Prof Aims to Inform Public, Dispel Myths on COVID-19 Through Science Explained [35]
April 1, 2021	Lawrence Goodridge Ed McBean Heather Murphy Marc Habash	U of G Researchers Testing Wastewater for New COVID-19 Variants [36]
March 25, 2021	Gabrielle Brankston Amy Greer	Many Canadian Employees Unable to Self-Isolate When Necessary, U of G Survey Finds [37]
March 24, 2021	Glen Pyle	Researchers Study COVID-19 and Heart Health Links [38]
March 23, 2021	Scott Weese	Veterinary Infectious Disease Researcher Discusses COVID-19 Variants in Pets [39]
February 11, 2021	Byram Bridle	5 Factors That Could Dictate the Success or Failure of the COVID-19 Vaccine Rollout [40]
February 11, 2021	Gabrielle Brankston Madhur Anand Monica Cojocaru	Three U of G Women Scientists Discuss How the Pandemic Has Affected Their Work [41]
January 4, 2021	Byram Bridle	CTV's W5 Features U of G Vaccine Researcher [42]
December 7, 2020	Lee Niel Anastasia Stellato	Dogs Separated From Owners Show Stress During Vet Visits, U of G Research Finds [43]
December 2, 2020	Scott Weese	NBC News Consults U of G Zoonotic Disease Expert [44]
December 2, 2020	Amy Greer	U of G Epidemiologist Makes Headlines on COVID-19 Spread [45]

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November 24, 2020	Byram W. Bridle Leonardo Susta Sarah Wootton	The Mink Link: How COVID-19 Mutations in Animals Affect Human Health [46]
November 19, 2020	Byram Bridle	U of G Immunologist Has Concerns Over COVID-19 Vaccine Candidates [47]
November 10, 2020	Amy Greer	Infectious Disease Modeller Discusses School Transmission With Global News [48]
October 28, 2020	Scott Weese	OVC Researcher on COVID-19 in Pets Makes Headlines [49]
October 28, 2020	Amy Greer	Toronto Star Consults U of G Disease Modeller on COVID in Schools [50]
October 14, 2020	Shayan Sharif	BBC News Discusses Vaccines with OVC Immunologist [51]
October 14, 2020	Scott Wees	Forbes, CBC News Consult U of G Veterinary Disease Expert [52]
October 8, 2020	Byram W. Bridle Shayan Sharif	Training Our Immune Systems: Why We Should Insist on a High-Quality COVID-19 Vaccine [53]
October 1, 2020	Lawrence Goodridge Ed McBean Andrew Papadopoulos Heather Murphy	U of G Researchers Testing University Residence Wastewater as Early Detector of COVID Outbreaks [54]
September 30, 2020	Katie Clow	U of G Online Survey to Evaluate Pandemic's Effects on Pets [55]
August 27, 2020	David Waltner-Toews	U of G Professor Emeritus Discusses Pandemics on TVO's The Agenda [56]
August 24, 2020	Amy Greer	U of G Infectious Disease Modeller Discusses Kindergarten

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		Reopenings [57]
August 4, 2020	Byram W. Bridle Shayan Sharif	OVC Experts Contributing to COVID-19 Fight [58]
July 29, 2020	Amy Greer	U of G Infectious Disease Modeller Discusses School Reopenings [59]
July 24, 2020	Byram W. Bridle Shayan Sharif	Why Vaccines Are Less Effective in the Elderly, and What It Means for COVID-19 [60]
July 15, 2020	Amy Greer	U of G Infectious Disease Modeller Makes Headlines [61]
July 14, 2020	Amy Greer	We Can Get Children Back to School Full Time, With the Right Strategy [62]
July 8, 2020	Amy Greer	Globe and Mail Consults U of G Disease Modeller [63]
June 30, 2020	Byram W. Bridle	National Geographic Consults U of G Immunologist [64]
June 23, 2020	Scott Weese	Using One Health-informed strategies to reduce COVID-19 impact on pets, livestock and wildlife [65]
June 22, 2020	Scott Weese	Veterinary Infectious Disease Expert Makes Headlines [66]
June 22, 2020	Byram W. Bridle	U of G Vaccine Researcher Makes Headlines [67]
June 19, 2020	Scott Weese	U of G Expert Urges Need for 'One Health' Approach to Fighting COVID-19 [68]
June 17, 2020	Byram W. Bridle Shayan Sharif	Short COVID-19 Vaccine Timelines Are Unrealistic and Put the Integrity of Scientists at Risk [69]

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June 1, 2020	Amy Greer	U of G's Amy Greer Featured on CBC's Quirks and Quarks [70]
May 28, 2020	Amy Greer	U of G Modelling Predicts COVID-19 Resurgence If Physical Distancing Relaxed [71]
May 26, 2020	Shayan Sharif Byram W. Bridle	Can Antibody Tests Tell Us Who Is Immune to COVID-19? [72]
May 21, 2020	Scott Weese	U of G Expert Discusses Adopting Pets During the Pandemic [73]
May 21, 2020	Byram Bridle Sarah Wootton Leo Susta	U of G COVID-19 Vaccine Research Awarded Provincial Funding [74]
May 13, 2020	David Waltner-Toews	U of G Prof Pens Book on Pandemics [75]
May 12, 2020	Amy Greer	Infectious Disease Expert Speaks with VICE [76]
May 11, 2020	Scott Weese	OVC Zoonosis Expert Speaks to Pittsburgh Post-Gazette [77]
April 29, 2020	Scott Weese Dorothee Bienzle	U of G Researchers Studying Coronavirus Infection in Pets [78]
April 27, 2020	Amy Greer	CTV Morning Show Speaks With U of G Disease Modeller [79]
April 23, 2020	Scott Weese	Washington Post Consults OVC Zoonosis Expert [80]
April 20, 2020	Jan Sargeant Sarah Totton	Can Your Pets Get the Coronavirus, and Can You Catch It From Them? [81]

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April 17, 2020	Scott Weese	Veterinary Disease Expert on Livestock and the New Coronavirus [82]
April 17, 2020	Amy Greer Wendy Xie Gabrielle Brankston	Data for National COVID-19 Tracker Provided by U of G Team [83]
April 13, 2020	Amy Greer	Disease Modeller Talks 'Dynamic' Distancing With Toronto Star [84]
April 9, 2020	Ashleigh Weeden	Rural Studies Expert Warns Against Cottaging During Pandemic [85]
April 9, 2020	Scott Weese	Pets Must Practise Physical Distancing Too, Says U of G Expert [86]
April 9, 2020	Amy Greer	Dynamic Physical Distancing Solution to Maintaining Health Care, Economy, Study Reveals [87]
April 8, 2020	Scott Weese	OVC Expert Makes Headlines on Infected Tiger, Vet Care [88]
April 8, 2020	Jeffrey Farber	U of G Food Safety Expert on Washing Food During Pandemic [89]
April 8, 2020	Jeffrey Farber	Food Safety Expert Discusses Cooking for Others [90]
April 7, 2020	Jeffrey Farber	Globe and Mail Consults Food Safety Expert on Safe Grocery Shopping [91]
March 25, 2020	Glen Pyle	U of G Prof and Student Write on COVID-19 and Heart Disease [92]
March 24, 2020	Scott Weese	TVO Talks to OVC Prof About COVID-19 in Animals [93]

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March 24, 2020	Faisal Moola	U of G Prof Talks About Wildlife During COVID-19 Pandemic [94]
March 23, 2020	Amy Greer	Disease Modelling Expert Makes Further Headlines [95]
March 19, 2020	Amy Greer	U of G Researcher Contributing to COVID-19 Tracker [96]
March 17, 2020	Scott Weese	Zoonotic Disease Expert Makes Headlines [97]
March 9, 2020	Amy Greer	U of G Disease Modelling Expert Makes Headlines [98]
March 6, 2020	Scott Weese	Washington Post, CBC Consult U of G Zoonotic Disease Expert [99]
March 4, 2020	Jeff Wichtel	The COVID-19 Outbreak Shows Human, Animal and Environmental Health Requires Co-ordinated Approach [100]
March 3, 2020	Amy Greer	CTV Consults U of G Disease Modelling Expert on COVID-19 [101]
March 2, 2020	Shayan Sharif	Pathobiology Expert Appears on CBC Radio, TV [102]
February 28, 2020	Amy Greer	U of G Expert Part of Canada's COVID-19 Pandemic Preparations [103]
February 13, 2020	Scott Weese	U of G Zoonotic Disease Expert Speaks to Toronto Star, Yahoo News [104]
January 31, 2020	Katie Clow	Vector-borne Disease Expert Makes Multiple CBC Appearances [105]
January 27, 2020	Scott Weese	Infectious Disease Expert Discusses Coronavirus with CBC [106]

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Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

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This is Exhibit "D" to the Affidavit

of Bonnie Mallard, sworn before me

on this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

March 3, 2021

Dear Professor Charlotte Yates, President and Vice-Chancellor, and **Professor Gwen Chapman**, Interim Provost and Vice-President (Academic):

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought (*i.e.* acquisition of immunity). In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have been commissioned by the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area. Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses. Among the many reasons for this is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to allow SARS-CoV-2 to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada. It has become clear that we can't continue to rely on continual lockdowns. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. **It is from this perspective that we would like to recommend the following core strategies to support re-opening the University of Guelph campus to in-person learning in the Fall 2021 semester:**

1. **Offer comprehensive and sensitive testing for evidence of seroconversion (antibodies) against SARS-CoV-2.** Ever-accumulating data demonstrate that both naturally acquired, and vaccine-induced immunity can provide at least some level of protection from reinfection from the parental and current variant forms of SARS-CoV-2. Evidence of protective immunity either prior to and/or after vaccination would provide valuable information to guide decisions. This testing should be offered to members of the university that are both on- and off-campus. Several options for antibody testing are currently available in Canada. For example, LifeLabs currently has a test available. Even better, we have a colleague at the University of British Columbia who has developed the most comprehensive and sensitive test for seroconversion that we are currently aware of. Through collaboration with this colleague, we would be happy to assist with getting a local lab (possibly our own Animal Health Laboratory, which has an excellent quality control program and experience getting novel tests up and running) set-up to run this cutting-edge test.
2. **Offer strategically prioritized vaccinations.** Vaccination against SARS-CoV-2 should be offered to individuals wanting to return to campus. Prioritization should be based on risk of an infection progressing to disease (*i.e.* COVID-19). If doses are limited, vaccines would best be used in individuals with no evidence of immunity (based on testing in highlighted in point #1). Importantly,

vaccines should be administered precisely according the protocol that was used to have them approved for emergency use until further data is available on alternative protocols. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented evidence of it being relatively ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf). Vaccinations should be offered to university community members that are both on- and off-campus.

3. **Offer rapid antigen screening tests to detect the presence of SARS-CoV-2.** This is currently being tested on campus, and if successful, it would be logical to implement this approach more widely. It is very convenient for the workplace and should be offered to university community members that are both on- and off-campus.
4. **Offer off-campus learning/working accommodations for high-risk individuals.**
5. **Consider implementing supplemental testing.** Additional tests could help manage COVID-19 on-campus. For example, testing wastewater from buildings on campus, with an emphasis on residences could help identify 'hot spots'.
6. **Consider incorporating comprehensive data collection in consultation with our Research Ethics Board.** A lack of concerted efforts to collect comprehensive data sets has slowed the progress of research in many jurisdictions in Canada. The University of Guelph could provide a detailed analysis to support a return to campus at other institutions. Our Department of Population Medicine would be well-equipped to oversee this type of data collection. However, the rollout of vaccines and tests should not be delayed for establishing such a data collection infrastructure; rather, the infrastructure for research-quality data collection could interface with the rollout when it is ready.

Note: Implementation of suggestions 1-5 could have an impact on public health directives. Specifically, it would facilitate discussions around reduced physical distancing. Reducing physical distancing from two meters to one meter in classrooms could have a major positive impact on returning to in-person learning.

We would be happy to offer advice as our campus community moves forward. Specifically, Dr. Bridle is willing to serve on any relevant advisory committees and/or he can be a point of contact for our group, with whom he consults regularly. We also have many colleagues in the fields of virology, immunology, and public health at a variety of institutions that we consult with. We look forward to hearing your thoughts about the University of Guelph showing leadership among the academic community in getting students back to in-class learning.

Sincerely,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

March 5, 2021

Dear Dr. Nicola Mercer, Medical Officer of Health and CEO of Wellington-Dufferin-Guelph Public Health:

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought (*i.e.* acquisition of immunity). In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have been commissioned by the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive and in-depth expertise in this area. Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses. Among the many reasons for this is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to allow SARS-CoV-2 to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada. It has become clear that we can't continue to rely on continual lockdowns. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. **It is from this perspective that we would like to recommend the following core strategies to support re-opening the City of Guelph and the surrounding regions by this Fall:**

1. **Offer comprehensive and sensitive testing for evidence of seroconversion (antibodies) against SARS-CoV-2.** Ever-accumulating data demonstrate that both naturally acquired, and vaccine-induced immunity can provide at least some level of protection from reinfection from the parental and current variant forms of SARS-CoV-2. Evidence of protective immunity either prior to and/or after vaccination would provide valuable information to guide decisions. Several options for antibody testing are currently available in Canada. For example, LifeLabs currently has a test available. Even better, we have a colleague at the University of British Columbia who has developed the most comprehensive and sensitive test for seroconversion that we are currently aware of. Through collaboration with this colleague, we would be happy to assist with getting a local lab (possibly our own Animal Health Laboratory, which has an excellent quality control program and experience getting novel tests up and running) set-up to run this cutting-edge test.
2. **Offer strategically prioritized vaccinations.** Prioritization should be based on risk of an infection progressing to disease (*i.e.* COVID-19). If doses are limited, vaccines would best be used in individuals with no evidence of immunity (based on testing highlighted in point #1). Importantly, vaccines should be administered precisely according to the protocol that was used to have them approved for emergency use until further data is available on alternative protocols. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented

evidence of it being relatively ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf).

3. **Offer rapid antigen screening tests to detect the presence of SARS-CoV-2.** This is currently being tested on the University of Guelph campus, and if successful, it would be logical to implement this approach more widely. It is very convenient for the workplace.
4. **Offer accommodations for remote working/learning for high-risk individuals.**
5. **Consider implementing supplemental testing.** Additional tests could help manage COVID-19. For example, testing wastewater from buildings, with an emphasis on high-density housing and workplaces could help identify 'hot spots'.
6. **Consider incorporating comprehensive data collection in consultation.** A lack of concerted efforts to collect comprehensive data sets has slowed the progress of research in many jurisdictions in Canada. The Wellington-Dufferin-Guelph Public Health in conjunction with the University of Guelph could provide a detailed analysis to support return-to-work and return-to-school policies at other institutions. Our Department of Population Medicine would be well-equipped to oversee this type of data collection. However, the rollout of vaccines and tests should not be delayed for establishing such a data collection infrastructure; rather, the infrastructure for research-quality data collection could interface with the rollout when it is ready.

Note: Implementation of suggestions 1-5 could have an impact on public health directives. Specifically, it would facilitate discussions around reduced physical distancing. Reducing physical distancing from two meters to one meter in workplaces and classrooms could have a major positive impact on returning to in-person work and learning.

We would be happy to offer advice as our regional community moves forward. Specifically, Dr. Bridle is willing to serve on any relevant advisory committees and/or he can be a point of contact for our group, with whom he consults regularly. We also have many colleagues in the fields of virology, immunology, and public health at a variety of institutions that we consult with. We look forward to hearing your thoughts about the Wellington-Dufferin-Guelph Public Health Unite showing leadership within Canada in getting local citizens back to in-person work and in-class learning.

Sincerely,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

March 16, 2021

Dear Fellow Canadians:

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought, which is acquisition of immunity against the virus SARS-CoV-2. In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have received funding from the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area.

Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses.

Among the many reasons for this virus becoming endemic is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to potentiate SARS-CoV-2 being able to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada.

It has become clear that we can't continue to rely on continual lockdowns due to the impact on mental health, delays to other medical treatments, a sinking economy, and so on. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. It is also important to remember that the majority of cases of COVID-19 in Canada are mild-to-moderate, and the death rate has been quite low (22,514 deaths out of 914,697 cases or 592/million as of March 16 2021 - Coronavirus Dashboard [ncov2019.live]). Sadly, at least 70% of those deaths have been in people over 80 years of age, in long-term care (Dr. R. Bibby, Sociologist, University of Lethbridge; http://www.reginaldbibby.com/specialcovid19analyses.html). On the upside, there is now also good evidence that the majority of those recovered from COVID-19 have protective immunity (reviewed by Sette and Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell (2021), DOI: https://doi.org/10.1016/j.cell.2021.01.007).

It is from this perspective that we have been advocating for several core strategies to support re-opening our country to in-person work and learning. An important aspect of this is offering strategically prioritized vaccinations. Specifically, we have been advocating for the **administration of safe and effective COVID-19 vaccines according the protocol that was used to have them approved** for emergency use, until further data is available and reviewed and approved by Health Canada to support alternative protocols. In support of this goal, we have two recommendations:

1. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented evidence of it being ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. Specifically, it was shown to be only 10% effective against the South African variant, with the cut-off for approval being 50%. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf). Additionally, its use has been suspended in at least ten European countries until undesirable potential side-effects can be further investigated. For Ontarians, the Chief Medical Officer definitively stated in a letter to pubic health units in the province that individuals may opt out of receiving the AstraZeneca vaccine on the basis that it is admittedly of lower efficacy than the others (see the highlighted text on page 2 of the attached letter).

2. The intervals for the two-dose COVID-19 vaccines should adhere to what was officially approved by Health Canada and the manufacturers, which is 21- and 28-days for the Pfizer and Moderna vaccines, respectively. The rationale for this is presented below...

The history of Canada's move to extend COVID-19 intervals to an unprecedented four months.

Last week, the CBC launched a story to highlight the path that has led many jurisdictions in Canada to begin implementing an interval of up to four months for both the Pfizer and Moderna COVID-19 vaccines (https://www.cbc.ca/news/health/canada-covid-19-vaccine-delay-risk-1.5939134). It apparently began with a letter from an epidemiologist at the British Columbian Centre for Disease Control to the editor of *The New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMc2036242). In this letter it was claimed that Pfizer failed to realize the efficacy of its own vaccine and that its effectiveness as a single-dose regimen is actually a remarkable 92%. It is important to note that this is based on an extrapolation of a statistically underpowered, biased, limited data set from a trial that was never designed to test single-dose efficacy. Further, the extrapolation required several assumptions to be made that may or may not be true; there simply is no empirical data to know either way.

What many do not realize is that the researchers for Pfizer published a rebuttal to this letter in which they stated: **"In response to Skowronski and De Serres: we would like to emphasize that alternative dosing regimens of BNT162b2 have not been evaluated."** Pfizer's own data has suggested that single-dose effectiveness might be just over 50%, with their admission of the caveat that their study was never designed to test this properly. Nonetheless, the idea that extended intervals will work well is being propagated, despite a lack of empirical evidence. Indeed, Dr. Bridle has confirmed via interviews with people coming out of local vaccine clinics that some of them are being told that a single dose has been shown to be 92% effective based on 'published data'. This is simply untrue and not the way science is supposed to work. The validity of alternative protocols is up for debate in the scientific community.

Any intervals that deviate from what Health Canada and the vaccine manufacturers have agreed to, represents experimentation, especially in the absence of any new validated data from a phase 3 clinical trial. However, in Ontario and many other jurisdictions in Canada, the change in the vaccine interval has been proposed. See the attached letter from Ontario's Chief Medical Officer as an example of this. In short, the intervals have been lengthened without sufficient empirical data to justify it. In contrast, the intervals provided by Health Canada are based on empirical data. The effectiveness of the two-dose regimens with 3- or 4-week intervals is known. The effectiveness of the two-dose regimens with any other interval is a 'best guess'. This background leads into a potentially more serious issue regarding informed consent...

Is informed consent being practiced properly in COVID-19 vaccine clinics?

In Ontario, the attached consent form should be hard-signed by everybody prior to receiving one of the experimental vaccines. Please note that this form requires a person to have read or to have read to them the vaccine information sheet (see the highlighted text on page 3 of the consent form). Please note the highlighted text on pages 4 and 6 of the vaccine information sheet that is appended to this letter. Consent is being given to receiving the dose at Health Canada's recommended interval of 3- (Pfizer) or 4-weeks (Moderna). No alternative intervals are described. Remarkably, however, many (if not most) attendees at the COVID-19 vaccine clinics are being told after receiving their first dose (*i.e.* once they are committed to the treatment) that they will likely have to wait up to four months to receive the second dose. **People are consenting to the 3-4-week interval** (3 weeks for Pfizer's vaccine; four weeks for the Moderna vaccine) **but are then being told that they cannot receive the second dose for another four months.** For those who would like to insist on receiving their vaccine as per Health Canada's recommended interval, we suggest you take a hard-copy of the vaccine information sheet to the clinic and have

them confirm that they will adhere to the protocol you are consenting to prior to letting them administer the first dose.

Why might the interval for two-dose vaccines matter?

Some proponents of lengthening the interval argue there can be no harm. However, there is some scientific basis for suggesting that lengthening intervals could cause harm: 1. The companies themselves suggest a single dose is significantly less efficacious than two doses. This could put individuals at prolonged risk of getting infected while waiting for the second dose. This could be a particular problem for those who are at high risk. 2. It is unknown if the duration of immunity (i.e. how long a person is protected) conferred by a single dose extends to four months; it is possible that there may be no protection at this point. 3. It is unknown if immunological memory conferred by the first vaccine will last long enough for a second dose, given four months later, to serve as a proper 'booster vaccine'. If a proper boost is not conferred, the two-dose effectiveness could be reduced below the 95% effectiveness shown with the approved interval. 4. Induction of long-term, relatively weak immunity could potentially promote the emergence of immune-evasive mutants. This would be similar to what has been observed over and over again with the emergence of dangerous antibiotic-resistant bacteria; it is potentiated by the misuse of the therapeutic agents designed to effectively treat the pathogens. Promotion of immune-evasive SARS-CoV-2 would put everyone at greater risk. Although these are cautionary possibilities, **they are no less valid than the speculations that led to adopting untested long intervals**. Given these are novel nucleic acid vaccine platforms, approved for emergency use only, it might be wise to err on the side of caution. The take-home message is: Longer intervals might be OK, but they also might create problems. We simply don't know yet. On this basis, **those who want to receive the vaccines according to how they were approved for emergency use should be entitled to this**. However, **public health officials seem to be over-riding this right, even though it contradicts their own informed consent procedure, Health Canada, and the vaccine manufacturers**.

With sincere concern for our fellow Canadians,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

March 23, 2021

Dear Fellow Canadians:

Scientists Express Urgent Concerns Over Current COVID-19 Vaccine Policies

University Of Guelph Faculty Speak Up:

The following urgent concerns are being expressed by the following faculty members at the University of Guelph:

- Dr. Byram Bridle is a viral immunologist
- Dr. Bonnie Mallard is an immunologist
- Dr. Neil Karrow is an immunologist

Generally, policies for COVID-19 have been generated with relatively little consultation with immunologists, including viral immunologists. However, at its core, COVID-19 is a problem at the interface of immunology and virology.

This interface is both in terms of its pathogenesis and the primary solution being sought, which is acquisition of immunity against the virus SARS-CoV-2. In addition to our group having in-depth knowledge of these fields, Dr. Bridle received funding from the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area. Please note that information about COVID-19 vaccines is rapidly changing. The information presented below is accurate as of March 23, 2021.

Has The Goal To Flatten The Curve Been Forgotten?

Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks. The purpose was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed.

Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses.

Will SARS-CoV-2 Become Endemic?

Among the many reasons for this virus becoming endemic is the propensity of SARS-CoV-2 to mutate over time. This will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly focused immunity that targets a single protein known as the spike.

These two major issues will combine to potentiate SARS-CoV-2 being able to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada.

How Can We Live With This Virus While Still Maximizing Health And Safety?

It has become clear that we can't continue to rely on continual lockdowns due to impact on mental health, delays to other medical treatments, a sinking economy and so on. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities.

It is also important to remember that the majority of cases of COVID-19 in Canada are mild-moderate, and the death rate has been quite low (22,676 deaths out of 933,798 cases or 596/million people as of March 22, 2021 - Coronavirus Dashboard (ncov2019.live).

Sadly, at least 70% of those deaths have been in people over 80 years of age, in long-term care (Dr. R. Bibby, Sociologist, at the University of Lethbridge – Research of Reginald W. Bibby (reginaldbibby.com)).

On the upside, there is now also good evidence that the majority of those recovered from COVID-19 have protective immunity (reviewed by Sette and Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell (2021), https://doi.org/10.1016/ j.cell.2021.01.007).

Therefore, we need to identify those with immunity from natural exposure using available antibody testing, and strategically prioritize those at highest risk, who need and want to be vaccinated, according to the manufacturers currently approved vaccination protocols.

How Can Vaccines Be Prioritized According To Manufacturers Approved Protocols?

It is from this perspective that we have been advocating for several core strategies to support re-opening our country to in-person work and learning. An important aspect of this is offering strategically prioritized vaccinations.

Specifically, we have been advocating for the administration of safe and effective COVID-19 vaccines according the protocol that was used to have them approved for emergency use, until further data is available and reviewed and approved by Health Canada to support alternative protocols.

In support of this goal, we have two recommendations:

1. Consideration should be given to avoiding the AstraZeneca vaccine, for which there is documented evidence of it being ineffective against the South African variant of SARS-CoV-2, which is now in Canada. It was only 10% effective against the South African variant, with the cut-off for approval being 50% (https://www.nejm.org/doi/full/10.1056/NEJMoa2102214?query=featured_home).

2. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf).

   For Ontarians, the Chief Medical Officer definitively stated in a letter to pubic health units in the province that individuals may opt out of receiving the AstraZeneca vaccine on the basis that it is admittedly of lower efficacy than the others (see the highlighted text on page 2 of the attached letter).

3. The intervals for the two-dose COVID-19 mRNA vaccines should adhere to what was officially approved by Health Canada and the manufacturers, which is 21- and 28-days for the Pfizer and Moderna vaccines, respectively. The rationale for this is presented below...

Why The Concern Over Changing The Manufacturers Approved Protocols?

The history of Canada's move to extend COVID-19 intervals to four months is unprecedented. Recently, the CBC launched a story to highlight the path that has led many jurisdictions in Canada to begin implementing an interval of up to four months for both the Pfizer and Moderna COVID-19 vaccines (https://www.cbc.ca/news/health/canada-covid-19-vaccine-delay-risk-1.5939134).

It apparently began with a letter from an epidemiologist at the British Columbian Centre for Disease Control to the editor of *The New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMc2036242).

In this letter it was claimed that Pfizer failed to realize the efficacy of its own vaccine and that its effectiveness as a single-dose regimen is a remarkable 92%. It is important to note that this is based on an extrapolation of a statistically underpowered, biased, limited data set from a trial that was never designed to test single-dose efficacy. Further, the extrapolation required several assumptions to be made that may or may not be true; there simply is no empirical data to know either way.

What many do not realize is that the researchers for Pfizer published a rebuttal to this letter in which they stated: "In response to Skowronski and De Serres: **we would like to emphasize that alternative dosing regimens of BNT162b2 have not been evaluated.**" Pfizer's own data has suggested that single-dose effectiveness might be just over 50%, with their admission of the caveat that their study was never designed to test this properly.

Nonetheless, the idea that extended intervals will work well is being propagated, despite a lack of empirical evidence. Indeed, Dr. Bridle has confirmed via interviews with people coming out of local vaccine clinics that some of them are being told that a single dose has been shown to be 92% effective based on 'published data'. This is simply untrue and not the way science is supposed to work. The validity of alternative protocols is up for debate in the scientific community.

Notably, on March 22nd, Canada's chief science adviser, Dr. Mona Nemer, spoke out against lengthening dosing intervals for Canadian seniors, citing not only a lack of scientific evidence to support it, but even emerging evidence to contraindicate it (https://www.ctvnews.ca/health/coronavirus/research-doesn-t-back-vaccine-dose-delay-for-seniors-canada-s-chief-science-adviser-says-1.5358075).

Any intervals that deviate from what Health Canada and the vaccine manufacturers have agreed to, represents experimentation, especially in the absence of any new validated data from a phase 3 clinical trial. However, in Ontario and many other jurisdictions in Canada, the change in the vaccine interval has been implemented.

See the attached letter from Ontario's Chief Medical Officer as an example of this. In short, the intervals have been lengthened without sufficient empirical data to justify it. In contrast, the intervals provided by Health Canada are based on empirical data. The effectiveness of the two-dose regimens with three-

or four-week intervals is known. The effectiveness of the two-dose regimens with any other interval is a 'best guess'. This background leads into another potentially serious issue regarding informed consent...

Is Informed Consent Being Practiced Properly In Canadian COVID-19 Clinics?

According to Ontario's Ministry of Health website, the attached consent form should be hand-signed by everybody prior to receiving one of the experimental vaccines. Please note that this form requires a person to have read or to have read to them the vaccine information sheet (see the highlighted text on page 3 of the consent form). Please note the highlighted text on pages 4 and 6 of the vaccine information sheet that is appended to this letter.

The Ontario Ministry of Health website appears to be requiring consent to be given to receiving the second dose of the mRNA vaccines at Health Canada's recommended interval of three- (Pfizer) or four-weeks (Moderna). No alternative intervals are described. Remarkably, however, most attendees at the COVID-19 vaccination clinics are being told that they cannot receive the second dose for another four months.

For those who would like to insist on receiving their vaccine as per Health Canada's recommended interval, we suggest you take a hard-copy of the vaccine information sheet to the clinic and have them confirm that they will adhere to the protocol you are consenting to prior to letting them administer the first dose.

WHY MIGHT THE INTERVAL FOR TWO-DOSE VACCINES MATTER?

Some proponents of lengthening the interval argue there can be no harm. However, there is some scientific basis for suggesting that lengthening intervals could cause harm:

1. The companies themselves suggest a single dose is significantly less efficacious than two doses. This could put individuals at prolonged risk of getting infected while waiting for the second dose. This could be a particular problem for those who are at high risk.

2. It is unknown if the duration of immunity (*i.e.* how long a person is protected) conferred by a single dose extends to four months; it is possible that there may be no protection at, or even before this point.

3. It is unknown if immunological memory conferred by the first vaccine will last long enough for a second dose, given four months later, to serve as a proper 'booster vaccine'. If a proper boost is not conferred, the two-dose effectiveness could be reduced below the 95% effectiveness shown with the approved interval.

4. Induction of long-term, relatively weak immunity could potentially promote the emergence of immune-evasive mutants. This would be similar to what has been observed over and over again with the emergence of dangerous antibiotic-resistant bacteria; it is potentiated by the misuse of the therapeutic agents designed to effectively treat the pathogens.

Promotion of immune-evasive SARS-CoV-2 would put everyone at greater risk. Although these are cautionary possibilities, they are no less valid than the speculations that led to adopting untested long

intervals. Given these are novel nucleic acid vaccine platforms, approved for emergency use only, it might be wise to err on the side of caution.

5. A pre-print of a relevant scientific article was posted on-line (https://www.medrxiv.org/content/10.1101/2021.03.03.21251066v1). It has not yet undergone peer review. However, we routinely review these kinds of articles and have concluded that the core data set appears to be valid. This article describes results of a study with the Pfizer vaccine. Importantly, the authors have concluded "since the majority of vaccinees did not obtain neutralizing antibody titers after the first vaccination, we suggest that **postponing a second vaccination with this vaccine is neither advisable for younger nor elderly populations**." In short, a single dose of Pfizer's vaccine would be expected to leave most people unprotected against SARS-CoV-2. Therefore, extending the interval to four months would not meet the goal of getting twice as many people partially protected, as our public health officials are claiming. Instead, it could cause large numbers of people to be left unprotected for a prolonged period.

What's the Take-Home Message?

A longer interval might be okay for the Moderna vaccine, but it also might create problems. We simply don't know yet. Cutting-edge data from a properly conducted scientific study suggested that a prolonged interval for the Pfizer vaccine is dangerous. On this basis, those who want to receive the vaccines according to how they were approved for emergency use should be entitled to this.

However, public health officials seem to be over-riding this right, even though it appears to contradict Health Canada, the vaccine manufacturers, Canada's chief science advisor, and the informed consent procedure posted on the Ontario Ministry of Health website.

With sincere concern for our fellow Canadians,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

This is Exhibit "E" to the Affidavit of

Bonnie Mallard, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

Re: smear campaign

Byram Bridle <bbridle@uoguelph.ca>

Sun 5/30/2021 12:15 PM

To: Glen Pyle <gpyle@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>; Karen Mantel <kmantel@uoguelph.ca>; Jane Dawkins <jdawkins@uoguelph.ca>
Bcc: Bonnie Mallard <bmallard@ovc.uoguelph.ca>; Niel Karrow <nkarrow@uoguelph.ca>

Glen,

I do not use social media. So, yes, it has been happening without my knowledge.If I ever have a problem with someone's science on campus, I take it up with them. This would have been the respectful thing to do. The major problem here was the fact that you did not condemn an egregious act against a colleague when you had the opportunity.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
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Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
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https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

From: Glen Pyle <gpyle@uoguelph.ca>
Sent: Sunday, May 30, 2021 11:00 AM
To: Byram Bridle <bbridle@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>; Karen Mantel <kmantel@uoguelph.ca>; Jane Dawkins <jdawkins@uoguelph.ca>
Subject: RE: smear campaign

Hi Byram.

I am not slamming you behind your back. As you note, it is a public forum and I am presenting data from studies.

Glen.

W. Glen Pyle, PhD
Senior Career Investigator
Improving the Heart & Brain Health for Women in Canada, Heart & Stroke Foundation
Distinguished Professor, Innovation in Teaching
Co-Lead, COVID-19 Resources Canada Science Explained
Professor & Assistant Chair, Department of Biomedical Sciences
Ontario Veterinary College, University of Guelph
Associate Member, IMPART, Dalhousie University
LinkedIn: www.linkedin.com/in/glenpyle
Twitter: @glenpyle

"By a divine paradox, wherever there is one slave there are two. So in the wonderful reciprocities of being, we can never reach the higher levels until all our fellows ascend with us."
-- Edwin Markham

-------- Original message --------
From: Byram Bridle <bbridle@uoguelph.ca>
Date: 2021-05-30 4:24 AM (GMT-05:00)
To: Glen Pyle <gpyle@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>, Shayan Sharif <shayan@uoguelph.ca>, Brandon Lillie <blillie@uoguelph.ca>, Karen Mantel <kmantel@uoguelph.ca>, Jane Dawkins <jdawkins@uoguelph.ca>
Subject: Re: smear campaign

Glen,

I was just sent even more tweets from you that slam my interview. This is absolutely disgusting. You do realize don't you that I could not possibly show the scientific basis for my statements on a radio show, right? Since you are 'just down the hall from me' why don't you drop by sometime for a real scientific debate. You are obviously the local expert on COVID-19 vaccines, not me. If you have issues, why not talk to me directly? Why, instead, are you slamming me behind my back and in public forums?

Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
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https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

From: Byram Bridle <bbridle@uoguelph.ca>
Sent: Sunday, May 30, 2021 4:10 AM
To: Glen Pyle <gpyle@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>; Karen Mantel <kmantel@uoguelph.ca>; Jane Dawkins <jdawkins@uoguelph.ca>; Charlotte Yates <cyates@uoguelph.ca>; Gwen Chapman <gwen.chapman@uoguelph.ca>; Cate Dewey <c.dewey@exec.uoguelph.ca>
Subject: Re: smear campaign

Glen,

Can you please explain your role in the smear campaign against me? Who is the scientist that made the website to slander me? I need this information now! ...or are you going to continue to revel in the harm being caused to a colleague that you are embarrassed about? If I do not receive a reply from you by noon on Monday, I will contact the police to see if they can get the information from you.

Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

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Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

From: Byram Bridle <bbridle@uoguelph.ca>
Sent: Sunday, May 30, 2021 3:58 AM
To: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>
Cc: Karen Mantel <kmantel@uoguelph.ca>; Jane Dawkins <jdawkins@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>
Subject: Re: smear campaign

I just received this...

https://twitter.com/DFisman/status/1398756044004802565

David Fisman on Twitter

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"I've had questions over the past 48 h about vaccine safety concerns aired Dr Byram Bridle at @UofGuelphOAC in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here: https://t.co/GOrR5vQVvb"

twitter.com

Glen Pyle is all over this. He seems to be loving the bashing I am taking. He even states embarrassment when correcting someone to note that I am from OVC, not OAC. Is David Fisman the one who made the website?

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
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Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
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https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

From: Byram Bridle
Sent: Sunday, May 30, 2021 2:07 AM
To: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>
Cc: Karen Mantel <kmantel@uoguelph.ca>; Jane Dawkins <jdawkins@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>
Subject: smear campaign

Dear Jeff and Shayan,

It has been brought to my attention that a smear campaign has been launched against me because I answered a question about COVID-19 vaccines that was posed to me by a radio show host. Everything I said is backed up by peer-reviewed scientific articles. Of course, however, I had no way to show these references in the context of a radio interview. FYI, this libelous website was set-up...

http://byrambridle.com/

Because of this I have found myself the victim of vicious attacks. This has forced me to cancel my commitment to a grant review panel for CIHR (reviews were due tomorrow [Mon.], the panel was to meet the week after). I have had to leave them and applicants short of eight reviews. This is a very embarrassing thing to do and reflects very poorly on me as a professional. I have also had to contact two editors to plead for extensions to submission deadlines for two manuscripts from my group that were due tomorrow (Monday). This is taking a toll on my mental and physical health. I should not have to be up at 2 in the morning on a Sunday having to deal with this. Thankfully, I have had numerous colleagues, both locally and from around the world jump to my defence. I have already been in contact with a legal team that has offered to investigate should I wish to follow through. There is a second lawyer who may be willing to help. Of incredible concern was this tweet that was forwarded to me....

https://twitter.com/glenpyle/status/1398810510234206210

Glen Pyle | #GetVaccinated on Twitter

"@maggieoutabout @DFisman @UofGuelphOAC It's not a hacker. The person who made it has contacted me. They are a scientist."

twitter.com

...I demand to know what Glen's role is in this. Did he condone this? Was he part of this? He certainly knows who made the website and did not speak out against it. The website also uses an article that Glen wrote to try to slam me. I will wait to see if this can be handled internally. However, I am ready to pull the trigger on a police investigation and getting a lawyer involved. Since I have had to, with enormous embarrassment, cancel my work obligations, I am now free most of Monday. I would like to deal with this ASAP. None of this adheres to the principle of academic freedom. To protect myself, I now feel obligated to disseminate the scientific sources of my comments. I am currently writing a comprehensive document to prove that the science underpinning my comments is legitimate. I should not be having to waste so much time and energy on something like this. I am disgusted. Especially if a colleague within OVC is involved in some way. I have never had anything but the most collegial interactions with Glen in the past. We served together on the Pet Trust grant review panel. Why didn't he use this public forum to condemn a vicious attack on a colleague???!!!??? Instead, he is implying that the slander is legitimate by assuring the public that it was written by a scientist that he can back-up. This has got very ugly very quickly.

Do you have any more information that you can provide to me?

What is the immediate next step?

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
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Department of Pathobiology
University of Guelph
50 Stone Road East

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Guelph, Ontario, Canada
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Re: misinformation

Byram Bridle <bbridle@uoguelph.ca>

Mon 5/31/2021 6:05 AM

To: J. Scott Weese <jsweese@uoguelph.ca>
Cc: Shayan Sharif <shayan@uoguelph.ca>; Jeffrey Wichtel <jwichtel@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>
Bcc: Bonnie Mallard <bmallard@ovc.uoguelph.ca>; Niel Karrow <nkarrow@uoguelph.ca>

Scott,

This was just sent to me...

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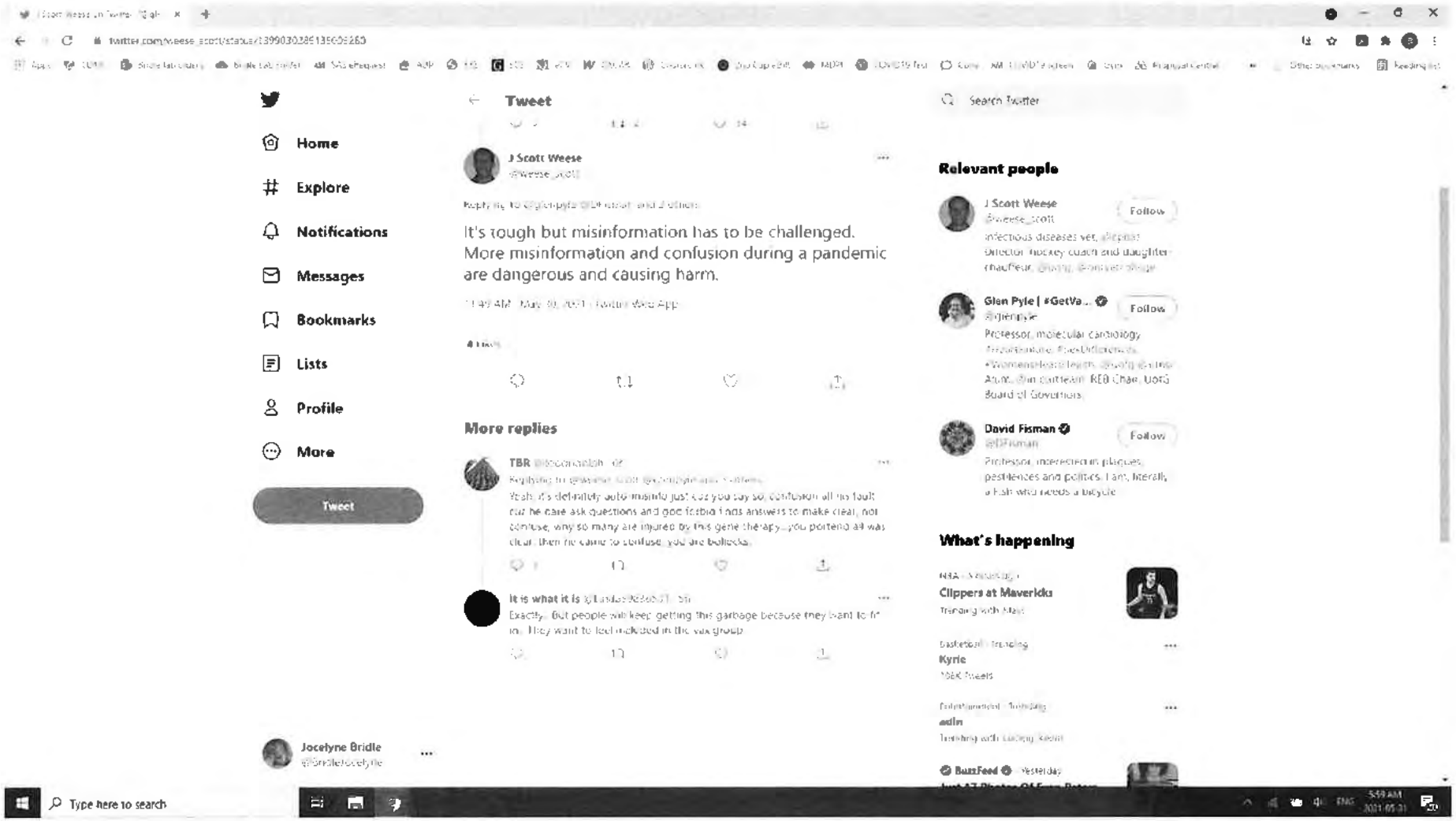

I'm glad to see that others thought it equally silly for you to discredit someone with zero evidence to back it up! Come on, you are not 10 years old anymore. Please act your age. Like it or not, I'm not going to conform to your way of thinking about the pandemic and I have scientifically valid reasons for it. I am allowed to be an independent critical thinker.

Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology

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Building #89 (NW corner Gordon/McGilvray)
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Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

From: Byram Bridle
Sent: Monday, May 31, 2021 5:51 AM
To: J. Scott Weese <jsweese@uoguelph.ca>
Cc: Shayan Sharif <shayan@uoguelph.ca>; Jeffrey Wichtel <jwichtel@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>
Subject: misinformation

Scott,

I see you have entered the foray...

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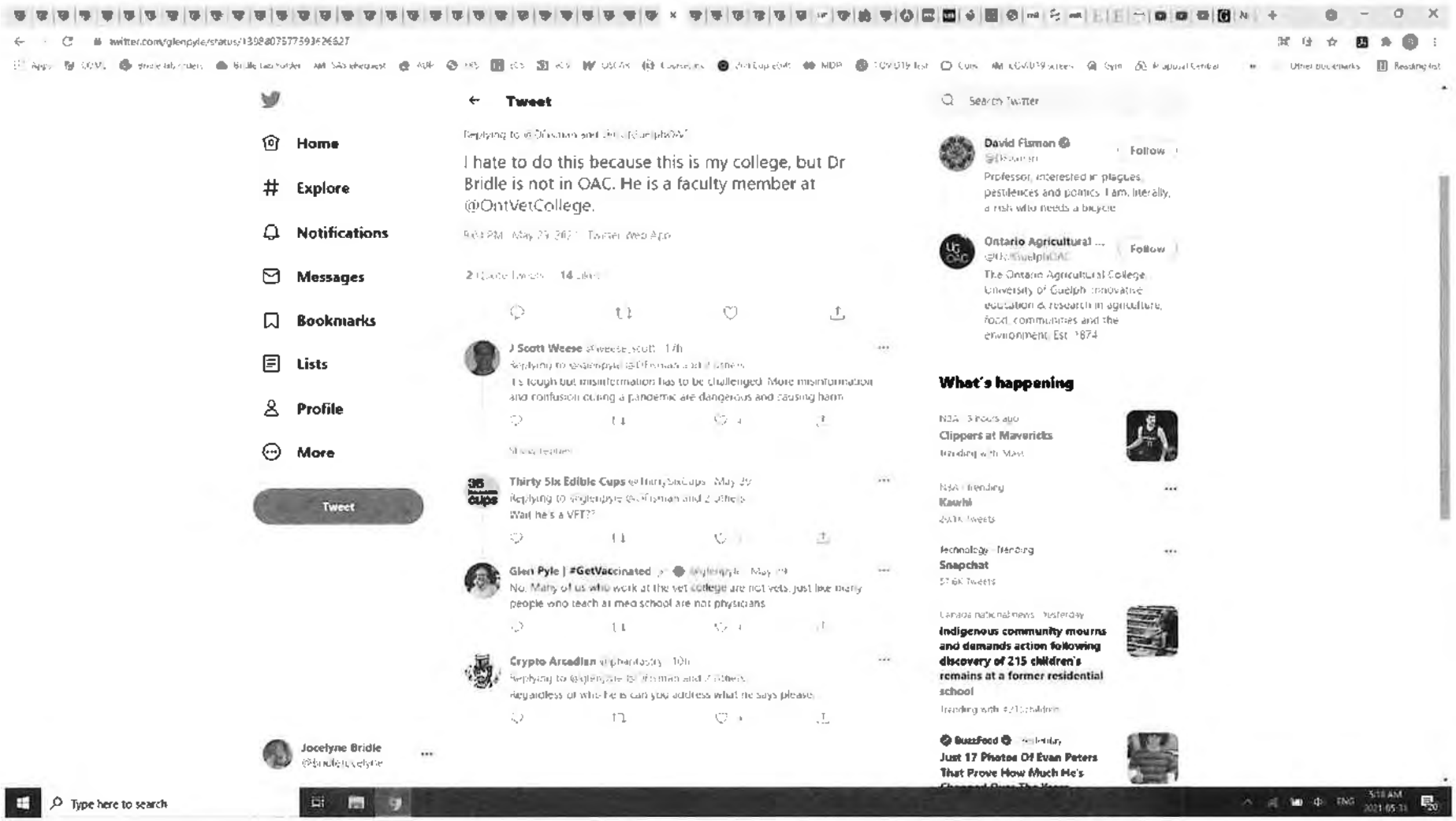

...what information are you referring to Scott? And what misinformation did I give? Interestingly, since your communication was in text, you had ample opportunity to describe: (a) what exactly you were rebutting in terms of the science I was interviewed about; and (b) citations to back-up your claim of misinformation. This is akin to saying "my colleague is giving misinformation and I can prove it with my lack of information to back up my claim". I gave a five-minute interview over the radio. You do realize that I can't show papers via the air waves, right? So what information are you criticizing? Did you have any idea what papers I was referring to? FYI, I have attached a brief report to back-up my very legitimate concerns for the health and safety of all Canadian children. I would be happy to debate with you anytime about COVID-19 vaccines if you like to do so. In the report that I have attached, please go to the link to Pfizer's own biodistribution data showing that their vaccine platform travels far and wide throughout the body and accumulates in many tissues. Also, see their report to the European Medicines Agency in which they admit that they have no pharmacokinetic/biodistribution data with the actual vaccine that is going into our children. These are basic studies that should always be done prior to any vaccine being used. Using this vaccine in children without proper biodistribution and additional

safety data that looks at the effect of depositing the vaccine into a plethora of tissues is scientific blasphemy. Do you really think, on this basis, that there are no legitimate safety issues that should be addressed? ...because I can tell you from years of experience that is not how one goes about developing a novel treatment with integrity.

Next time, before you go ahead and fuel a fire that is roasting a colleague, please consider talking to me to determine what my rationale is. What you did here was immature and disrespectful. Do you realize the harm this smear campaign is doing to me?

I must say, it's great to have colleagues like you and Glen around. It is creating a great collegial work environment.

Jeff and Shayan: is this behaviour from Glen and Scott going to be condoned? Jeff, you will recall that Scott already implied that I didn't have the right to hold an opposing view in a recent department meeting. In the current situation, it is ridiculous that I have to present a report to show my colleagues that I actually know what I'm talking about just so I can get them to leave me alone in the world of social media. I think that this harassment in the workplace needs to stop.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
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Building #89 (NW corner Gordon/McGilvray)
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https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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UNIVERSITY of GUELPH

This is Exhibit "F" to the Affidavit of

Bonnie Mallard, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

COVID-19 Vaccines and Children:

A Scientist's Guide for Parents

by

Dr. Byram W. Bridle, PhD

Associate Professor of Viral Immunology

June 15, 2021

Canadian Covid Care Alliance
Alliance canadienne pour la prévention et prise-en-charge de la covid

EXECUTIVE SUMMARY

Pfizer BioNTech's COVID-19 mRNA vaccine has been *Authorized under an Interim Order* by Health Canada for use in Canadians as young as 12 years old, with mandatory commitments for the monitoring of long-term safety and efficacy. Authorization under an Interim Order means additional information is needed on the safety, efficacy, and quality of the vaccine, including in children and adolescents, to support the future full market approval and licensing of the vaccine.

There is some uncertainty regarding the long-term safety of Pfizer BioNTech's COVID-19 vaccine in all individuals, and especially in children, youth, and younger adults of child-bearing age. Indeed, some key safety studies appear to have been missed in the rush to roll out the vaccines, and more is being learned about the vaccines every day. For example, there was a previously wide-held assumption that vaccination with the mRNA vaccines is safe because it is a localized event in the body, with the vaccine remaining limited to the shoulder muscle following injection and triggering an immune response in the local lymph nodes. However, there is evidence that Pfizer's COVID-19 vaccine does not remain at the injection site. In fact, once injected, the vaccine contents appear to travel extensively throughout the body, to the brain and other sensitive tissues, such as bone marrow, spleen, liver, adrenal glands, ovaries *etc.* Whether these body sites are involved in producing the spike protein is not known, as this was never studied. Nonetheless, new data have been published that, following vaccination with the Moderna vaccine (an mRNA vaccine very similar to Pfizer's mRNA vaccine), the spike protein can enter the circulatory system. Presumably, this means the spike protein can travel extensively throughout the body. It is important to understand which organs are producing the spike protein, what factors result in the spike protein entering the circulation, how long the spike protein circulates, and in which body fluids (*e.g.*, semen, saliva, breast milk, urine) the spike protein is present. This information is incredibly important because recent data have come to light that the spike protein is "biologically active". This means that the spike protein is not just an antigen that is recognized by the immune system as being foreign. It means that the spike protein, itself, can interact with receptors throughout the body, called ACE2 receptors, potentially causing undesirable effects such as damage to the heart and cardiovascular system, blood clots, bleeding, and neurological effects. Although some might argue that the risk of the spike protein causing this type of damage is only a theoretical risk, when we are mass vaccinating a population of predominantly healthy people, including children, adolescents, and adults of child-bearing age, there is absolutely no room for avoidable error.

The current scientific uncertainties demand that the administration of Pfizer's COVID-19 vaccine to children, adolescents, and young adults of child-bearing age be paused until proper scientific studies that focus on the safety and pharmacokinetics and biodistribution of the vaccines and the vaccine-encoded spike protein can be conducted. Halting the vaccination can be done safely because:

- The risk of severe and potentially lethal COVID-19 in these specific populations is so low that we need to be very certain that risks associated with mass vaccination are not higher;
- Asymptomatic members of this population are not a substantial risk for passing COVID-19 to others; and

- There are effective early-treatment strategies for the very few children, adolescents, and young adults of child-bearing age who may be at risk of developing severe COVID-19, such as ivermectin, fluvoxamine, and budesonide.

It is not appropriate to use an "experimental" vaccine in a population group unless the benefit of vaccination exceeds the risk of vaccination in that population group. With risk of severe COVID-19 in children, adolescents, and young adults of child-bearing age already so low, the benefit of vaccinating these population groups with a vaccine for which neither the long-term safety nor efficacy is known cannot be concluded to exceed the risk. In other words, the risk of serious COVID-19 is so low in children, adolescents, and young adults of child-bearing age that the standards for safety must be set much higher for them.

Contents

Who is Dr. Bridle?

I am an Associate Professor of Viral Immunology in the Department of Pathobiology at the University of Guelph in Canada. My research program focuses on the development of vaccines to prevent infectious diseases and treat cancers, as well as studying the body's immune response to viruses. I teach several courses at the undergraduate and graduate levels on the topics of immunology, virology, and cancer biology. The overall aim of my research efforts is to develop safe and effective new therapies for people. Indeed, one of my previous cancer therapies progressed into four human clinical trials. I am also involved in training Canada's next generation of multidisciplinary researchers, especially in vaccinology. I received funding from the Ontario Government (COVID-19 Rapid Research Fund, Ministry of Colleges and Universities) and Government of Canada (Pandemic Response Challenge Program, National Research Council of Canada) to develop vaccines against COVID-19. The scope of this research is limited to the pre-clinical realm and is years away from being ready for testing in a clinical trial. Since I do not hold any commercial interests, this is not considered a conflict of interest that would preclude me from publishing my research findings. If that were the case, most researchers could never comment on topics relevant to their area of expertise, because they receive funding in that area. Further, my laboratory's vaccine vectors also express the spike protein of SARS-CoV-2. As such, what I am presenting here affects my vaccines as much as anyone else's. I also hold numerous grants in support of my cancer research and basic viral immunology research programs, including, but not limited, to the Canadian Institutes for Health Research, Natural Sciences and Engineering Research Council of Canada, Canadian Cancer Society, and Cancer Research Society. Since the COVID-19 pandemic was declared, I have been actively involved in providing fact-based; balanced, scientific answers to questions posed by the public to help them make fully informed decisions. This has included ~150 media engagements ranging from radio shows, published articles, and appearances on televised news programs, spanning the local to international scope. I was also an invited keynote speaker for two international conferences that focused on COVID-19 and served as an invited member of several COVID-19-focused discussion panels. Vaccinology is a sub-discipline of immunology. I teach the value of high-quality, well-validated, robustly safety-tested vaccines and promote their use. I consider vaccines that have been developed on a foundation of sound science to be the most efficient type of medicine; they have cost-effectively saved millions of people from sickness and/or death. However, I am concerned that the risk-benefit profile of SARS-CoV-2 vaccines currently being used in Canada and elsewhere may not be appropriate for the mass immunization of children, youth, and young adults of child-bearing age. My scientific reasoning substantiated by the peer-reviewed literature is contained within this guide.

What is the Canadian COVID Care Alliance (CCCA)?

The CCCA is an alliance of independent Canadian scientists, physicians and other health professionals, committed to providing top-quality and balanced evidence-based information to

the Canadian public about COVID-19 so that hospitalizations can be reduced, lives can be saved, and our country can be safely restored as quickly as possible.

Disclaimer

The comments in this guide are mine alone and do not necessarily reflect the opinions held by my academic institution or the agencies funding my research program. Nevertheless, these comments have been vetted and supported by many like-minded researchers and physicians associated with the CCCA.

Preamble

Although I have tried to be reasonably comprehensive in my presentation of relevant facts about COVID-19 vaccines, I could have written much more; hundreds of pages, in fact. However, I feel that the current content represents the most important information that parents will need to make informed decisions about vaccinating their children. As children in Canada who are 12 and older can be vaccinated without parental consent, this guide also serves to share information and encourage open discussions between parents and their older children, so that the choice to consent or not consent is truly "informed". There will be many people who will challenge the content of this guide. I respect others' opinions and decisions. I simply ask for similar respect in return. I am a public servant providing information for which I have substantial expertise. It is being done from the perspective of having a genuine concern for the well-being of Canadian youth. I urge everyone to follow the weight of validated scientific data. I ask you to challenge information that is accompanied by loose claims of being 'data from on the ground' or 'data from the front lines', which often lack scientific rigor and a 'big picture' perspective, especially in an era of extensive social media censorship. Follow the weight of the validated data when deciding which evidence is relevant and reliable in your decision-making process.

Important note: many treasured colleagues from within and outside Canada have helped me piece together this story. Without them, we would not have made all the scientific links that are described in this guide. As such, **I can take only partial credit for this work.** Instead, I am fronting a larger group of physicians and researchers; consolidating our conversations and sharing of scientific articles into my own words. Sadly, many of these experts and professionals currently feel the need to remain anonymous to protect themselves from potentially career-ending reprisals when objective scientific evidence is presented publicly.

I have included some citations and links for important statements to show that they are backed by sound science. In many cases, there are other scientific articles that could have been referenced. However, the purpose of this document is not to provide an exhaustive list of references, but rather to provide sufficient evidence to support my concerns. My goal is not to prove that Canada's COVID-19 vaccines are unsafe, but to highlight the substantial uncertainties that exist in the current base of safety evidence and my consequent discomfort with the mass

vaccination of our youth. The proper scientific process dictates that the burden of proof of safety is on vaccine manufacturers and health protection agencies. Most importantly, a lack of proof of harm is not proof of safety.

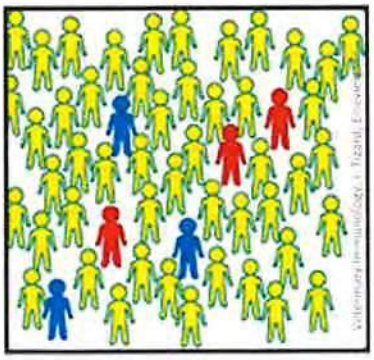
I first presented some of the information that is in this guide during a radio interview on May 27, 2021. This was a truncated ~five-minute sound bite that triggered a public smear campaign, including a slanderous website, a fake Twitter account, and harassment in the workplace. Nobody involved in the establishment of the smear campaign reached out to me to respectfully discuss the science. As a result, I wrote, along with collaborators, a brief two-page 'guide' to provide some key scientific references. Here, I have assembled a much more comprehensive guide, written with the goal of trying to communicate complex scientific principles to a lay person, yet with sufficient scientific rigour to also address experts. As I have often done with presentations and articles over the past year, I have set up this guide to answer the most common questions that I have received from the public. It is with sincere concern, and with the best interests of my fellow Canadians in mind, that I present you with the information that follows.

The problem: COVID-19

"COVID-19" is a disease that develops in a subset of individuals infected with a virus that is known as 'severe acute respiratory syndrome-coronavirus-2' (SARS-CoV-2). In the vast majority of cases of SARS-CoV-2 infections, people remain healthy (*i.e.* they are 'asymptomatic') or develop only mild to moderate symptoms of illness. However, in some cases, severe, and potentially lethal pneumonia, occasionally accompanied by other inflammatory events causing bleeding, clotting and/or neurological impairment, can develop in people in high-risk demographics, which includes the frail elderly and individuals who are immunocompromised (*i.e.* their immune systems do not function properly). Many people who become infected with SARS-CoV-2 do not develop the disease called COVID-19.

What is 'herd immunity'?

The concept of 'herd immunity' means that a virus will stop spreading among a population once most of the people in that population acquire a protective immune response. Importantly, this does not require every person to become immune, just a large majority. There are two ways for people to acquire immunity to SARS-CoV-2 and thus avoid the debilitating effects of COVID-19:



1. Natural infection:

When infected with SARS-CoV-2, most people clear this virus from their body by mounting a robust, long-lasting immune response that targets multiple components of the virus[1]. These people will be protected from re-infection with the same variant of SARS-CoV-2 and, due to the breadth of a natural immune response, will also likely have some degree of protection against emerging new variants of SARS-CoV-2. Indeed, most people who have naturally acquired immunity should not be at risk of developing severe disease even if variants arise that can effectively bypass the narrower immunity conferred by COVID-19 vaccines that are focused on a single component of SARS-CoV-2, such as the spike protein[2]. Interestingly, a landmark study in Canada suggested that a majority of healthy adults in British Columbia have evidence of pre-existing or naturally acquired immunity to SARS-CoV-2[3].

2. Vaccination:

Vaccines that have undergone properly conducted preclinical studies and the full suite of clinical trials to ensure they are (i) effective; and (ii) have excellent short-term and long-term (*i.e.* a minimum of two years; preferably longer) safety profiles, can allow an individual to become immune to a virus without having to be naturally infected.

How do vaccines work?

A successful vaccine must provide two things:

Thing 1: The virus or a piece(s) of the virus (*i.e.* a target for the immune system).

Thing 2: A danger signal (*i.e.* something that tells the person's immune system that the target it is seeing is dangerous and, therefore, worth responding to).

An effective vaccine simulates just enough of a natural infection, to trigger a person's body to develop an appropriate immune response without causing disease. Then, when the person becomes infected the first time by the natural virus, their body's immune system senses it is seeing the virus for the second time. This is because an immune response triggered by successful vaccination involves the body's development of 'immunological memory'. Therefore, the person's vaccine-primed immune response to the natural viral exposure will be faster and more robust, and the virus will be cleared without the person experiencing disease. Mass vaccination can accelerate progress of a population towards herd immunity.

How do Canada's COVID-19 vaccines work?

Canada currently has four COVID-19 vaccines that Health Canada has "Authorized by Interim Order". The Interim Orders enable the widespread deployment of the vaccines while the Phase 3 clinical studies (experiments in people) are being conducted. In the Phase 3 studies, all vaccine recipients must be followed for two years following the administration of the second vaccine dose. As long-term effects of the vaccine have yet to be understood, the vaccine is largely investigational. This is why the authorizations are "interim" and continued use is contingent on the collection of additional data from the Phase 3 studies, as well as other surveillance systems to assess the safety and effectiveness of the vaccines. Because the COVID-19 vaccines are being administered in Canada under experimental trial conditions, people receiving these vaccines should provide informed consent prior to being immunized. Informed consent demands that people be provided with all the known pros and cons, in an objective fashion and without undue pressure or coercion. This is a basic tenet of bioethics. Anyone administering a COVID-19 vaccine should be able to explain the benefits and risks based on the weight of the evidence provided in peer-reviewed, published scientific papers. Lay persons are encouraged to ask public health officials to explain the rationale for any statements made regarding COVID-19 vaccines and to have the sources of this information identified. Numbers in printed documents that do not contain citations do not necessarily reflect the robustness of the scientific literature.

The four COVID-19 vaccines currently being used in Canada include:

1. AstraZeneca/COVISHIELD vaccine (ChAdOx1-S):

These are two different names for the same vaccine (COVISHIELD is the brand name of AstraZeneca's vaccine that is manufactured by Verity Pharmaceuticals Inc. with the Serum Institute of India). Developed by AstraZeneca and Oxford University, the backbone of this vaccine is an adenovirus that does not cause disease in people. This adenovirus virus carries genetic material that provides instructions for a cell to manufacture a piece of SARS-CoV-2 (*i.e.*, the spike protein). When this adenovirus-based vaccine gets injected into the shoulder muscle, it is intended to infect cells and use the 'machinery' in these cells to manufacture small amounts of the SARS-CoV-2 spike protein. The SARS-CoV-2 spike protein and the adenovirus backbone provide the 'thing 1' and 'thing 2', respectively, that are needed to trigger an immune response.

Unfortunately, the rollout of the AstraZeneca vaccine in Canada proved to be a frustrating and complicated series of ever-changing, safety-triggered, recommendations given to a growing number of confused and distrusting members of the public. While many other countries paused their AstraZeneca vaccination programs to investigate safety issues related to potentially fatal blood clots, Canadians were told the AstraZeneca vaccine was safe for some population segments

and vaccinations with the AstraZeneca vaccine were initiated. After other countries practiced due diligence and confirmed that blood clotting was an adverse event associated with this vaccine, Canadians were then told that it was too unsafe for those under 55 years of age. Then Canadians between 40-55 years of age were told it was safe enough for them to use. Several weeks later, the message changed again, and the current messaging is that it is too unsafe to use as a first does in much of Canada. Millions of Canadians who received a single dose of this vaccine have since been wondering what to do. This highlights why the scientific method exists and why it should not be over-ridden by zealous public health officials. Safety testing should never be cut short. In many parts of Canada, the AstraZeneca vaccine is generally being used only for second doses for individuals who have had a first dose of the AstraZeneca vaccine and do not wish to have a second dose of another vaccine. The vaccine is irrelevant to Canadian children, youth, and young adults of child-bearing age, as it was never authorized for use in these population groups.

2. Janssen vaccine (Ad26.COV2.S):

This vaccine is made by Johnson & Johnson. Like the AstraZeneca vaccine, the Johnson & Johnson vaccine uses an adenovirus, albeit a different one. The way this vaccine works is similar to the AstraZeneca vaccine. After injection, cells infected with the adenovirus start to manufacture a spike protein that is very similar to that of the SARS-CoV-2 spike protein. There has been some public acknowledgement that this vaccine might also be associated with blood clots, and Health Canada has noted in their website notices of April 26th 2021 to healthcare professionals that "[v]ery rare cases of thrombosis in combination with thrombocytopenia, in some cases accompanied by bleeding, have been observed following vaccination with Janssen COVID-19 vaccine. A causal relationship with the vaccine is considered plausible." In considering the request for the Janssen vaccine to be Authorized Under Interim Order, Health Canada yet again acknowledged that "[i]mportant limitations of the data at this time include the lack of information on the long-term safety and effectiveness of the vaccine, interactions with other vaccines, and the lack of data in sub-populations (*e.g.* pregnant/breastfeeding women, pediatric population <18 years of age, patients with autoimmune or inflammatory disorders, immunocompromised patients and frail patients with comorbidities)." At the timing of writing this article, this vaccine has not been authorized for use in Canadian children, youth, and young adults of child-bearing age.

3. Pfizer BioNTech vaccine (BNT162b2):

This vaccine relies on technology that, prior to the COVID-19 pandemic, was not previously used in humans, except in small-scale clinical trials (such as a clinical trial of a rabies mRNA vaccine)[4]. The backbone of the Pfizer BioNTech vaccine is a lipid nanoparticle (a small bubble of fat). Inside the nanoparticle is a 'messenger ribonucleic acid' (mRNA). This is a tiny piece of genetic material that provides the instructions for a cell to manufacture a modified version of the SARS-CoV-2 spike protein. When these nanoparticles are injected into the body, they are

intended to fuse with cells with which they come into contact. When this happens, the mRNA migrates from the lipid nanoparticle and into the cell and the cell 'machinery' then uses this mRNA 'blueprint' to manufacture the modified version of the SARS-CoV-2 spike protein. This protein is the 'thing 1' that provides one of the two signals required for the immune system to become activated. It is not entirely clear what provides 'thing 2'. However, mRNA vaccines promote inflammation that can cause injury to normal tissue. When cells are injured, they release 'danger signals'. This might be what is providing the second signal ('thing 2') needed to induce an immune response.

Pfizer's vaccine has been associated with anaphylactic reactions in a small subset of individuals. These are serious allergic reactions that can be life-threatening. At the time of writing this guide, **the Pfizer vaccine is the only one that has received Authorization under Interim Order for Canadian children and adolescents 12 to 15 years of age.** In its decision-making process, Health Canada declared; "Health Canada has conducted a rigorous scientific review of the available medical evidence to assess the safety of the Pfizer-BioNTech COVID-19 vaccine. No major safety concerns have been identified in the data that we reviewed" [emphasis added]. Health Canada also acknowledged that "One limitation of the data at this time is the lack of information on the long-term safety and efficacy of the vaccine. The identified limitations are managed through labelling and the Risk Management Plan. The Phase 3 Study is ongoing and will continue to collect information on the long-term safety and efficacy of the vaccine. There are post-authorization commitments for monitoring the long-term safety and efficacy of Pfizer-BioNTech COVID-19 vaccine." Specifically related to the authorization for adolescents 12 to 15 years of age, "Health Canada declared, Health Canada has placed terms and conditions on this authorization requiring Pfizer-BioNTech to continue providing information to Health Canada on the safety, efficacy and quality of the vaccine in this younger age group to ensure its benefits continue to be demonstrated once it is on the market."

4. Moderna vaccine (mRNA 1273 SARS-CoV-2):

The Moderna vaccine also is an mRNA-based vaccine and, therefore, works the same way as Pfizer's COVID-19 vaccine. This vaccine has also been associated with anaphylactic reactions in a small subset of individuals. On June 7th 2021, Moderna had filed an application to extend the Authorization under an Interim Order to adolescents aged 12 to 17 years. At the time of writing this guide, Health Canada had not issued its decision.

None of Canada's COVID-19 vaccines can, in and of themselves, infect people with the SARS-CoV-2 virus, per se. Rather, these vaccines trigger the cells in a person's own body to manufacture one of the proteins that is a component part of SARS-CoV-2, and all the vaccines cause a person to make a modified version of the spike protein from SARS-CoV-2. The AstraZeneca vaccine contains the manufacturing blueprint for the exact same spike protein as is found on SARS-CoV-2. In contrast, the other three vaccines in use in Canada contain the manufacturing blueprint for a modified version that scientists refer to as the 'prefusion-stabilized spike'. All four vaccines are

designed to use the body's internal capability to manufacture the spike protein to then trigger the body's immune response.

What are the known serious adverse events that are associated with COVID-19 vaccines?

Using the United States Vaccine Adverse Event Reporting System (U.S. VAERS), as of June 11th 2021, the 20 most frequently reported adverse events (presented in descending order) were headache, pyrexia (fever), fatigue, chills, pain, nausea, dizziness, pain in extremity, injection site pain, myalgia (muscle pain), injection site erythema (redness), arthralgia (joint stiffness), pruritus (itching), rash, dyspnoea (difficulty breathing), injection site swelling, injection site pruritus (itching), vomiting, and asthenia (weakness). These side effects are common side effects and are similar to those reported in the Phase 3 clinical trials. Although these symptoms can be severe in some people and can result in an inability to perform daily activities, they usually subside over one to three days.

The mRNA vaccines (Pfizer and Moderna) can, in rare cases, cause anaphylaxis. Since this can be potentially fatal, these vaccines are often administered in special vaccine clinics that are staffed with personnel trained to treat people who may experience anaphylactic shock. The reason this problem is thought to be limited to the mRNA vaccines is likely due to a pre-existing allergy against something present in the liposome nanoparticles (the small bubble of fat) that are the part of the vaccine that envelopes the mRNA material. One of the liposome ingredients that might be the culprit is polyethylene glycol (PEG).

Based on data from international regulatory agencies (such as the Norwegian Medicines Agency), the adenovirus-based vaccines (*i.e.* AstraZeneca and Janssen) have been implicated in causing a very serious type of blood clot (a cerebral venous sinus thrombosis) that is simultaneously associated with a low platelet count and bleeding following vaccination. This is one of the reasons the AstraZeneca vaccine has largely been suspended for use in Canada, with the exception of use for second doses in those who received the AstraZeneca as their first dose and wish to stay with the same vaccine brand.

Are there other serious adverse events associated with COVID-19 vaccines that are being investigated?

Side effects that are rarer, including those that are serious or life-threatening, are still being learned about. For example, the United States Centers for Disease Control and Prevention (CDC) announced, only on June 11th 2021, that an Emergency Meeting would be held on June 18th 2021 to discuss reports of inflammation of the heart resulting from use of the Pfizer and Moderna vaccines in young males 16 to 24 years of age. It has been approximately six months since the vaccines were authorized under an emergency use in the U.S., and only now is this

association being recognized. There are many reasons why it is difficult to identify serious side effects that are rare or that occur only over a longer period of time or in a specific population group or sex. These difficulties are described below.

Difficulty #1: Too Soon to Tell for Sure

Pfizer and Moderna each initiated large, Phase 3 trials that were randomized, double-blind, and placebo-controlled. The placebo group is important because it serves as the reference group and helps in the interpretation of side effects experienced in the vaccine group. At the time that the vaccines were granted emergency use authorization, each company had safety and efficacy data for an average of only two months following the administration of the second vaccine dose; in the study in adolescents, most subjects had safety and efficacy data for either one or two months. According to the original protocols, every individual in the study is supposed to be followed for a total of two years following their second dose.

Difficulty #2: Abandoning the Control Group

The vaccines have been authorized under emergency use in many key countries, globally; and fear-based pressures imposed by public health agencies to vaccinate everyone has triggered study participants to want to know which study group they had been allocated to, so that those in the placebo group could be vaccinated. The studies have therefore been unblinded, meaning there is no longer a placebo group. This means that a rigorous assessment of safety in the context of a well-controlled clinical study is no longer possible, and there must be increased reliance on vaccine post-deployment, passive surveillance systems. Of course, this, itself, is challenging, given that there is uncertainty in both the numerator (the number of vaccine-related adverse events) and the denominator (the number that is typical for that event, otherwise referred to as the "background incidence" of the event). Moreover, it is extremely difficult to prove definitively that an event is caused by (and not just associated with) vaccination when using passive surveillance systems.

Difficulty #3: Under-Reporting of Adverse Events

The problem with passive adverse event reporting systems, which is the type of system that both Canada and the U.S. are relying on, is that there is a notorious problem of adverse event under-reporting. This is because reporting is voluntary; people may be unaware there are ways to report adverse events; people are often discouraged from reporting adverse events; people (including attending physicians) assume the condition is not related to vaccination; or people may not be able to report their adverse events (if they are severely disabled, ill, or deceased). Most disconcerting is the situation, as we see in Canada, where adverse event reports attempted to be submitted by medical professionals are pre-screened and sometimes rejected by pre-screening authorities. Consequently, adverse event databases can easily fail to identify potential concerns, or underestimate problems to an unknown degree and are, therefore, not a source of

accurate numbers to calculate true risk. For example, using the U.S. VAERS, it was estimated that the risk of anaphylaxis was 4.7 per million for the Pfizer vaccine and 2.5 per million for the Moderna vaccine[5]; however, in an active surveillance study of 64,900 healthcare workers who had been vaccinated, the rate was actually 216 per million[5], representing a potential rate of under-reporting of 46- to 86-fold. Despite these limitations, passive surveillance systems are useful for identifying potential risks that could then be investigated in properly designed safety studies.

Difficulty #4: Lack of Global Consistency and Thoroughness in Defining Events of Special Interest

Using the U.S. VAERS and similar adverse event reporting systems around the world, there is continuous monitoring of adverse events of special interest. But each jurisdiction is left to their own discretion to decide which, if any, particular adverse events of special interest will receive closer scrutiny. For example, the European Medicines Agency has compiled a list of important medical events (IMEs) which are always to be classified as serious (the IME list). The IMEs that are most frequently reported following COVID-19 vaccination (in descending order) are:

- Fainting (syncope)
- Blood clot(s) in the lungs
- Anaphylactic reaction
- Deep vein thrombosis
- Pneumonia
- Low blood platelet count (thrombocytopenia)
- Blood clot(s) or bleeding in the brain
- Hallucinations
- Cerebral stroke
- Loss of consciousness

Definitive cause-and-effect relationships for these events have not yet been established; it is hoped that with additional surveillance and time, clarity on the role of the vaccines in the cause of these events will be better understood. In the meantime, given that the spike protein is biologically active and there are mechanisms that could potentially explain some of these IMEs (discussed further below), there is good reason for genuine concern.

Why weren't serious adverse events identified before vaccines were rolled out?

Problems like anaphylactic shock (a severe allergic reaction) and potentially fatal blood clots were not identified until most of the experimental COVID-19 vaccines were used widely among the public[5, 6]. Janssen's study of the Johnson & Johnson vaccine did suggest some propensity for blood clotting. As for anaphylactic reactions, people with a history of allergies were excluded from the earlier clinical trials.

Another reason why some problems were not identified earlier is because short-cuts were taken with the traditional approach to vaccine research. Specifically, **the time taken to assess safety was too short**. Instead of taking the usual ~4-10 years to undergo thorough *in vitro* (*i.e.*, benchtop) tests, pre-clinical (*i.e.*, animal) studies, and then sequential clinical testing (*i.e.*, human Phase 1, 2 and 3 trials), COVID-19 vaccines were developed and assessed for safety and efficacy in less than one year. This meant that only very short-term safety scenarios could be evaluated. Of equal concern, **the number of people that were evaluated in clinical trials was too small** to capture rare but dangerous side-effects. This is unfortunate, because we have seen in Canada that rare but serious problems can lead to a vaccine program being suspended. Indeed, in Canada, a risk of blood clots for the AstraZeneca vaccine of 1 out of every 55,000 people vaccinated was deemed to be too dangerous, leading to its use being halted. Authorization under Interim Order for COVID-19 vaccines was granted after they were evaluated for a short duration in about 20,000 people. This means these studies could, at best, detect serious side effects that would occur in at least 1 out of every 20,000 people. In other words, the study design included a test population that was too small to identify vaccines that may be too dangerous for Canadians.

A clinical trial was conducted to justify using the Pfizer vaccine in Canadian children and adolescents; was it flawed as well?

Yes. First, it was far too short in duration to have any chance of assessing anything other than short-term harm. Also, in light of the information provided above, one needs to consider the following: only 1,131 adolescents between the ages of 12 and 15 received the vaccine in this study. This means that the study would have only been able to detect a serious side effect that occurs in 1 out of every 1,131 adolescents that are vaccinated; but a 1 in 55,000 risk was deemed to be too dangerous for adults for whom SARS-CoV-2 represents a greater risk. Furthermore, based on the recent observation of increased risk of heart inflammation following immunization with either the Pfizer or Moderna vaccine in young males, it appears serious side effects may be a function of both age and sex. In this regard, the Pfizer study of only 1,131 subjects provides even less robust data...enough to detect a serious gender-differentiating side effect that occurs in one out of approximately 565 (*i.e.*, 1,131÷2) males vaccinated and one out of approximately 565 females vaccinated.

But we have been told that adolescents and children can: (a) die from COVID-19, (b) suffer severe disease, and (c) be asymptomatic spreaders of SARS-CoV-2 and, therefore, kill others. Don't these risks suggest that children, youth, and young adults of child-bearing age should be vaccinated?

No, they don't. Let's break this down...

(a) Deaths due to COVID-19 are extremely rare in young Canadians. In sixteen months 13 Canadians under the age of 20 have died of 266,852 with confirmed SARS-CoV-2 infection (data from the Government of Canada, as of June 11, 2021). Because many children have asymptomatic infections, the true denominator is likely greater. This loss of 13 lives is indeed a tragedy, but no more so than the ~2,266 Canadians under the age of 20 who die from other causes every 16 months. Basic cost-benefit analyses have been largely ignored during the pandemic. The fear of young people dying from SARS-CoV-2 has reached a point where we seem to have placed a much higher value on lives lost due to COVID-19 than lives lost to any other causes.

SARS-CoV-2 is not a problem of pandemic proportions for all demographics. Infection fatality rate (IFR) is a way to assess how dangerous a pathogen is. The IFR is calculated based on the number of people who die, from among the total number infected. Early in the declared COVID-19 pandemic, it was estimated that the IFR for SARS-CoV-2 was ~10-fold higher than for a serious outbreak of an influenza virus, or ~1%; maybe even as high as 10%. Indeed, the IFR for a bad 'flu' season can be as high as ~0.1%[7]. This IFR for influenza is calculated despite the high use of influenza vaccines that are commonly given seasonally to target populations. It is important to note that calculating an accurate IFR requires having accurate data for the denominator in the equation, which is the total number of people that have been infected.

Exacerbated by Canada's lack of testing for evidence of seroconversion (*i.e.* when virus-specific antibodies are present in an individual, which indicates they were infected) against SARS-CoV-2, it has been impossible to ascertain how many Canadians have been infected. However, as data have accumulated in countries that did practice due diligence in this area, the total number of infections that have occurred keeps getting re-adjusted to higher numbers. This is due to phenomena such as the large number of people who were infected but did not realize it, because they never became ill (they never developed COVID-19). As a result, the actual calculated IFR for SARS-CoV-2 has been steadily declining. Remarkably, as the data regarding total infections have become more accurate, the IFR for SARS-CoV-2 has most recently been estimated to be only ~0.15%[8]. It is likely that this IFR will drop even further as the extent of unnoticed infections is further elucidated.

Indeed, a recent study found that ~90% of randomly tested healthy adults in British Columbia had evidence of natural immunity to SARS-CoV-2[9]. This indicates that the denominator for determining the true IFR is likely substantially higher than previously appreciated, which would mean the IFR is less than 0.15%[9]. Further, this IFR includes the high-risk frail elderly, immunocompromised, smokers, highly obese people, and those with diabetes, pulmonary and cardiovascular disease. For Canadians who are outside of these high-risk demographics, the IFR would be much less than 0.15%, especially for children. Therefore, COVID-19 does not represent a substantial risk to children, youth, and young adults of child-bearing age[10].

(b) Very few children are at risk of developing severe COVID-19. It is challenging to know how small this risk is because public health officials have refused to differentiate the nature of the 'cases' of COVID-19 that have been reported. Many estimates of children in hospital with COVID-19 include children who were admitted for other reasons but had tested positive with SARS-CoV-2. The reality is that most cases in children and adolescents are mild. In fact, most children do not get sick at all after being infected with SARS-CoV-2. Children have a lower risk of developing disease, especially severe forms, compared to adults. This is in large part because they express in their lungs and airways lower concentrations of the "ACE2 receptor", a protein on the surface of various cells in the body that serves as a point of attachment for the SARS-CoV2 spike protein, and that when "docked" enables entry of the virus into the cell for subsequent replication and spread of infection.

(c) Asymptomatic transmission of SARS-CoV-2 is negligible. The definition of an asymptomatic individual is a person who is known to be infected with a microorganism but fails to develop symptoms associated with a disease. Indeed, we are all 'asymptomatic carriers' in the sense that we harbor trillions of bacteria and viruses in and on our bodies. However, these normal microbiomes usually do not cause us any disease, unless we become immunosuppressed or unless 'safe' microbes get transferred to anatomical locations where they can potentiate disease (*e.g.* fecal-to-oral transfer of some strains of *Escherichia coli*). So, in the context of SARS-CoV-2, an asymptomatic carrier would be defined as an individual who is infected with the virus but fails to develop COVID-19. A colleague of mine recently asked this rhetorical question: "didn't we previously call an asymptomatic person 'healthy'?"

A study of the prevalence of SARS-CoV-2 in ~10 million people in Wuhan, China found no evidence of asymptomatic transmission[11]. In the United Kingdom, the 'Scientific Advisory Group for Emergencies' recommended that "Prioritising rapid testing of symptomatic people is likely to have a greater impact on identifying positive cases and reducing transmission than frequent testing of asymptomatic people in an outbreak area"[12]. Consequently, they have asked their government to change their testing policy by moving away from asymptomatic testing. The World Health Organization notes that "Most PCR assays are indicated as an aid for diagnosis, therefore, health care providers must consider any result in combination with timing of sampling, specimen type, assay specifics, clinical observations, patient history, confirmed status of any contacts, and epidemiological information"[13].

On its own, a positive result on a PCR test to detect SARS-CoV-2 is insufficient to diagnose COVID-19, yet this has become routine in Canada. In addition to the potential for false positive tests, true positive results can also be obtained from genomes of SARS-CoV-2 particles that are no longer infectious. An example of the latter would be an individual who has mounted an effective immune response and may have remnant replication-incompetent viral particles or partially degraded viral genetic material. Indeed, following clearance of SARS-CoV-2 from the body, full and/or partial genomes of SARS-CoV-2 can remain for up to several weeks. One key reason for this is that some phagocytic cells, which are a component of the innate immune

system, can be long-lived. Phagocytosis, which is the engulfment and digestion of SARS-CoV-2, is a mechanism to kill and remove the virus from the body and to activate other white blood cells. As such, these can be a source of SARS-CoV-2 genetic material that could be amplified by a PCR test. However, this genetic material would not have the potential to cause COVID-19. Persistence of whole or partial genetic material that is not associated with infectious particles is well-documented for a variety of other viruses, including measles[14], Middle East Respiratory Syndrome (MERS)-coronavirus[15], and other coronaviruses[16].

Too often, a positive PCR test for the presence of SARS-CoV-2, is being used, on its own, to define positive cases of COVID-19. However, the presence of a portion of the viral genome in an individual, on its own, does not necessarily equate with disease (*i.e.* COVID-19). To be declared a COVID-19 "case", the infection would also have to be associated with expected signs such as antibody development and/or symptoms of disease. This is known as a clinical diagnosis and would be based on evaluation by a physician, in conjunction with test results. A gold-standard test for infectivity of a virus is a cell-based functional assay that determines the potential for the virus sample to cause cell death. However, such an assay is not in routine use in Canada. Absence of such an assay further confounds any meaningful interpretation of positive results in asymptomatic people. Drawing conclusions based solely on the results of laboratory tests, would take the diagnosis of diseases out of the hands of physicians, and place the onus for this on technicians employed by testing laboratories. Further confounding this issue is the fact that cases of COVID-19 can be claimed in the absence of confirming infection with SARS-CoV-2 (this is known as "ICD code U07.2 COVID-19, virus not identified")[17]. Worse, the definition of a case of COVID-19 has changed over time in Canada. Indeed, the government of Canada has stated the following on their website: "Previous versions of the COVID-19 case definition are available upon request. Please email COVID19Surveillance@canada.ca to request a copy or for more information."[17]

Positive PCR tests for SARS-CoV-2 in asymptomatic people are often based on what scientists call 'high cycle numbers' (also called "cycle thresholds" or Ct"). PCR tests that only yield a positive result at high cycle numbers brings into question whether or not these individuals actually harbor infectious viral particles. This, combined with the absence of a functional cell-based assay to prove infectivity, renders results of asymptomatic testing nearly impossible to interpret accurately. Indeed, the World Health Organization, agreeing with many health professionals around the world, has emphasized that spreading of SARS-CoV-2 by asymptomatic individuals is rare and an emphasis should be placed, therefore, on testing people with signs or symptoms of illness, not those who are apparently healthy[18]. Of particular concern is the high cycle numbers being used by labs in Ontario (*i.e.* up to 38 cycles being defined as 'positive' by Public Health Ontario[19]), to define a COVID-19 positive "case." Several studies have been conducted to determine the highest number of PCR cycles at which live SARS-CoV-2 from a sample could be successfully cultured in cells. These studies suggest that appropriate cycle thresholds were 25[20], 22-27[21], and 30[22] cycles. This indicates that tests with positive results obtained above 22-30 cycles are not clearly supportive of the presence of live (*i.e.* replication-competent) SARS-CoV-2. The logical conclusion is that it is erroneous to declare samples that test

positive at high cycle numbers, especially those above 30, as being "positive" for infectious SARS-CoV-2. Appendix 1 shows results of a published study that depicts the numbers of PCR cycles at which asymptomatic people tested positive for SARS-CoV-2 relative to that observed for people with symptomatic infections[23]. Remarkably, if the cut-off for positive test results was set to Ct values of 22 or 30 (*i.e.* the point beyond which samples fail to yield potentially infectious virus particles), the vast majority of 'positive test results' would be rendered negative. It was even concluded in a study by La Scola B, *et al.*, that patients testing 'positive' at cycle numbers above 33 could likely be discharged from hospitals[24]. This means that an unknown number of positive cases reported in Ontario were likely not true positives of COVID-19. This is further supported by evidence that asymptomatic people have detectable SARS-CoV-2-specific memory T immune cells after exposure to the virus, which would be inconsistent with a risk of them harboring and spreading the virus to others[25].

Importantly, false positive test results, which have a greater risk of happening among asymptomatic people, have been shown to have numerous negative consequences in terms of physical and mental health, and causes financial losses[26]. Testing of asymptomatic people for the presence of portions of the SARS-CoV-2 genome makes neither medical nor economic sense. Positive test results from asymptomatic individuals cannot be interpreted in a clinically meaningful way. Although asymptomatic transmission is theoretically possible, it is improbable that it is occurring in substantial numbers and does not represent a significant risk of causing COVID-19-related hospitalizations or deaths in others.

For all the aforementioned reasons, **it is wrong to label children as being asymptomatic spreaders of SARS-CoV-2** that will sicken and kill others. Indeed, as reported by L. T. Brandal *et al.*, "under 14 year olds are not the drivers of SARS-CoV-2 transmission"[27]. A study in England concluded "SARS-CoV-2 infections and outbreaks were uncommon in educational settings", with staff (adults), not students (children) being the primary source of infections[28].

Now that the reasons that were used to justify using an experimental COVID-19 vaccine in children have been put into a reasonable perspective, let's continue talking about the vaccine technology.

Why was the spike protein from SARS-CoV-2 chosen as a target for the immune system?

Electron micrograph of a coronavirus

The spike protein gives SARS-CoV-2 its 'crown-like' appearance, which means it looks like it has a 'corona'. This protein allows the virus to attach to our cells and then infect them. If antibodies can bind to and 'block' all the spike proteins on the surface of the virus, then it could not infect our cells. Moreover, the binding of antibodies to even a part of the virus can tag it for attack by cells of our immune system. As such, COVID-19

vaccines currently being used in Canada instruct our cells to manufacture the spike protein in order to trigger our bodies to mount an immune response against this protein with the hope that the ensuing antibodies will get into our lungs and airways and block the virus, should we be infected in the future.

What should we know about the SARS-CoV2 spike protein?

Before we go any further with the story about COVID-19 vaccines, there is important information that you need to know about the spike protein from SARS-CoV-2.

The spike protein from SARS-CoV-2 has the potential to damage cells in the body

In cases of severe COVID-19, problems can extend well beyond pneumonia and the associated inflammation in the lungs. The disease can progress beyond the lungs and into other parts of the body. In severe infections, SARS-CoV-2 can cause damage to the cardiovascular system (*i.e.* heart and blood vessels). In fact, some have referred to severe COVID-19 as largely being a vascular disease[29, 30, 31]. Blood clots, bleeding and/or damage to the heart have all been linked to severe COVID-19. Severe COVID-19 can also cause neurological problems (*i.e.* damage in the brain). A series of recent scientific publications provide some evidence that this damage throughout the body may not require an intact SARS-CoV-2 particle. Instead, the spike protein from SARS-CoV-2 might be responsible for at least some of the damage that occurs in severe cases of COVID-19[32]. This is because there are many cells other than those in the lungs and airways that feature the receptor for the spike protein, known as the ACE2 receptor. Most notably, platelets and cells lining blood vessels can express high concentrations of this receptor. Importantly, autopsies performed on patients who died from severe COVID-19 revealed that free spike protein from SARS-CoV-2, not the intact virus, was responsible for substantial damage throughout the body. Notably, blood vessels in the skin, fat, and the brain were found to express high concentrations of the ACE2 receptor that the spike protein binds to. There was a lot of spike protein found in these tissues, with little to no evidence of the intact virus being present. Indeed, the authors of the study that described these autopsies concluded "COVID-19 represents a viral infection with limited sites of infectious virions but deadly sequelae due to the effective manner in which pseudovirions in the context of released viral proteins activate synergistic microvascular pathways of tissue destruction throughout the body."[33] In lay language, proteins like the spike protein, not the intact virus, appear to mediate

much of the damage in the body in people who suffer from severe COVID-19. When the spike protein binds to these receptors, there are several events that can take place:

1. Proteins (called 'complement proteins') that are part of our innate immune system can get activated, causing inflammation that can damage or destroy the cells lining blood vessels and/or platelets[34]. Platelets that are required for clotting of blood also express ACE2 receptors that can bind with spike protein with dire consequences. Damage and destruction of platelets can cause their numbers to go down (a condition known as "thrombocytopenia"), and if platelet counts get too low and blood vessels are damaged, bleeding cannot be stopped. Therefore, the spike protein can potentiate bleeding.

2. Binding of the spike protein to platelets can also cause the platelets to become activated[35]. Activated platelets tend to clump, which can lead to the formation of clots. There is evidence that the spike protein can interact with other proteins in the blood to promote clotting[36]. As such, the spike protein can promote blood clotting.

3. Spike proteins binding to the cells that line our blood vessels can cause these cells to express proteins (known as 'caspases') that can cause the cells to die[33]. This is similar to findings from the 2002-2004 SARS outbreak where the spike protein from the original SARS-CoV could cause cells to die when it was being manufactured inside of them[37]. Dying cells that have been manufacturing the vaccine-encoded spike protein would release free spike protein or portions thereof.

4. Spike proteins binding to the cells that line our blood vessels can cause these cells to over-produce cell-signalling cytokines that can potentially contribute to dangerous 'cytokine storms' (overly robust and severe inflammation)[33, 38].

Of additional concern is the knowledge that the spike protein is capable of dissociating into two parts and these smaller subunits (S1 and S2) can cross the blood-brain barrier where they can potentially cause damage in the brain[39]. Indeed, people who have died from severe COVID-19 with neurological signs were found to have the spike proteins but not the intact virus in their brains[40]. These neurological signs could be seen in laboratory studies when spike proteins were injected into the blood of mice.

Conclusion: The spike protein, if it gets into circulation, has the potential to cause damage to the cardiovascular system and other tissues.

Back to the vaccines

Now that there is a clear understanding that the spike protein from SARS-CoV-2 is a dangerous toxin when it gets into the blood and is distributed throughout the body, we can continue with the story about COVID-19 vaccines.

Evidence that mRNA-based COVID-19 vaccines can get distributed throughout the body

When the COVID-19 vaccines were designed, it was not appreciated that the spike protein could potentially damage cells in the body. As a consequence, administration of the current COVID-19 vaccines can put people at risk of damaging their cells, especially if expression of the spike protein is not limited to the vaccine injection site. An assumption was made with these vaccines that has proven to be incorrect. The assumption was that mRNA vaccines, which are a new technology, would behave the same as traditional vaccines. It was thought by many that mRNA vaccines would stay at the injection site and the only other place they would go is to the draining lymph nodes in the immediate vicinity of the injection site. More specifically, it was thought that cells of the immune system would come to the site of injection and create pieces of the virus and take these pieces to the lymph nodes where they would be shown to B and T cells (*i.e.*, B and T lymphocytes). The B and T cells would then get activated, multiply to large numbers (this is why lymph nodes swell when a person is mounting an immune response) and then head out into the body to search for the pathogen. Notably, B cells are the source of antibodies. Unfortunately, researchers have come to learn that **the mRNA vaccines do not stay in the shoulder muscle**. In fact, **they have the potential to spread far and wide throughout the body via the blood**. Obviously, this is a very serious conclusion to draw, so let's walk through the solid scientific evidence that demonstrates this potential for biodistribution.

A report that Pfizer provided to the Japanese government (see Appendix 2) was published as reference #25 in an article[41] published in *BMJ* that can be found at this link. In section 2.6.5.5B of the report to the Japanese government there is a table containing lipid nanoparticle biodistribution data. This table shows where their surrogate "vaccine" (*i.e.* represented in the laboratory test by little bubbles of surrogate fat containing an analytical detection marker) ended up in the body of immunized rats, used in the laboratory as surrogates for humans. A portion of the table is reproduced below. Please review the data so you can get the full picture. I would like to highlight some observations. First, as shown in the blue rectangle that I added to the table, a lot of the surrogate vaccine dose remained at the injection site, as one would expect. Remarkably, however, most of the vaccine dose had gone elsewhere. The right side of the table (shown in the report to the Japanese government but not below) shows that 50-75% of the vaccine dose failed to remain the site of injection. The big question is, where did it go? Looking at the other tissues shows some of the places it went and accumulated. The red rectangle shows that **the surrogate vaccine was circulating in the blood**. There is also evidence that a substantial amount of the vaccine went to places like the spleen (green rectangle), liver (brown rectangle), ovaries (yellow

rectangle), adrenal glands (purple rectangle), and bone marrow (orange rectangle). The vaccine went to other places as well, such as testes, lungs, intestines, kidneys, thyroid gland, pituitary gland, uterus, *etc*. **The surrogate vaccine tested in a laboratory setting was widely distributed throughout the laboratory animals' bodies.**

Species (Strain):	
Sex Number of Animals:	Male and female 5 animals/sex
Feeding Condition:	
Method of Administration:	I
Dose:	50 µg [^{3}H]
Number of Doses:	
Detection:	Radioactivity quant
Sampling Time (hour):	0.25, 1, 2, 4,

Sample	Mean total lipid concentration (µg lipid equivalent g (or mL) (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	16.2
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77
Brain	0.045	0.100	0.138	0.115	0.075	0.069	0.068
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546
Injection site	128	394	311	338	213	195	165
Kidneys	0.391	1.16	2.05	0.924	0.590	0.426	0.425
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34
Liver							
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED **Test A**

Sample	Total Lipid concentration (µg lipid equivalent g (or mL)) (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.159	0.290	0.405	0.534	0.554	0.727
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192
Ovaries (females)	0.104	1.34	1.64	2.34	3.59	5.24	12.3
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.153	0.170
Salivary glands	0.084	0.195	0.255	0.220	0.135	0.170	0.264
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253
Small intestine	0.050	0.221	0.476	0.879	1.28	1.39	1.47
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112
Spleen	0.554	2.47	7.73	10.3	22.1	29.1	23.4
Stomach	0.017	0.065	0.115	0.144	0.208	0.152	0.215
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320
Thymus	0.055	0.243	0.340	0.335	0.196	0.207	0.331
Thyroid	0.155	0.536	0.842	0.851	0.543	0.578	1.00
Uterus (females)	0.043	0.205	0.305	0.140	0.287	0.289	0.456
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420
Plasma	3.97	8.13	8.90	5.50	2.36	1.78	0.805
Blood:Plasma ratio[a]	0.515	0.515	0.550	0.510	0.555	0.530	0.540

Based on the results of this biodistribution test, further tests should have been required in order to assess the impacts on more tissues and for a longer time before the vaccine was authorized for use, especially in growing children, adolescents, and young adults of child-bearing age. The vaccine manufacturer, researchers and regulatory authorities alike should have also looked more comprehensively at the potential for the test animals to shed the vaccine by assessing saliva, urine, and feces. Note that there was evidence of some trafficking of the vaccine to the salivary gland and bladder, which indicates there is potential for some degree of shedding of the vaccine from the body. Further, the biodistribution of the spike protein that is created by the body after vaccination should be carefully mapped. Studies such as these should be performed in at least two animal models, with one of these not being a rodent model since rodents have levels of ACE2 receptor binding affinity that is far less than that of humans and may, as a result, underestimate the impact of spike protein on humans. There should also have been an evaluation of where the vaccine and the spike protein were going in humans in a very limited Phase 1 clinical safety trial. **This may not have mattered as much if the protein encoded by the mRNA was inert, although the risks of autoimmunity with the deposition of the lipid nanomaterials at different organs are certainly worthy of consideration. But now that we know the spike protein encoded by the mRNA has**

its own biological activities of concern, there is even greater potential for damage to organs and tissues arising from circulating vaccine material.

Although not as detailed as the data in the report to the Japanese government, Pfizer's report to the European Medicines Agency states similar findings regarding the broad distribution of their vaccine platform throughout the body. The report is in Appendix 3. Of great concern is the following excerpt from section 2.3.2 on page 45: "**No traditional pharmacokinetic or biodistribution studies have been performed with the [Pfizer-BioNTech] vaccine candidate BNT162b2**". If this is the first time this vaccine technology platform has been rolled out for wide distribution to humans, and if the Japanese biodistribution data showed evidence of spread of the surrogate vaccine material, one must ask **why was this experimental vaccine allowed to be used in people without it having undergone a crucial biodistribution study first?** This would have told us where the vaccine was going in the body before its use in people.

Supporting the need to address uncertainties and concerns regarding the biodistribution of the vaccine and the resulting spike protein is a peer-reviewed scientific paper that has just been accepted for publication. It describes a study in which 13 healthcare workers were assessed for the presence of the spike protein in their blood after receiving Moderna's vaccine (an mRNA vaccine with essentially identical platform technology as the Pfizer-BioNTech vaccine). Notably, the spike protein, (or the portion of it that binds to ACE2 receptor), could be found in the circulation in 3 out of the 13 people (and in 11 out of the 13 people), respectively[42]. The spike protein could be detected in the blood up to two weeks post-vaccination in most individuals and at 28 days post-vaccination in one individual. Some may argue that the concentration of the protein was low in most of the people studied. However, a protein circulating at a low concentration for up to two or more weeks could accumulate on cells over time as the blood constantly perfuses *(i.e.*, flows through) bodily tissues. Further, the biodistribution studies in the appendices suggest the spike protein could potentially be concentrated in many tissues that would not be evident by looking in blood alone. The possibility also exists that there were spike proteins already bound to ACE2 on the cells lining the blood vessels, but this was not investigated. Regardless, low concentrations of the spike protein in circulation would be expected in this small-scale study. High concentrations of a protein that can cause damage to blood vessels in a large number of people would not be consistent with a low incidence of severe adverse events. Remember, the AstraZeneca vaccination program was suspended in Canada due to a 1:55,000 incidence of blood clots. If spike proteins in blood were responsible for a severe side-effect, one would expect to see high concentrations of this protein in only one out of many thousands of people; a phenomenon that would likely not be detected in an analysis of only 13 people. Clearly, more work is needed here to assess the biodistribution of spike proteins in the human body after vaccination.

In a pre-print article (note: this means the paper has not yet undergone independent scientific peer review), there are data that indicate mRNA can even be detected in breast milk post-vaccination. This aspect of the study was downplayed but provides proof-of-principle that

this can happen. Knowing what we now know, it would not be surprising to have the spike protein in the breast milk of some lactating women if they were to be vaccinated. Proteins circulating in the blood usually get concentrated in breast milk. Notably, there have been some adverse events reported of infants experiencing bleeding in their gastrointestinal tracts after suckling from mothers who had received a COVID-19 vaccine. Here are some examples from the U.S. VAERS (I haven't checked for more since May 2021):

Serious Adverse Events Related to Breastfeeding After Receiving a COVID-19 Vaccine

- VAERS ID #945282; a 32-year-old mother had her 2-month-old breastfeeding daughter die 7 days after the mother had received the Pfizer-BioNTech vaccine
- VAERS ID #949926; a 34-year-old mother had her 4-month-old breastfeeding boy pass blood and mucous in the stools starting 2 days after the mother had received the Moderna vaccine
- VAERS ID #992676; a 30-year-old mother had her 2-month-old breastfeeding boy experience anorexia, spitting up, discoloured bloody feces, vomiting of blood, ulceration of the stomach, and bleeding in the gastrointestinal tract starting 2 days after the mother had received the Moderna vaccine

There were also other types of adverse events in infants associated with breastfeeding from mothers who had recently received a COVID-19 vaccine. For the sake of brevity, I have listed the VAERS ID #s here; anyone can look them up in the publicly available VAERS database.

- VAERS ID #s: 903355, 911226, 913968, 913971, 918972, 921052, 927664, 936865, 939409, 974519, 978085, 978485, 984448 (mother) - 984602 (infant), 1049482, 1105816, 1168901, 1171284

There is also a pre-print article that describes how an adenovirus-based vaccine can result in spike proteins damaging the vascular system. These types of vaccines are currently not being given to children in Canada. The mechanism is different from the mRNA-based vaccines, but the outcome is similar. The authors of this paper have coined an interesting term to describe the effect of a COVID-19 vaccine causing the same damage to the body that SARS-CoV-2 does; they called it "vaccine-induced COVID-19 mimicry syndrome".

It turns out that the suggested wide distribution of mRNA vaccines throughout the body has a historical precedent, such as for immunizing against influenza for example[43]. However, many people do not realize that lipid nanoparticles were not designed to function as vaccines. They were designed to serve as gene therapies or carry drug cargo throughout the body[44], including into the brain where attempts could be made to treat diseases such as Alzheimer's disease, Parkinson's disease, and brain cancers. Of substantial concern is the use of PEG, which has been associated with anaphylactic shock in some people after receiving a mRNA vaccine. PEG was added to lipid nanoparticles in the early days of drug development to promote much wider distribution throughout the body. Specifically, when PEG is added to lipid nanoparticles, it helps

the particles avoid being consumed by cells throughout the body, especially cells of the immune system, that would limit the distribution of the mRNA cargo[45, 46]. Indeed, addition of PEG to lipid nanoparticles was hailed as a breakthrough because "This effect is substantially greater than that observed previously with conventional liposomes and is associated with a more than 5-fold prolongation of liposome circulation time in blood"[45]. In retrospect, it seems that another mistake may have been made in the rush to get these vaccines into people: Arguably, the PEG component should have been removed from the lipid nanoparticle formulation. This likely would have resulted in lipid nanoparticles with a greater tendency to remain at the injection site and be picked up by the very cells of the immune system that we want to induce an immune response.

Conclusion: The assumption that COVID-19 vaccines remain at the injection site (*i.e.* the shoulder muscle) is not borne by the evidence. Laboratory studies have shown that the vaccine itself, and the spike protein that it encodes, may get into the blood, and be distributed widely throughout the body. Vaccines targeting the spike protein from SARS-CoV-2 were designed to induce antibodies that would bind to this protein to prevent the virus from being able to infect our bodies. The spike protein was supposed to be the 'first thing' that a vaccine must provide; a target for the immune system. We did not appreciate the potential for the spike protein alone to cause damage to cells in the body. We now understand that the current COVID-19 mRNA vaccines have the potential to be distributed throughout the body, thereby potentially and inadvertently inoculating many tissues with a protein that is possibly harmful. If unknown damage is being caused in some organs, this might not be clearly evident until years after vaccination. The data presented here do not provide proof of long-term harm. However, it provides the rationale for asking a number of safety questions. These questions should be thoroughly investigated in safety studies prior to using COVID-19 vaccines in children, adolescents, and young adults of child-bearing age.

A concern beyond circulating spike proteins: the potential for induction of autoimmunity

Some scientists have proposed that the spike protein from SARS-CoV-2 might have portions that are very similar to proteins in our own bodies[47]. If true, inducing immunity against the spike protein could theoretically promote autoimmune disorders. Indeed, two researchers found there was cross-reactivity between antibodies induced against the spike protein and several 'self' proteins[48]. This led to the recommendation almost one year ago to avoid targeting the entire spike protein in vaccines and instead target only portions of the protein that are not

similar to proteins in our own bodies. Unfortunately, autoimmune diseases can be insidious and take years for symptoms to become apparent.

The broad distribution of an mRNA vaccine throughout the body implicates other mechanisms that could lead to autoimmune disease. First, the mRNA vaccines promote robust inflammation. This is why many people have sore shoulders after being immunized. Promotion of inflammation in critical tissues, such as the ovaries, after being seeded with the vaccine could have dire consequences. Tissues like the ovaries are not supposed to become inflamed. This is because inflammation causes a lot of bystander damage to normal tissues, which is unwanted in an organ designed for reproduction. Also, the vaccine-encoded spike protein is designed to remain anchored on the surface of the cell that has manufactured it. If antibodies are present, such as would be the case several days after vaccination or natural infection, they could bind to the spike proteins on cells throughout our body, resulting in their destruction. Let's take the ovaries, again, as a theoretical scenario. If they were to undergo any type of tissue destruction, there is the possibility of proteins being released that the immune system has never seen before. This is because our immune systems learn to tolerate 'self' at a very young age. However, organs like the ovaries and testes start to express new proteins during puberty that the immune system has not been tolerized against. If these get released due to tissue damage, this could provide the same two signals that a vaccine needs to activate the immune system; signal 1 (target protein) and signal 2 (damage-associated danger signals). This could result in an autoimmune response against the organ. In this example (ovaries), such damage might not become apparent until years later when attempting to have a baby. This is speculation but is based on a huge body of scientific literature looking at how autoimmune diseases get started. Notably, this could potentially happen in any of the tissues seeded with the vaccine if they start to express the spike protein. This is certainly worthy of investigation before the mass vaccination of children, adolescents, and young adults of child-bearing age.

Even the fact that the current COVID-19 vaccines cause muscle cells in the shoulder to express the spike protein, is a potential problem. This could potentially result in immune responses being mounted against muscle tissue. This is of particular concern, because Israel has started to suspect a link between COVID-19 vaccines and inflammation in the heart muscle (a condition known as myocarditis). Indeed, this potential link is being actively investigated by the European Medicines Agency, as well as by the U.S. CDC. Again, with these kinds of concerns being raised in the global community, one must wonder why these vaccines are pushed so hard upon Canadian youth who are not at high risk of severe COVID-19. It will be a tragedy if we repeat something similar to or even worse than the AstraZeneca vaccine fiasco with our young people.

Why doesn't everyone who gets vaccinated experience a severe side-effect?

The spike protein likely does not get into circulation in every person. Indeed, in the study of 13 people vaccinated with the Moderna vaccine, ten had no evidence of the spike protein and

two had no evidence of the S1 subunit (a fragment of the spike protein) in their blood[42]. Also, it is important to remember that following vaccination, people manufacture the spike protein in their own cells. The amount and quality of mRNA in each dose of the vaccine can vary from batch to batch. The stability of the mRNA is also dependent on its handling as it is very temperature sensitive. So different people will receive different amounts of the active mRNA. People that receive the same amount of mRNA can produce different amounts of the spike protein depending on how metabolically active their cells are. And there are likely numerous other factors, including body size, *etc.* All of this could contribute to substantial variability in the concentration of spike proteins that a person produces. Notably, a standard vaccine injection might be expected to have a different impact in a 75-pound youth than in a 200-pound adult. The adverse events that we know about seem relatively rare. Some adverse events may go undetected. For example, knowing that the spike protein gets into circulation and knowing that it can kill platelets, it would not be surprising if most people have some loss of platelets after getting vaccinated. Also, platelets could pick up the mRNA from the circulating lipid nanoparticles and then display the spike protein on their surface, which would tag them for destruction by the ensuing antibody response. However, platelet counts are not being routinely monitored after people leave vaccination clinics, nor have the vaccine companies publicly released their data showing platelet counts post-immunization. Indeed, in a first-in-human study of BNT162b1, an earlier prototype of the Pfizer BioNTech BNT162b2 vaccine in use today, that encoded the S1 subunit of the spike protein (which contains the portion of the spike protein that binds to ACE2 receptors, called the receptor binding domain), platelet numbers dropped following vaccination in both the young and older adults studied[49]. Unfortunately, clinical chemistry and haematology values following vaccination with the BNT162b2 vaccine, which is the one currently being used to vaccinate people, were not published in Pfizer's first-in-human study[50].

One would be unaware if they were experiencing a loss of platelets unless their platelet count became dangerously low and they suffered trauma that would cause bleeding. Of greater concern is the potential for serious adverse events that we may not know about for quite some time. For example, damage to the ovaries or testicles might result in infertility that would not become apparent until attempting to have children. The oocytes that are present in the ovaries of newborn baby girls represent that female's life-long fixed supply of oocytes, which are the precursor of eggs. These oocytes cannot reproduce or regenerate if damaged or destroyed. Damage to the uterus could potentiate spontaneous abortions or miscarriages during pregnancy. The fact is, there is a clearly established set of biological mechanisms that raise numerous legitimate scientific concerns about COVID-19 vaccines. **We can't simply hope that none of these concerns end up being realized.** Instead, we must return to following the scientific method. We should stop the roll-out of the vaccination program for children, youth and young adults of child-bearing age, and ask the manufacturers of COVID-19 vaccines to take the time to conduct the proper biodistribution and safety studies to answer these emerging questions, and then conduct an accurate re-evaluation of the risk of COVID-19 versus the risks associated with the experimental COVID-19 vaccines.

Is the Pfizer BioNTech vaccine losing its effectiveness?

The stated purpose of vaccinating children, youth, and young adults of child-bearing age is to protect them from infection and reduce the risk of them transmitting SARS-CoV-2 to older adults. Therefore, it is important to note that the current COVID-19 vaccines fail to induce what we call 'sterilizing immunity'. This means that vaccinated individuals can still get infected with SARS-CoV-2, potentially become ill, and potentially transmit the virus to others. This is why vaccinated individuals are not exempt from lockdown policies and are still encouraged to wear masks. Importantly, there is evidence that the 'Delta variant' of SARS-CoV-2 has changed enough to be able to start evading the immunity conferred by the Pfizer BioNTech vaccine[51]. Indeed, the earlier 'South African' variant rendered AstraZeneca's vaccine only 10% effective[52]. With new variants on the horizon that will almost inevitably be able to bypass vaccine-induced immunity, this raises another question about whether the potential risks associated with the current vaccines are worth the minimal protection they will confer in the long-term to children, youth, and young adults of child-bearing age.

The Pfizer BioNTech vaccine might cause an excessive number of serious side-effects in young Canadians

As noted previously, Pfizer conducted an extremely small and very short-term clinical trial to test their vaccine in adolescents between the ages of 12-15 years. The results were reported in a fact sheet to the U.S. Food and Drug Administration. In this document, Pfizer defined severe adverse events as follows:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above

No deaths occurred in this small study, but Pfizer did note the following on page 27 of their fact sheet: "Serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.1% of placebo recipients." Much larger numbers of adolescents would have to be studied to provide conclusive evidence, but these limited data suggest the risk of serious adverse events

may have been 0.3% higher in the vaccinated group (not statistically significant in this small study).

As discussed previously, adverse events of special interest are being monitored, although the thoroughness is questionable, and the transparency of such activity is spotty at best. For example, the European Medicines Agency has compiled a list of important medical events (IMEs) which are always to be classified as serious (the IME list). The IMEs that are most frequently reported following COVID-19 vaccination include (in descending order):

- Fainting (syncope)
- Blood clot in the lungs
- Anaphylactic reaction
- Deep vein thrombosis
- Pneumonia
- Low blood platelet count (thrombocytopenia)
- Blood clots or bleeding in the brain
- Hallucinations
- Cerebral stroke
- Loss of consciousness

As the number of adolescents studied in the Pfizer trial was so small, it remains unclear whether adolescents also will experience these IMEs. It is not appropriate or ethical to experiment with youth, especially when their risk of severe COVID-19 is so low.

A side note about blood donations

Although not directly related to vaccinating children, adolescents, and young adults of child-bearing age, it is important to recognize that if the spike protein, which can cause substantial damage, gets into the blood after vaccination, this could have implications for donating blood. It would be unwise to infuse a blood product into a potentially fragile patient if it is contaminated with the spike protein. Worse, Pfizer's own biodistribution data demonstrate that the vaccine itself, not the spike protein, circulates in blood for at least two days post-immunization. Intravenous infusion of mRNA that can produce the spike protein in cells of the recipient should not be infused into patients who require blood. Remember, not only is there a risk of free-floating and cell-expressed spike proteins, but the lipid nanoparticles themselves can promote anaphylactic shock in a small subset of people. Of concern, Canadian Blood Services currently states their approval for receiving blood donations from people who have received a COVID-19 vaccine, without deferral. This is based on assumptions made using traditional vaccines that remain at the injection site, not novel mRNA-based vaccines that have been shown in laboratory studies to travel throughout the body. **This practice should be halted immediately** until it can be determined how long it takes for the lipid nanoparticles, and spike proteins to disappear from the blood. Canadian Blood Services should then recommend deferring blood

donations from vaccinated individuals until there is no risk of transferring lipid nanoparticles, mRNA, or spike proteins. The small-scale study that has looked at circulating levels of spike proteins suggests that it might not be safe to use blood products from a vaccinated individual for at least 4-5 weeks post-immunization[42]. In the United Kingdom, the National Health Service Blood and Transplant has recommended that, "COVID-19 vaccine – please wait 7 full days from your vaccine before donating on the 8th day. If you had side effects from the vaccine such as headache, temperature, aches, and chills, please wait 28 days from your recovery". It is unfortunate that there is not international collaboration with regards to recommendations for the donation of blood after COVID-19 vaccination.

What options are we left with if we pause the vaccination roll-out for children, adolescents, and young adults of child-bearing age?

Canada abandoned the original goal of learning to live with SARS-CoV-2 after the initial 2-3-week 'flattening of the curve' of daily cases of COVID-19 early in the year 2020. A massive amount of scientific data about COVID-19 has been compiled over the past 16 months. But we have not been following the accumulating science. It can direct us towards what one of my colleagues likes to call a 'rapid but soft landing.' The purpose of this guide was not to build a detailed exit strategy. However, I have also been closely following the scientific literature about strategies that can be used to effectively treat COVID-19, especially if they are implemented as an early out-patient, at-home treatment before the disease progresses to a level requiring hospitalization. Some, but all too few Canadian physicians, are aware of, or using, these early at-home treatment protocols. These protocols include safe and highly effective drugs like ivermectin, fluvoxamine, budesonide, zinc, melatonin, vitamin C, vitamin D, and many others. Several cocktails of approved drugs have proven to be particularly effective and are described in a variety of websites including TreatEarly.org, c19protocols.com, and FLCCC.net. There is now an avalanche of scientific data in support of these treatment options, but this digresses into an area beyond the scope of this guide. Unfortunately, the use of these effective therapies has never been promoted in Canada even though they could have prevented a lot of sickness and deaths and would have reduced the burden on intensive care units. Many people do not realize that the Interim Order or emergency use authorization of COVID-19 vaccines would have been contraindicated if there was acknowledgement of effective treatment strategies. This rule is in place to protect Canadians from being experimented on when there are viable alternatives that are known to be safe. However, it is never too late to do the right thing. Canada panicked and threw out pandemic preparedness plans at all its public institutions. Sometimes poor decisions occur when being made during a crisis and in the absence of established guidelines. It is time to move on. By promoting widespread use of effective treatments for COVID-19, Canada can safely narrow its experimental vaccination program and call for the science to catch up before subjecting our children, adolescents, and young adults of child-bearing age to potential harm.

Concluding remarks

Looking back through this report, it is clear that there are too many warning signals to ignore. Each individual signal may present a particular level of uncertainty, but when all the signals are considered together, the alert is deafening and must not be ignored. We must halt the vaccination of our children, adolescents, and young adults of child-bearing age. This can be done safely and expeditiously because:

- The risk of severe and potentially lethal COVID-19 in these specific populations is so low that we need to be very certain that risks associated with mass vaccination are not higher;
- Asymptomatic members of this population are not a substantial risk for passing COVID-19 to others; and
- There are effective early-treatment strategies and considerations for the very few children, adolescents, and young adults of child-bearing age who may be at risk of developing severe COVID-19.

Our younger generations of Canadians are our treasures and our future. Let's not put their futures at unnecessary risk by forcing upon them experimental vaccines that present newly identified and still-to-be-clarified dangers. Proof-of-principle now exists to demonstrate the current crop of vaccines may be dangerous. This risk, no matter how theoretical, must be further investigated and all concerns put to rest prior to the vaccination of our youth. It's time to sort out the science and reduce the pressures on parents and their children so they can make truly informed decisions. It is time to pass the torch from the pharmaceutical companies and hand it to the leaders and innovators among our community of physicians and researchers who have the skills, knowledge and experience to optimize excellent treatment strategies encompassing repurposed drugs that can be deployed to reduce the future casualties of this war against COVID-19.

What to do next?

If interested in obtaining more information relevant to COVID-19, please go to the Canadian COVID Care Alliance (CCCA) website at https://www.canadiancovidcarealliance.org/. There is an option to join an e-mail list if you are interested in receiving news from the CCCA.

An example of the expertise represented within CCCA's membership and their balanced scientific messaging with an emphasis on charting a safe but rapid exit from the cycles of lockdowns can be found here: https://trialsitenews.com/covid-19-expert-panel-the-path-forward-for-canadians-trialsite-webinar/. This discussion panel was set-up after the governments of Alberta, Saskatchewan, and Ontario failed to respond to invitations to engage scientists and physicians in respectful public discussions of the scientific knowledge that has accumulated about COVID-19.

Interviews that include one of the original inventors of mRNA vaccine technology (Dr. Robert Malone) opining on findings described in this guide can be found here and here.

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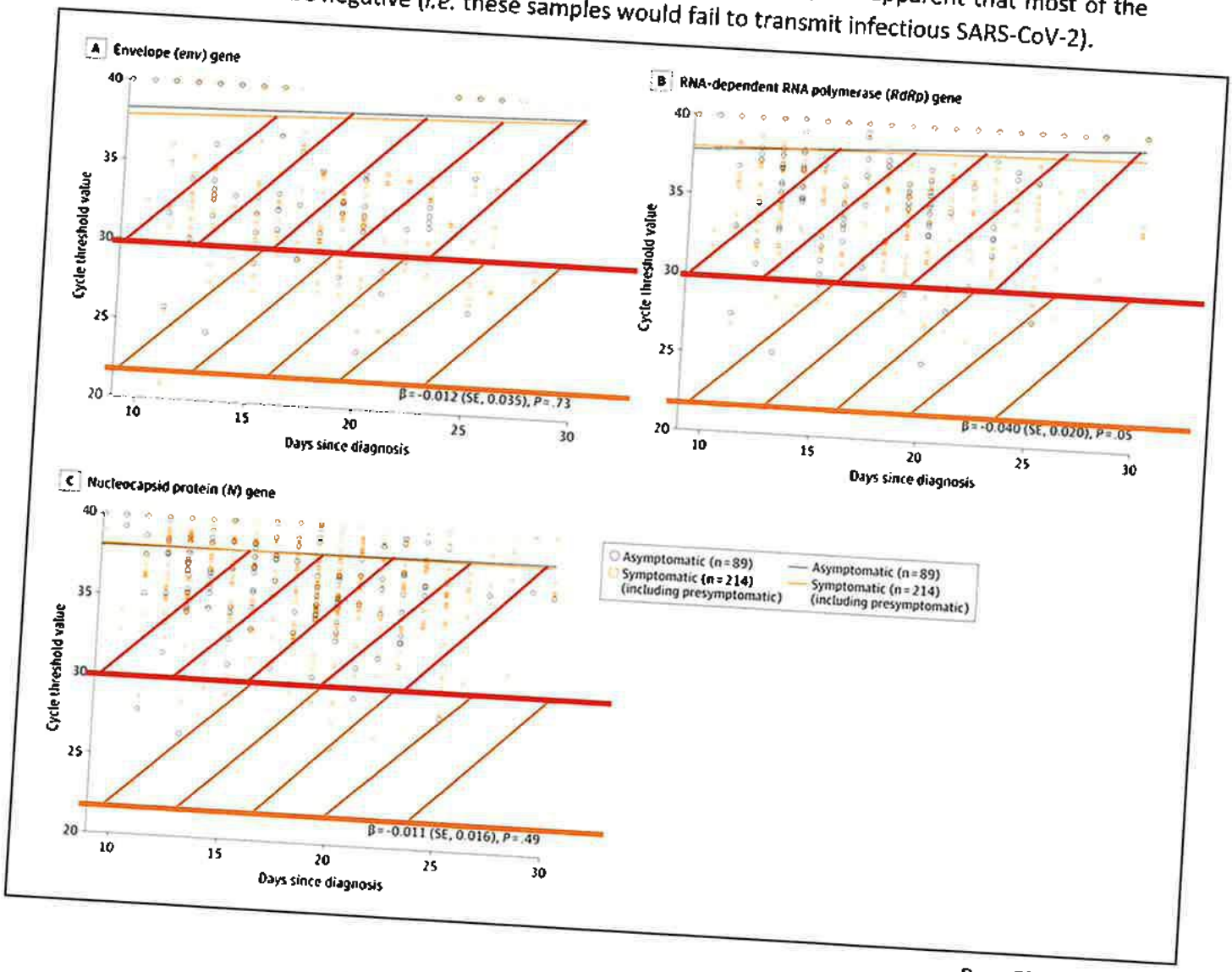
Appendix 1

Most 'positive' results for the SARS-CoV-2 PCR test are negative based on the gold standard virology assay. Shown are graphs from Figure 2 of a paper published in the *Journal of the American Medical Association* (*JAMA Intern Med.* 2020; 180(11): 1447-1452. doi:10.1001/jamainternmed.2020.3862). The argument being made was that the frequency at which asymptomatic people tested positive for SARS-CoV-2 was like that observed for people with symptomatic infections. However, new cut-offs for a positive test result were placed at 22 (orange line) and 30 (red line) PCR cycles. These are the limits (depending on the laboratory) at which replication-competent SARS-CoV-2 can no longer be recovered from samples according to the gold standard functional virology assay. When this is done, it is apparent that most of the results would be negative (*i.e.* these samples would fail to transmit infectious SARS-CoV-2).



Appendix 2

Pfizer's Report to the Japanese Government

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LIST OF FIGURES

本項で使用する用語・略語

用語・略号	省略していない表現または定義
ALC-0159	本剤に添加される PEG 脂質
ALC-0315	本剤に添加されるアミノ脂質
[^{3}H]-CHE	Radiolabeled [Cholesteryl-1,2-^{3}H(N)]-Cholesteryl Hexadecyl Ether : 放射性標識 ［コレステリル-1, 2-^{3}H(N)］ヘキサデシルエーテル
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine : 1,2-ジステアロイル-sn-グリセロ-3-ホスホコリン
GLP	Good Laboratory Practice : 医薬品の安全性に関する非臨床試験の実施の基準
LNP	Lipid-nanoparticle : 脂質ナノ粒子
modRNA	Nucleoside-modified mRNA : 修飾ヌクレオシド mRNA
mRNA	Messenger RNA : メッセンジャーRNA
m/z	m/z（m・オーバー・z）：イオンの質量を統一原子質量単位（＝ダルトン）で割って得られた無次元量をさらにイオンの電荷数の絶対値で割って得られる無次元量
PEG	Polyethylene glycol : ポリエチレングリコール
PK	Pharmacokinetics : 薬物動態
RNA	Ribonucleic acid : リボ核酸
S9	Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g : 肝ホモジネートを 9000 g で遠心分離した上清画分
WHO	World Health Organization : 世界保健機関

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Toronto Superior Court of Justice / Cour supérieure de justice

1. まとめ

BNT162b2（BioNTech コード番号：BNT162，Pfizer コード番号：PF-07302048）は，重症急性呼吸器症候群コロナウイルス 2（SARS-CoV-2）のスパイク糖タンパク質（S タンパク質）全長体をコードする修飾ヌクレオシド mRNA（modRNA）であり，SARS-CoV-2 による感染症に対する mRNA ワクチンの本質として開発が進められている。BNT162b2 の製剤化にあたっては，2 つの機能脂質である ALC-0315（アミノ脂質）および ALC-0159（PEG 脂質）ならびに 2 つの構造脂質として DSPC（1,2-distearoyl-sn-glycero-3-phosphocholine）およびコレステロールと混合することで BNT162b2 を封入する脂質ナノ粒子（LNP）が形成される（以降，「BNT162b2 封入 LNP」）。

BNT162b2 封入 LNP の非臨床薬物動態を評価するために，LNP に含まれる ALC-0315 および ALC-0159 の吸収（PK），代謝および排泄を評価する in vivo および in vitro 試験ならびに BNT162b2 の代替レポーターとしてルシフェラーゼまたは放射能標識した脂質を利用した生体内分布試験を実施した。

感染症予防を目的としたワクチンの開発では全身曝露量の評価を必要としないことを踏まえ（WHO, 2005；感染症予防ワクチンの非臨床試験ガイドライン）[1,2]，BNT162b2 封入 LNP の筋肉内投与による PK 試験は実施しなかった。また，本剤に含有される他の 2 種類の脂質（コレステロールおよび DSPC）は天然に存在する脂質であり，内在性脂質と同様に代謝，排泄されると考えられる。加えて，BNT162b2 は取り込んだ細胞中のリボヌクレアーゼにより分解されて核酸代謝され，BNT162b2 由来の S タンパク質はタンパク分解を受けると予想される。以上のことから，あらためてこれらの成分の代謝および排泄を評価する必要はないと考えられた。

BNT162b2 の代替レポーターとしてルシフェラーゼをコードする RNA を封入した LNP（ルシフェラーゼ RNA を BNT162b2 封入 LNP と同一の脂質構成を持つ LNP に封入：以降，「ルシフェラーゼ RNA 封入 LNP」）を Wistar Han ラットに静脈内投与した PK 試験では，血漿，尿，糞および肝臓試料を経時的に採取して，各試料中の ALC-0315 および ALC-0159 濃度を測定した。その結果，ALC-0315 および ALC-0159 は血中から肝臓にすみやかに分布することが示された。また，ALC-0315 および ALC-0159 はそれぞれ投与量の約 1%および約 50%が未変化体として糞中に排泄され，尿中においてはいずれも検出限界未満であった。

生体内分布試験では，ルシフェラーゼ RNA 封入 LNP を BALB/c マウスに筋肉内投与した。その結果，ルシフェラーゼの発現が投与部位でみられ，それより発現量は低値であったものの肝臓でも認められた。ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現も投与後 6 時間に認められ，投与後 48 時間までに消失した。また，ルシフェラーゼ RNA 封入 LNP の放射能標識体をラットに筋肉内投与して生体内分布を定量的に評価したところ，放射能濃度は投与部位で最も高値であった。投与部位以外では肝臓が最も高かった（投与量の最大 18%）。

ALC-0315 および ALC-0159 の代謝を CD-1/ICR マウス，Wistar Han または Sprague Dawley ラット，カニクイザルもしくはヒトの血液，肝ミクロソーム，肝 S9 画分および肝細胞を用いて in vitro で評価した。また，上記のラット静脈内投与 PK 試験で採取した血漿，尿，糞および肝臓試料を用いて in vivo 代謝についても検討した。これら in vitro および in vivo 試験から，ALC-0315 および ALC-0159 は，試験したいずれの動物種でも，それぞれエステル結合およびアミド結合の加水分解により緩徐に代謝されることが示された。

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以上の非臨床薬物動態評価より，循環血中に到達した LNP は肝臓に分布することが示された。また，ALC-0315 および ALC-0159 の消失には，それぞれ代謝および糞中排泄が関与することが示唆された。

2. 分析法

報告書番号：PF-07302048_06[redacted]_072424

GLP 非適用のラット静脈内投与 PK 試験（M2.6.4.3 項）で LNP の構成脂質である ALC-0315 および ALC-0159 濃度を定量するために適切な性能を有する LC/MS 法を開発した。すなわち，20 µL の血漿，肝ホモジネート（肝臓の 3 箇所から採取した切片を用いてホモジネートを調製し，それらをプールしたものを適宜，ブランクマトリクスで希釈），尿および糞ホモジネート（適宜，ブランクマトリクスで希釈）試料をそれぞれ内部標準物質（PEG-2000）を含有するアセトニトリルで除タンパクした後，遠心分離し，その上清を LC-MS/MS 測定に供した。

3. 吸収

報告書番号：PF-07302048_06[redacted]_072424，概要表：2.6.5.3

ALC-0315 および ALC-0159 の体内動態を検討するため，ルシフェラーゼ RNA 封入 LNP を雄性 Wistar Han ラットに 1 mg RNA/kg の用量で単回静脈内投与し，経時的（投与前，投与後 0.1，0.25，0.5，1，3，6 および 24 時間ならびに投与後 2，4，8 および 14 日）に血漿および肝臓をスパースサンプリングにより採取（3 匹/時点）した。血漿中および肝臓中の ALC-0315 および ALC-0159 濃度を測定し，PK パラメータを算出した（Table 1）。血中の ALC-0315 および ALC-0159 は，投与後 24 時間までにすみやかに肝臓へ分布した。また，投与後 24 時間の血漿中濃度は最高血漿中濃度の 1%未満であった（Figure 1）。見かけの終末相消失半減期（t½）は血漿中および肝臓中で同程度で，ALC-0315 は 6～8 日，ALC-0159 は 2～3 日であった。本試験の結果から，肝臓が血中からの ALC-0315 および ALC-0159 を取り込む主要組織の 1 つであることが示唆された。

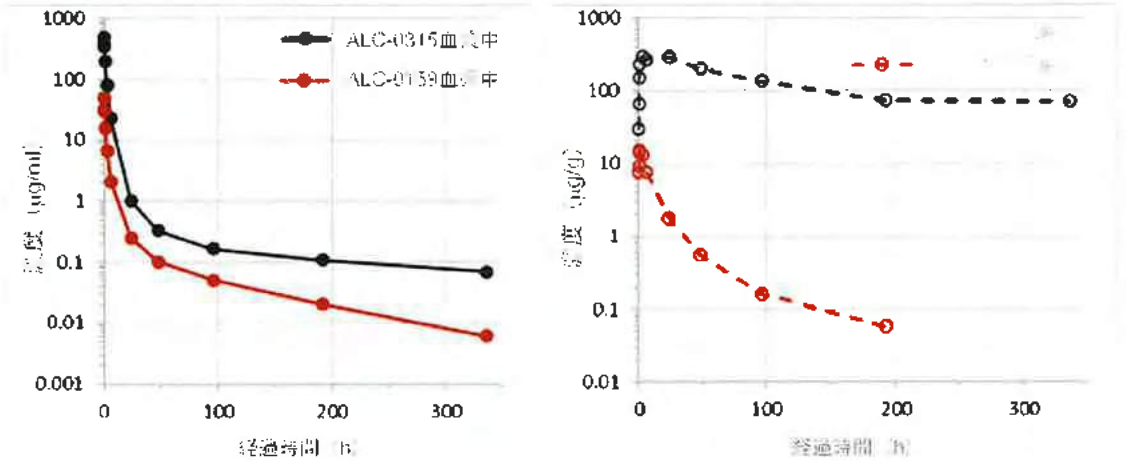
本試験において実施した ALC-0315 および ALC-0159 の尿中および糞中濃度の検討結果については M2.6.4.6 項で述べる。

Table 1 ルシフェラーゼ RNA 封入 LNP を Wistar Han ラットに 1 mg RNA/kg の用量で静脈内投与したときの ALC-0315 および ALC-0159 の薬物動態

分析物	分析物の投与量 (mg/kg)	性/N	t½ (h)	AUC_{inf} (µg•h/mL)	AUC_{last} (µg•h/mL)	肝臓への分布割合 (%)[a]
ALC-0315	15.3	雄/3[b]	139	1030	1020	60
ALC-0159	1.96	雄/3[b]	72.7	99.2	98.6	20

a. ［最高肝臓分布量 (µg)］/［投与量 (µg)］として算出。
b. 各時点 3 匹。スパースサンプリング。

Figure 1 ルシフェラーゼ RNA 封入 LNP を Wistar Han ラットに 1 mg RNA/kg の用量で静脈内投与したときの ALC-0315 および ALC-0159 の血漿および肝臓中濃度

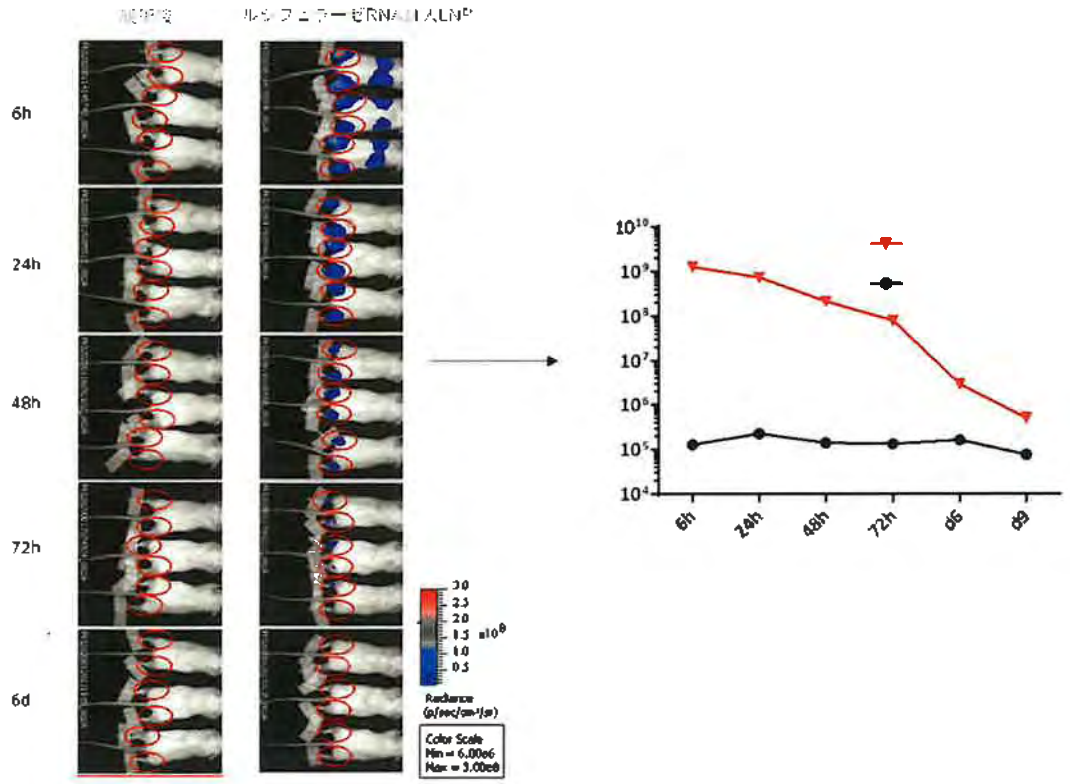


4. 分布

報告書番号：R-[redacted]-0072，185350，概要表：2.6.5.5A，2.6.5.5B

雌性 BALB/c マウス（3 匹）にルシフェラーゼ RNA 封入 LNP を投与し，ルシフェラーゼ発光を代替マーカーとして BNT162b2 の生体内分布を検討した。すなわち，ルシフェラーゼ RNA 封入 LNP をマウスの左右の後肢に各 1 μg RNA（計 2 μg RNA）の用量で筋肉内投与した。その後，ルシフェラーゼ発光検出の 5 分前に発光基質であるルシフェリンを腹腔内投与し，イソフルラン麻酔下，in vivo における発光を Xenogen IVIS Spectrum を用いて投与後 6 および 24 時間ならびに 2，3，6 および 9 日に測定することにより，ルシフェラーゼタンパクの同一個体での経時的な発現推移を評価した。その結果，ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現も投与後 6 時間からみられ，投与後 48 時間までに消失した。肝臓への分布は局所投与したルシフェラーゼ RNA 封入 LNP の一部が循環血中に到達し，肝臓で取り込まれたことを示すものと考えられた。M2.6.4.3 項で詳述したように，ラットにルシフェラーゼ RNA 封入 LNP を静脈内投与した場合には，肝臓が ALC-0315 および ALC-0159 の主要な分布臓器であることが示唆されており，このことはマウスに筋肉内投与した本試験結果の所見と符合するものであった。なお，ラット反復投与毒性試験で肝障害を示す毒性所見は認められていない（M2.6.6.3 項）。

Figure 2 ルシフェラーゼ RNA 封入 LNP を筋肉内投与した BALB/c マウスにおける生体内発光



雌雄 Wistar Han ラットに，[^{3}H]-コレステリルヘキサデシルエーテル（[^{3}H]- CHE）で標識した LNP を用いたルシフェラーゼ RNA 封入 LNP を 50 μg RNA の用量で筋肉内投与し，投与後 15 分ならびに 1，2，4，8，24 および 48 時間の各時点において雌雄各 3 匹から血液，血漿および組織を採取し，液体シンチレーション計数法により放射能濃度を測定することで LNP の生体内分布を評価した。雌雄ともに，放射能濃度はいずれの測定時点においても投与部位が最も高値であった。血漿中の放射能濃度は投与後 1～4 時間で最も高値を示した。また，主に肝臓，脾臓，副腎および卵巣への分布がみられ，これらの組織において放射能濃度が最も高くなったのは投与後 8～48 時間であった。投与部位以外での投与量に対する総放射能回収率は肝臓で最も高く（最大 18%），脾臓（1.0%以下），副腎（0.11%以下）および卵巣（0.095%以下）では肝臓と比較して著しく低かった。また，放射能の平均濃度および組織分布パターンは雌雄でおおむね類似していた。

BNT162b2 がコードする抗原の生体内発現分布は LNP 分布に依存すると考えられる。本試験で用いたルシフェラーゼ RNA 封入 LNP の脂質の構成は，BNT162b2 の申請製剤と同一であることから，本試験結果は BNT162b2 封入 LNP の分布を示すと考えられる。

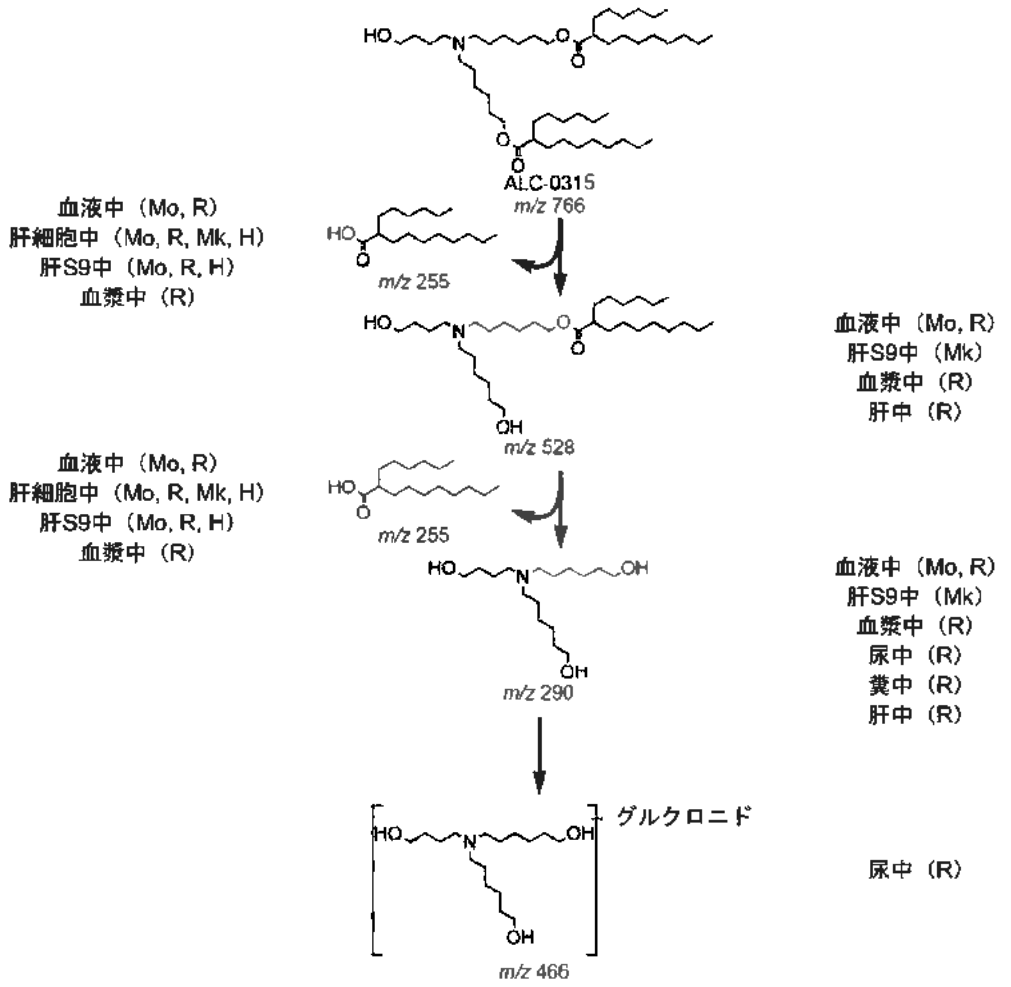
5. 代謝

報告書番号：01049-[redacted]008，01049-[redacted]009，01049-[redacted]010，01049-[redacted]020，01049-[redacted]021，01049-[redacted]022，PF-07302048_05[redacted]_043725，概要表：2.6.5.10A，2.6.5.10B，2.6.5.10C，2.6.5.10D

CD-1/ICR マウス，Wistar Han または Sprague Dawley ラット，カニクイザルならびにヒトの肝ミクロソーム，肝 S9 画分および肝細胞を用いて，ALC-0315 および ALC-0159 の in vitro 代謝安定性を評価した。ALC-0315 または ALC-0159 を各動物種の肝ミクロソームまたは肝 S9 画分（120 分間インキュベーション）もしくは肝細胞（240 分間インキュベーション）に添加して，インキュベーション後の未変化体の割合を測定した。その結果，ALC-0315 および ALC-0159 はいずれの動物種・試験系でも代謝的に安定であり，未変化体の最終的な割合は 82%超であった。

さらに ALC-0315 および ALC-0159 の代謝経路について in vitro および in vivo で評価した。これらの試験では，CD-1 マウス，Wistar Han ラット，カニクイザルおよびヒトの血液，肝 S9 画分および肝細胞を用いて in vitro での代謝を評価した。また，ラット PK 試験で採取した血漿，尿，糞および肝臓試料を用い，in vivo での代謝を評価した（M2.6.4.3 項）。試験結果から，ALC-0315 と ALC-0159 の代謝はいずれも緩徐であり，それぞれエステル結合およびアミド結合の加水分解により代謝されることが明らかになった。Figure 3 および Figure 4 に示した加水分解による代謝は，評価したすべての動物種でみられた。

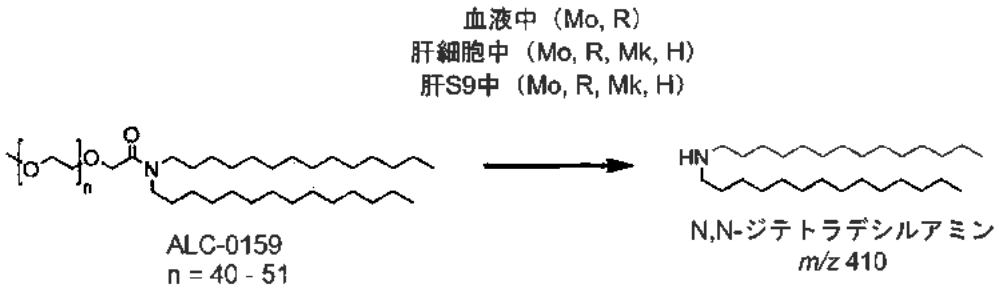
Figure 3 種々の動物種での ALC-0315 の推定生体内代謝経路



H：ヒト，Mk: サル，Mo：マウス，R：ラット

ALC-0315 はエステル加水分解を 2 回連続で受けることにより代謝される。この 2 回の加水分解により，最初，モノエステル代謝物（*m/z* 528），次に二重脱エステル化代謝物（*m/z* 290）が生成される。この二重脱エステル化代謝物はさらに代謝され，グルクロン酸抱合体（*m/z* 466）となるが，このグルクロン酸抱合体はラット PK 試験で尿中にのみ検出された。また，2 回の加水分解の酸性生成物がいずれも 6-ヘキシルデカン酸（*m/z* 255）であることも確認された。

Figure 4 種々の動物種での ALC-0159 の推定生体内代謝経路



H：ヒト，Mk: サル，Mo：マウス，R：ラット

ALC-0159 は，アミド結合の加水分解により *N,N*-ジテトラデシルアミン（*m/z* 410）が生成される経路が主要な代謝経路であった。この代謝物は，マウス・ラットの血液ならびにマウス・ラット・サル・ヒトの肝細胞および肝 S9 画分中に検出された。In vivo 試料からは ALC-0159 の代謝物は確認されなかった。

6. 排泄

ルシフェラーゼ RNA 封入 LNP を 1 mg RNA/kg の用量でラットに静脈内投与した PK 試験（M2.6.4.3 項）で経時的に採取した尿および糞中の ALC-0315 および ALC-0159 濃度を測定した。ALC-0315 および ALC-0159 の未変化体はいずれも尿中に検出されなかった。一方，糞中には ALC-0315 および ALC-0159 の未変化体が検出され，投与量当たりの割合はそれぞれ約 1%および約 50%であった。また，Figure 3 に示したように，ALC-0315 の代謝物が尿中で検出された。

7. 薬物動態学的薬物相互作用

本ワクチンの薬物動態学的薬物相互作用試験は実施していない。

8. その他の薬物動態試験

本ワクチンのその他の薬物動態試験は実施していない。

9. 考察および結論

ラット PK 試験において，血漿および肝臓中 ALC-0315 濃度は，投与後 2 週間までに最高濃度のそれぞれ約 7000 分の 1 および約 4 分の 1 に減少し，ALC-0159 濃度はそれぞれ約 8000 分の 1 および約 250 分の 1 に減少した。t½は血漿中および肝臓中で同程度で，ALC-0315 は 6～8 日，ALC-0159 は 2～3 日であった。血漿中 t½値は，それぞれの脂質が LNP として組織中に分布し，その後，消失過程で血漿中に再分布したことを表すと考えられる。

ALC-0315 の未変化体は尿中と糞中のいずれにもほとんど検出されなかったが，ラット PK 試験で採取した糞および血漿試料からモノエステル代謝物，二重脱エステル化代謝物および 6-ヘキシルデカン酸が，尿からは二重脱エステル化代謝物のグルクロン酸抱合体が検出された。この代謝過程が ALC-0315 の主要消失機序と考えられるが，この仮説を検証する定量データは得られていない。一方，ALC-0159 は投与量の約 50%が未変化体として糞中に排泄された。In vitro 代謝実験において，アミド結合の加水分解により緩徐に代謝された。

BNT162b2 がコードする抗原の生体内発現分布は LNP 分布に依存すると考えられることから，BALB/c マウスにルシフェラーゼ RNA 封入 LNP を筋肉内投与し，代替レポータータンパク質の生体内分布を検討した。その結果，ルシフェラーゼの発現が投与部位においてみられ，それより発現量は低値であったものの肝臓でも認められた。ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現は投与後 6 時間から認められ，投与後 48 時間までに消失した。肝臓への分布は局所投与したルシフェラーゼ RNA 封入 LNP が循環血中に到達し，肝臓で取り込まれたことを示すものと考えられた。また，ラットにルシフェラーゼ RNA 封入 LNP の放射能標識体を筋肉内投与したところ，放射能濃度は投与部位で最も高値を示した。投与部位以外では，肝臓で最も高く，次いで脾臓，副腎および卵巣でも検出されたが，これらの組織における投与量に対する総放射能回収率は肝臓より著しく低かった。この結果は，マウス生体内分布試験において肝臓でルシフェラーゼ発現がみられたことと符合した。なお，ラット反復投与毒性試験で肝障害を示す毒性所見は認められなかった（M2.6.6.3 項）。

以上の非臨床薬物動態評価より，循環血中に到達した LNP は肝臓に分布することが示された。また，ALC-0315 および ALC-0159 の消失には，それぞれ代謝および糞中排泄が関与することが示唆された。

10. 図表

図表は本文中および概要表に示した。

参考文献

1 World Health Organization. Annex 1. Guidelines on the nonclinical evaluation of vaccines. In: WHO Technical Report Series No. 927, Geneva, Switzerland. World Health Organization; 2005:31-63.

2 感染症予防ワクチンの非臨床試験ガイドラインについて（薬食審査発 0527 第 1 号，平成 22 年 5 月 27 日）

2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test item	Method of Administration	Testing Facility	Report Number
Single Dose Pharmacokinetics					
Single Dose Pharmacokinetics and Excretion in Urine and Feces of ALC-0159 and ALC-0315	Rat (Wistar Han)	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	IV bolus	Pfizer Inc[a]	PF-07302048_06[redacted]_072424
Distribution					
In Vivo Distribution	Mice BALB/c	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	IM Injection	[redacted][b]	R-[redacted]-0072
In Vivo Distribution	Rat (Wistar Han)	modRNA encoding luciferase formulated in LNP comparable to BNT162b2 with trace amounts of [^{3}H]-CHE as non-diffusible label	IM Injection	[redacted][c]	185350
Metabolism					
In Vitro and In Vivo Metabolism					
In Vitro Metabolic Stability of ALC-0315 in Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	ALC-0315	In vitro	[redacted][d]	01049-[redacted]008
In Vitro Metabolic Stability of ALC-0315 in Liver S9	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 liver fractions	ALC-0315	In vitro	[redacted][d]	01049-[redacted]009

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2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test item	Method of Administration	Testing Facility	Report Number
In Vitro Metabolic Stability of ALC-0315 in Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	ALC-0315	In vitro	[redacted][a]	01049-[redacted]010
In Vitro Metabolic Stability of ALC-0159 in Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	ALC-0159	In vitro	[redacted][a]	01049-[redacted]020
In Vitro Metabolic Stability of ALC-0159 in Liver S9	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 fractions	ALC-0159	In vitro	[redacted][a]	01049-[redacted]021
In Vitro Metabolic Stability of ALC-0159 in Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	ALC-0159	In vitro	[redacted][a]	01049-[redacted]022
Biotransformation of ALC-0159 and ALC-0315 In Vitro and In Vivo in Rats	In vitro: CD-1 mouse, Wistar Han rat, cynomolgus monkey, and human blood, liver S9 fractions and hepatocytes In vivo: male Wistar Han rats	ALC-0315 and ALC-0159	In vitro or IV (in vivo in rats)	Pfizer Inc[c]	PF-07302048_05[redacted]_043725

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2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test item	Method of Administration	Testing Facility	Report Number

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; IM = Intramuscular; IV = Intravenous; LNP = lipid nanoparticles; S9 = Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g.

a. La Jolla, California.
b. [redacted], Germany.
c. [redacted], UK.
d. [redacted], China.
e. Groton, Connecticut.

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2.6.5.3. PHARMACOKINETICS: PHARMACOKINETICS AFTER A SINGLE DOSE

Test Article: modRNA encoding luciferase in LNP
Report Number: PF-07302048_06[redacted]_072424

Species (Strain)	Rat (Wistar Han)	
Sex/Number of Animals	Male/ 3 animals per timepoint[a]	
Feeding Condition	Fasted	
Method of Administration	IV	
Dose modRNA (mg/kg)	1	
Dose ALC-0159 (mg/kg)	1.96	
Dose ALC-0315 (mg/kg)	15.3	
Sample Matrix	Plasma, liver, urine and feces	
Sampling Time Points (h post dose):	Predose, 0.1, 0.25, 0.5, 1, 3, 6, 24, 48, 96, 192, 336	
Analyte	ALC-0315	ALC-0159
PK Parameters:	Mean[b]	Mean[b]
AUC_{inf} (µg•h/mL)[c]	1030	99.2
AUC_{last} (µg•h/mL)	1020	98.6
Initial $t_{½}$ (h)[d]	1.62	1.74
Terminal elimination $t_{½}$ (h)[e]	139	72.7
Estimated fraction of dose distributed to liver (%)[f]	59.5	20.3
Dose in Urine (%)	NC[g]	NC[g]
Dose in Feces (%)[h]	1.05	47.2

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; AUC_{inf} = Area under the plasma drug concentration-time curve from 0 to infinite time; AUC_{last} = Area under the plasma drug concentration-time curve from 0 to the last quantifiable time point; BLQ = Below the limit of quantitation; LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA; PK = Pharmacokinetics; $t_{½}$ = Half-life.

a. Non-serial sampling, 36 animals total.
b. Only mean PK parameters are reported due to non-serial sampling.
c. Calculated using the terminal log-linear phase (determined using 48, 96, 192, and 336 h for regression calculation).
d. ln(2)/initial elimination rate constant (determined using 1, 3, and 6 h for regression calculation).
e. ln(2)/terminal elimination rate constant (determined using 48, 96, 192, and 336 h for regression calculation).
f. Calculated as follows: highest mean amount in the liver (µg)/total mean dose (µg) of ALC-0315 or ALC-0159.
g. Not calculated due to BLQ data.
h. Fecal excretion, calculated as: (mean µg of analyte in feces/ mean µg of analyte administered) × 100

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2.6.5.5A. PHARMACOKINETICS: ORGAN DISTRIBUTION

Test Article: modRNA encoding luciferase in LNP
Report Number: R-[redacted]-0072

Species (Strain):	Mice (BALB/c)
Sex/Number of Animals:	Female/3 per group
Feeding Condition:	Fed ad libitum
Vehicle/Formulation:	Phosphate-buffered saline
Method of Administration:	Intramuscular injection
Dose (mg/kg):	1 µg/hind leg in gastrocnemius muscle (2 µg total)
Number of Doses:	1
Detection:	Bioluminescence measurement
Sampling Time (hour):	6, 24, 48, 72 hours; 6 and 9 days post-injection

Time point	Total Mean Bioluminescence signal (photons/second)		Mean Bioluminescence signal in the liver (photons/second)
	Buffer control	modRNALuciferase in LNP	modRNALuciferase in LNP
6 hours	1.28×10^{5}	1.26×10^{9}	4.94×10^{7}
24 hours	2.28×10^{5}	7.31×10^{8}	2.4×10^{6}
48 hours	1.40×10^{5}	2.10×10^{8}	Below detection[a]
72 hours	1.33×10^{5}	7.87×10^{7}	Below detection[a]
6 days	1.62×10^{5}	2.92×10^{6}	Below detection[a]
9 days	7.66×10^{4}	5.09×10^{5}	Below detection[a]

LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA.
a. At or below the background level of the buffer control.

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

in :	Rat (Wistar Han)
x/Nu	Male and female/3 animals/sex/timepoint (21 animals/sex total for the 50 µg dose)
:	Fed ad libitum
i :	Intramuscular injection
:	50 µg [^{3}H]-08-A01-C0 (lot # NC-0552-1)
b r	1
:	Radioactivity quantitation using liquid scintillation counting
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, and 48 hours post-injection

Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL) (males and females combined)							% of administered dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
ip u	0.057	0.100	0.126	0.128	0.093	0.084	0.181	--	--	--	--	--	--	--
	0.271	1.48	2.72	2.89	6.80	13.8	18.2	0.001	0.007	0.010	0.015	0.035	0.066	0.106
	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
	0.091	0.195	0.266	0.276	0.340	0.342	0.687	--	--	--	--	--	--	--
	0.479	0.960	1.24	1.24	1.84	2.49	3.77	--	--	--	--	--	--	--
	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
	0.282	1.03	1.40	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030
	128	394	311	338	213	195	165	19.9	52.6	31.6	28.4	21.9	29.1	24.6
	0.391	1.16	2.05	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
nt i	0.013	0.048	0.093	0.287	0.649	1.10	1.34	0.008	0.025	0.065	0.192	0.405	0.692	0.762
i	0.737	4.63	11.0	16.5	26.5	19.2	24.3	0.602	2.87	7.33	11.9	18.1	15.4	16.2
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09	0.052	0.101	0.178	0.169	0.122	0.101	0.101

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Sample	Total Lipid concentration (µg lipid equivalent/g [or mL]) (males and females combined)							% of Administered Dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	--	--	--	--	--	--	--
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37	--	--	--	--	--	--	--
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	--	--	--	--	--	--	--
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	--	--	--	--	--	--	--
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4	0.013	0.093	0.325	0.385	0.982	0.821	1.03
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420	--	--	--	--	--	--	--
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805	--	--	--	--	--	--	--
Blood:Plasma ratio[a]	0.815	0.515	0.550	0.510	0.555	0.530	0.540	--	--	--	--	--	--	--

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

-- = Not applicable, partial tissue taken; [^{3}H]-08-A01-C0 = An aqueous dispersion of LNPs, including ALC-0315, ALC-0159, distearoylphosphatidylcholine, cholesterol, mRNA encoding luciferase and trace amounts of radiolabeled [Cholesteryl-1,2-3H(N)]-Cholesteryl Hexadecyl Ether, a nonexchangeable, non-metabolizable lipid marker used to monitor the disposition of the LNPs; ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N--ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4--hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; LNP = Lipid nanoparticle; mRNA = messenger RNA.

a. The mean male and female blood:plasma values were first calculated separately and this value represents the mean of the two values.

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2.6.5.9. PHARMACOKINETICS: METABOLISM IN VIVO, RAT

Test Article: modRNA encoding luciferase in LNP
Report Number: PF-07302048_05[redacted]_043725

Species (Strain):	Rat (Wistar Han)
Sex/ Number of animals	Male/ 36 animals total for plasma and liver, 3 animals for urine and feces
Method of Administration:	Intravenous
Dose (mg/kg):	1
Test System:	Plasma, Urine, Feces, Liver
Analysis Method:	Ultrahigh performance liquid chromatography/ mass spectrometry

Biotransformation	m/z	Metabolites of ALC-0315 Detected			
		Plasma	Urine	Feces	Liver
N-dealkylation, oxidation	102.0561[a]	ND	ND	ND	ND
N-Dealkylation, oxidation	104.0706[b]	ND	ND	ND	ND
N-dealkylation, oxidation	130.0874[a]	ND	ND	ND	ND
N-Dealkylation, oxidation	132.1019[b]	ND	ND	ND	ND
N-dealkylation, hydrolysis, oxidation	145.0506[a]	ND	ND	ND	ND
Hydrolysis (acid)	255.2330[a]	+	ND	ND	ND
Hydrolysis, hydroxylation	271.2279[a]	ND	ND	ND	ND
Bis-hydrolysis (amine)	290.2690[b]	+	+	+	+
Hydrolysis, glucuronidation	431.2650[a]	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	464.2865[a]	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	466.3011[b]	ND	+	ND	ND
Hydrolysis (amine)	528.4986[b]	+	ND	ND	+
Hydrolysis (amine), Glucuronidation	704.5307[b]	ND	ND	ND	ND
Oxidation to acid	778.6930[a]	ND	ND	ND	ND
Oxidation to acid	780.7076[b]	ND	ND	ND	ND
Hydroxylation	782.7232[b]	ND	ND	ND	ND
Sulfation	844.6706[a]	ND	ND	ND	ND
Sulfation	846.6851[b]	ND	ND	ND	ND
Glucuronidation	940.7458[a]	ND	ND	ND	ND
Glucuronidation	942.7604[b]	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = minor metabolite as assessed by ultraviolet detection.
a. Negative ion mode.
b. Positive ion mode.

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2.6.5.10A. PHARMACOKINETICS: METABOLISM IN VITRO

Test Article: ALC-0315
Report Numbers: 01049-[redacted]008
01049-[redacted]009
01049-[redacted]010

Type of Study:	Stability of ALC-0315 In Vitro		
Study System:	Liver Microsomes + NADPH	S9 Fraction + NADPH, UDPGA, and alamethicin	Hepatocytes
ALC-0315 Concentration:	1 µM	1 µM	1 µM
Duration of Incubation (min):	120 min	120 min	240 min
Analysis Method:	Ultra-high performance liquid chromatography-tandem mass spectrometry		

Incubation time (min)	Percent ALC-0315 remaining													
	Liver Microsomes					Liver S9 Fraction				Hepatocytes				
	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
15	98.77	94.39	96.34	97.96	100.24	97.69	98.85	99.57	95.99	--	--	--	--	--
30	97.78	96.26	97.32	96.18	99.76	97.22	99.62	96.96	97.32	101.15	97.75	102.70	96.36	100.72
60	100.49	99.73	98.54	100.00	101.45	98.61	99.62	99.13	94.98	100.77	98.50	102.32	97.82	101.44
90	97.78	98.66	94.15	97.96	100.48	98.15	98.85	98.70	98.33	101.92	99.25	103.09	100.0	100.36
120	96.54	95.99	93.66	97.71	98.31	96.76	98.46	99.57	99.33	98.85	97.38	99.61	96.36	100.72
180	--	--	--	--	--	--	--	--	--	101.15	98.88	103.47	95.64	98.92
240	--	--	--	--	--	--	--	--	--	99.62	101.12	100.00	93.82	99.64
$t_{1/2}$ (min)	>120	>120	>120	>120	>120	>120	>120	>120	>120	>240	>240	>240	>240	>240

-- = Data not available; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the lipid nanoparticle formulation used in BNT162b2; Cyno = Cynomolgus; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; NC = not calculated; SD = Sprague Dawley; $t_{1/2}$ = half-life; WH = Wistar-Han; UDPGA= uridine-diphosphate-glucuronic acid trisodium salt.

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2.6.5.10B. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0159
Report Numbers: 01049-[redacted]020
01049-[redacted]021
01049-[redacted]022

Type of Study:	Liver Microsomes + NADPH	Stability of ALC-0159 In Vitro	Hepatocytes
Study System:		S9 Fraction + NADPH, UDPGA, and alamethicin	
ALC-0159 Concentration:	1 µM	1 µM	1 µM
Duration of Incubation (min):	120 min	120 min	240 min
Analysis Method:	Ultra-high performance liquid chromatography-tandem mass spectrometry		

Incubation time (min)	Percent ALC-0159 remaining													
	Liver Microsomes					Liver S9 Fraction				Hepatocytes				
	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
15	82.27	101.24	112.11	100.83	99.59	98.93	84.38	91.30	106.73	--	--	--	--	--
30	86.40	93.78	102.69	85.12	92.28	91.10	90.87	97.96	107.60	100.85	93.37	113.04	90.23	106.34
60	85.54	98.34	105.38	86.36	95.53	102.85	97.97	105.56	104.97	94.92	91.81	105.07	92.93	101.58
90	85.41	95.44	100.90	94.63	97.97	90.75	93.51	108.33	109.36	94.28	90.25	112.80	94.59	92.67
120	95.87	97.10	108.97	93.39	93.09	106.76	92.70	105.74	119.59	87.08	89.47	104.11	97.51	96.04
180	--	--	--	--	--	--	--	--	--	94.92	93.96	102.90	89.81	93.66
240	--	--	--	--	--	--	--	--	--	102.75	94.93	98.79	92.93	102.57
t½ (min)	>120	>120	>120	>120	>120	>120	>120	>120	>120	>240	>240	>240	>240	>240

-- = Data not available; ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the lipid nanoparticle formulation used in BNT162b2; Cyno = Cynomolgus; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; NC = not calculated; SD = Sprague Dawley; WH = Wistar-Han; UDPGA= uridine-diphosphate-glucuronic acid trisodium salt.

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2.6.5.10C. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0315

Report Number: PF-07302048_05[redacted]_043725

Type of study	Metabolism of ALC-0315 In Vitro			
Study system	Blood	Hepatocytes	Liver S9 Fraction	
ALC-0315 concentration	10 µM	10 µM	10 µM	
Duration of incubation	24 h	4 h	24 h	
Analysis Method:	Ultrahigh performance liquid chromatography/ mass spectrometry			

Biotransformation	m/z	Blood				Hepatocytes				Liver S9 Fraction			
		Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human
N-dealkylation, oxidation	102.0561[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	104.0706[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-dealkylation, oxidation	130.0874[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	132.1019[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-dealkylation, hydrolysis, oxidation	145.0506[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (acid)	255.2330[a]	+	+	ND	ND	+	+	+	+	ND	ND	ND	+
Hydrolysis, hydroxylation	271.2279[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine)	290.2690[b]	+	+	ND	ND	ND	ND	ND	ND	ND	ND	+	ND
Hydrolysis, glucuronidation	431.2650[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	464.2865[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	466.3011[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (amine)	528.4986[b]	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (amine), glucuronidation	704.5307[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	+	ND
Oxidation to acid	778.6930[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Oxidation to acid	780.7076[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydroxylation	782.7232[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sulfation	844.6706[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sulfation	846.6851[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Glucuronidation	940.7458[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Glucuronidation	942.7604[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = metabolite present.
a. Negative ion mode.
b Positive ion mode.

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2.6.5.10D. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0159

Report Number: PF-07302048_05[redacted]_043725

Type of study	Metabolism of ALC-0159 In Vitro			
Study system	Blood	Hepatocytes		Liver S9 Fraction
ALC-0159 concentration	10 µM	10 µM		10 µM
Duration of incubation	24 h	4 h		24 h
Analysis Method:	Ultrahigh performance liquid chromatography/ mass spectrometry			

Biotransformation	m/z	Blood				Hepatocytes				Liver S9 Fraction			
		Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human
O-Demethylation, *O*-dealkylation	107.0703[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, *O*-dealkylation	151.0965[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, *O*-dealkylation	195.1227[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis, *N*-Dealkylation	214.2529[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	227.2017[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (amine)	410.4720[b]	+	+	ND	ND	+	+	+	+	ND	ND	ND	ND
N,*N*-Didealkylation	531.5849[b]	ND	ND	ND	ND	ND	ND	ND	ND	+	+	+	+
N-Dealkylation	580.6396[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, oxidation	629.6853[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydroxylation	633.6931[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ω-Hydroxylation, Oxidation	637.1880[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (acid)	708.7721[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = metabolite present.
a. Negative ion mode.
b Positive ion mode.

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Appendix 3

Pfizer's Report to the European Medicines Agency

SCIENCE MEDICINES HEALTH

19 February 2021
EMA/707383/2020 Corr.1*[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Comirnaty

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] * *Correction dated 19 February 2021 to clarify ERA statement*

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
BDR	blinded data review
BLQ	below the level of quantitation
BMI	body mass index
CD	Circular dichroism
CDC	Centers for Disease Control and Prevention (United States)
CGE	Capillary gel electrophoresis
COVID-19	coronavirus disease 2019
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRF	case report form
CRM	Clinical Reference Material
CRO	contract research organization
CSR	clinical study report
CV	curriculum vitae
C&E	Cause and Effect Matrices
DCT	data collection tool
DLS	Dynamic Light Scattering
DMC	data monitoring committee
DOE	Design of experiments
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
e-diary	electronic diary
EU	European Union
FIH	first-in-human
FSFV	first subject first visit
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCS	human convalescent serum
HCV	hepatitis C virus
HCV	Ab hepatitis C virus antibody
HIV	human immunodeficiency virus
HPLC-CAD	High-Performance Liquid Chromatography - Charged Aerosol Detector
IA	interim analysis
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
IPT-C	In-process testing control
IPT-M	In-process testing monitoring
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IVT	in vitro transcription
IWR	interactive web response
LAL	Limulus Amebocyte Lysate
LC-UV/MS	Liquid Chromatography – Ultraviolet / Mass Spectometry
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mRNA	Messenger ribonucleic acid
modRNA	nucleoside-modified messenger ribonucleic acid

NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NMT	Not more than
NOR	Normal Operating Range
NT50	neutralizing titer 50
NT90	neutralizing titer 90
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PAR	Proven Acceptable Range
(q)PCR	(quantitative) Polymerase Chain Reaction
PD	protocol deviation
Ph.Eur.	European Pharmacopoeia
PPQ	Process Performance Qualification
PRM	Primary Reference Material
Prevax	prevaccination
PT	preferred term
QA	quality assurance
QA	Quality Attribute
QTL	quality tolerance limit
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RDC	remote data capture
RNA	ribonucleic acid
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
RT-PCR	Real Time Polymerase Chain Reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRVA	shoulder injury related to vaccine administration
SMQ	standardized MedDRA queries
SOC	system organ class
Tdap	diphtheria vaccine toxoid; pertussis vaccine acellular 3 component; tetanus vaccine toxoid

TME	targeted medical event
TSE	Transmissible Spongiform Encephalopathy
UFDF	Ultrafiltration/diafiltration
US	United States
Vax	vaccination
VE	vaccine efficacy
WBC	white blood cell count
WCB	Working Cell Bank
WHO	World Health Organization
WRM	Working Reference Material
YOA	years of age

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioNTech Manufacturing GmbH submitted on 30 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Comirnaty, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 July 2020.

The applicant applied for the following indication:

"Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older. The use of Comirnaty vaccine should be in accordance with official guidance."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0480/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0480/2020 was not yet completed as some measures were deferred.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, as it is intended for the prophylaxis of a life-threatening disease. In addition, the above-mentioned medicinal product is intended for use in an emergency situation, in response to public health threats duly recognised by the World Health Organisation and by the Union.

New active Substance status

The applicant requested the active substance Single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike

(S) protein of SARS-CoV-2 contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2. Steps taken for the assessment of the product[2]

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

The CHMP confirmed eligibility to the centralised procedure on	23 July 2020
Confirmation by ETF on the eligibly to the rolling review procedure on	24 July 2020
Agreement by ETF to start the rolling review procedure on	25 September 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	05 October 2020
The procedure (Rolling Review 1) started on	06 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	22 October 2020
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	28 October 2020
ETF discussions took place on	29 October 2020
Adoption of first Interim Opinion on the RR via 24 hour written procedure on	06 November 2020
The applicant submitted documentation as part of a rolling review on quality data to support the marketing authorisation application	06 November 2020

[2] These steps do not reflect the additional submissions made by the applicant during the active assessment phases.

The procedure (Rolling Review 2) started on	07 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, Peer Reviewer and ETF on	19 November 2020
BWP extraordinary adobe meeting was held on	24 November 2020
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF on	25 November 2020
ETF discussions took place on	26 November 2020
Adoption of the 2nd interim opinion for this rolling review on	30 November 2020
The application for the marketing authorisation was formally received by the EMA on	30 November 2020
The procedure started on	1 December 2020
BWP extraordinary adobe meeting was held on	15 December 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, peer reviewer and ETF on	16 December 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	16 December 2020
BWP extraordinary adobe meeting with an Oral Explanation by the applicant was held on	16 December 2020
ETF discussions took place on	17 December 2020
The Rapporteurs circulated the Joint Assessment Report to all CHMP members on	17 December 2020
BWP extraordinary adobe meeting was held on	18 December 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary meeting on	18 December 2020
CHMP extraordinary adobe meeting was held on	18 December 2020
The following GMP and GLP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– GMP inspections (distant assessments) of the sites Wyeth BioPharma, Andover (manufacturer DS, QC DS, QC DP) and Pfizer Inc., Chesterfield (QC DP, QC DP), both located in the USA, were carried out between 20 November 2020 and 02 December 2020. The outcome of the inspections carried out were issued on 15 December 2020.	15 December 2020
– A GLP inspection at a CRO in Germany between 3 to 6 November 2020. The outcome of the inspection carried out was issued on 6 November 2020.	6 November 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Comirnaty on	21 December 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human to human transmission. In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel Coronavirus (2019-nCoV) was the underlying cause. In early January 2020, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public, and the virus was categorized in the Betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 infections and the resulting disease COVID-19 have spread globally, affecting a growing number of countries. On 11 March 2020 the WHO characterized the COVID-19 outbreak as a pandemic. As of 01 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

2.1.2. Epidemiology and risk factors

Every individual is at risk of infection as there is no pre-existing immunity to the SARS-CoV-2. Following infection some but not all individuals develop protective immunity in terms of neutralising antibody responses and cell mediated immunity. However, it is currently unknown to what extent and for how long this protection lasts.

According to WHO 80% of infected individuals recover without need for hospital care, while 15% develop more severe disease and 5% need intensive care.

Increasing age and underlying medical conditions are considered risk factors for developing severe disease.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development. It has been shown that antibodies against the Spike protein neutralise the virus and prevent infection.

2.1.4. Clinical presentation and diagnosis

The presentation of COVID-19 is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic subjects, progression of disease may lead to acute respiratory distress syndrome requiring ventilation and subsequent multi-organ failure and death.

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

The US Centres for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrheal
- Vomiting
- Fatigue
- Headache
- Nasal congestion or runny nose
- Nausea

All ages may present with the disease, but notably case fatality rates (CFR) are elevated in persons >60 years of age. For example, in Italy the CFR was 0.3% in adults <40 years of age but 12.8% in adults 70 to 79 years of age and 20.2% in patients ≥80 years of age. Comorbidities are also associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease. Healthcare workers are overrepresented among COVID-19 patients due to occupational exposure to infected patients.

In most situations, a molecular test is used to detect SARS-CoV-2 and confirm infection. The reverse transcription polymerase chain reaction (RT-PCR) test methods targeting SARS-CoV-2 viral RNA are the gold standard in vitro methods for diagnosing suspected cases of COVID-19. Samples to be tested are collected from the nose and/or throat with a swab. Molecular methods used to confirm an active infection are usually performed within a few days of exposure and around the time that symptoms may begin.

2.1.5. Management

The management of COVID-19 has developed during 2020, and now includes antiviral therapy (e.g. remdesivir), antibodies administered from convalescent plasma and hyperimmune immunoglobulins, anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants. These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals who have COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for a prophylactic vaccine during the ongoing pandemic, both for protection of particularly vulnerable groups as well as mitigating the effects of the pandemic at a population level, e.g. to maintain a functioning health care system, and to avoid the social and economic consequences of the stringent measures needed to diminish virus spread. There is currently no approved vaccine in EU for prevention of COVID-19.

About the product

BNT162b is a mRNA vaccine for prevention of COVID-19. The vaccine is made of a mRNA encoding for the full-length SARS-CoV-2 spike glycoprotein (S) encapsulated in lipid nanoparticles (LNPs). The sequence of the S protein was chosen based on the sequence for the "SARS-CoV-2 isolate Wuhan-Hu-1", which was available when the program was initiated: GenBank: MN908947.3 (complete genome) and GenBank: QHD43416.1 (spike surface glycoprotein).

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2. The RNA contains common structural elements optimized for mediating high RNA stability and translational efficiency (see section 2.2). The LNPs protect the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (IM) delivery.

The mRNA is translated into the SARS-CoV-2 S protein in the host cell cytosol. The S protein is then expressed on the cell surface where it induces an adaptive immune response. The S protein is identified as a target for neutralising antibodies against the virus and is therefore considered a relevant vaccine component.

The vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) in two 30 µg doses of the diluted vaccine solution given 21 days apart.

Intended indication: *'Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older'.*

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive:

According to the Applicant, there is a positive benefit-risk balance for Comirnaty in the active immunisation to prevent COVID-19 disease caused by SARS-CoV-2, in individuals 16 years of age and older. This is based on evidence from the pivotal study C4591001 (also referred to as BNT162-02), a Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding Study investigating the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in healthy individuals.

The Applicant stated that the available data to date indicate that its vaccine was 95 percent effective and had no serious side effects, showing that the vaccine prevented mild and severe forms of COVID-19.

- It is likely that the applicant will be able to provide comprehensive data.

The Applicant intends to continue the ongoing pivotal Phase 3 study with participants as originally allocated for as long as possible, to obtain long-term data and to ensure sufficient follow-up to support a standard marketing authorisation. In case of availability of any COVID-19 vaccine, the sponsor will appeal to participants to remain in the ongoing study as originally randomized for as long as possible, ideally until a COVID-19 vaccine has full regulatory approval. In all cases, it is intended to follow participants up to the original planned 24 months post-vaccination, regardless of any participants opting to crossover from placebo to active vaccination. The safety and effectiveness of COMIRNATY in individuals <16 years of age have not been established for this application. Four studies in paediatric subjects are planned as laid down in the paediatric investigation plan. A study in pregnant women is also planned in the EU. A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of Comirnaty (Study C4591010) will be conducted in the EU using primary data collection that monitors a cohort of vaccinees and evaluates risk of AESIs. The Applicant will also conduct, non-interventional studies (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 in a real-world setting. These studies will allow to determine the effectiveness of vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups.

- Unmet medical needs will be addressed

According to the Applicant, as there is no approved other vaccine in the EU or successful COVID-19 therapy available in the EU, unmet medical need is existing and is likely to be addressed by this vaccine in view of the high level of protection observed in the pivotal clinical trial.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

According to the Applicant, Efficacy of COMIRNATY to prevent COVID-19 was demonstrated at the final analysis. The observed VE in each subgroup as defined by age, including elderly ≥ 65 years old, sex, race/ethnicity, country, obese subjects, and subjects at risk due to comorbidities, was overall consistent with the effectiveness of BNT162b2 to protect vaccinees against the disease. The benefit of immediate availability of Comirnaty through conditional marketing authorisation is based on the fact that there is no approved vaccine or successful COVID-19 therapy available in the European Union. An effective vaccine can impact the pandemic at this critical time and a COVID-19 vaccination program implemented soon can likely prevent further pandemic waves and thus substantially reduce mortality due to disease.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for dispersion for injection containing 225 µg/ 0.45 mL (prior to dilution) of BNT162b2 (5'capped mRNA encoding full length SARS-CoV-2 Spike protein) as active substance (AS).

Other ingredients are: ALC-0315 (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), 1,2-

Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose and water for injections.

The product is available in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Pack size: 195 vials.

The multidose (5 dose) vial is stored frozen and must be thawed prior to dilution. After thawing, the vaccine should be diluted and used immediately.

After dilution with 1.8 mL sodium chloride (0.9%) solution (not supplied), one dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

2.2.2. Active Substance

General Information

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimised sequence encoding the spike antigen of SARS-CoV-2. The vaccine is based on the spike glycoprotein (S) of SARS-CoV-2. The sequence was chosen based on the sequence for the "Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1". The protein sequence contains two proline mutation, which ensures an antigenically optimal pre-fusion confirmation (P2 S). The RNA does not contain any uridines; instead of uridine the modified N1-methylpseudouridine is used in RNA synthesis. The applicant will provide clarification on the mechanism of action for BNT162b2.

Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured and controlled by either Wyeth BioPharma Division, Andover, United States or by BioNTech Manufacturing GmbH, Mainz, Germany, and Rentschler Biopharma SE, Laupheim, Germany.

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release. These issues were classified as a Major Objection (MO). After further information was obtained from the sites and inspectors, the MO was considered resolved.

EU GMP certificates for the manufacturing and testing sites were subsequently obtained. In conclusion, appropriate manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing sites.

Description of manufacturing process and process controls

Information on the manufacturing process and process controls for both the Andover and the BNT Mainz & Rentschler manufacturing sites were provided.

The manufacturing process of BNT162b2 active substance involves five major steps. The RNA is synthesised from linear DNA via an in vitro transcription (IVT) step. The IVT step is followed by a number of purification and filtration steps. Lastly, the RNA undergoes a final filtration before being dispensed and stored frozen.

Flow diagrams were provided, presenting the process steps, process inputs and the process controls for each step. The purpose of each step in the manufacturing process is sufficiently described. The ranges of hold times and process parameters and routine in-process controls are listed with corresponding acceptance criteria, for each step. It is noted that not all process parameters are listed, but that the lists include all critical and several non-critical process parameters. It is agreed that the key process parameters are described in the dossier. The applicant has agreed to upgrade these parameters to critical process parameters (CPPs) and to include acceptable ranges for these CPPs. Updated information has been submitted during the procedure which comprised modifications of the acceptable ranges of several process parameters and the addition of some controls. The strategy is found acceptable, and the Applicant will provide information on acceptable ranges for some parameters.

The active substance is stored between -15°C and -25°C. Transportation using an insulated shipper is qualified and shipping time to finished product manufacturing sites are defined. Shipping validation of the intermediate has been agreed as recommendation.

The batch numbering system is sufficiently described.

Control of materials

An adequate overview of the raw materials and solutions used in the active substance manufacturing process is provided.

Representative certificates of analysis have been provided. The submitted information supports the appropriate quality of raw materials. It is recommended that the applicant should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials **(REC1)** and should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases **(REC2).** The description of synthesis of 5'cap and its related impurities were requested during the procedure. Appropriate information was given. The applicant should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021 **(REC3)**.

The BNT162b2 active substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA from transformed *Escherichia coli* cells.

The linear DNA template is not part of the final product but defines the sequence of the mRNA product and therefore it is fundamental to ensure the adequate control of the active substance. Changes to the manufacturing process of the linear DNA template (e.g. change to plasmid host cell) may result in a different impurity profile in the active substance. Additional details on the manufacturing process and the control strategy for this starting material, initially only shortly described, have been provided and the dossier will be updated accordingly.

The cell banks involved in the plasmid manufacturing process are described. Master cell bank (MCB) and working cell bank (WCB) qualification tests are listed. Relevant specifications are set and data from the current MCB and WCB are provided. The plasmid MCBs and WCBs are enrolled in a cell bank stability program. The strategy is considered adequate, noting that the dossier will be updated as appropriate. A protocol for establishment of future WCBs is provided.

Following fermentation, the cells are harvested and chemically lysed to recover the plasmid DNA. After this lysis step, the circular plasmid DNA is purified. The circular plasmid DNA is filtered and stored frozen. The strategy for establishing the initial shelf-life is endorsed and data provided support the proposed shelf life. A list of the raw materials as well as other materials used in the manufacture of the

linear DNA template is provided. All materials used are animal origin free and sourced from approved suppliers.

Specifications for the circular plasmid DNA as well as for the DNA linear template are provided. Process- and product-related impurities including host cell genomic DNA, RNA, proteins, endotoxins, bioburden and plasmid isoforms, for the plasmid DNA, are routinely quantified. The reference material is described. Implementation of any changes in the manufacture of the linear DNA template should be applied for in a variation application.

Control of critical steps and intermediates

Process parameters and tests that are used to control the process and active substance quality are provided. The list of CPPs was provided with corresponding updated acceptable ranges.

A summary of the quality attributes with the rationale for the criticality assignment is provided. The rationale for classification into CQA or QA is presented for each attribute and appears reasonable.

The in-process test methods are defined and described in the dossier.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The BNT162b2 active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial process validation/ process performance qualification batches at all sites. All acceptance criteria for the critical operational parameters and acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

In comparability studies, a decrease in RNA integrity was observed for the initial Process 2 batches compared to Process 1 batches. This is further discussed in the subsequent section on manufacturing process development. After adjustment of process parameters for CTP and ATP volumes, RNA integrity level is more consistent and verify that the volume adjustments made for ATP and CTP volumes consistently provide reproducible results with RNA integrity levels more similar to levels achieved in Process 1 batches. Since the target volumes for ATP and CTP have been increased, the proven acceptable ranges (PARs) ranges need to be adjusted and the dossier updated accordingly **(REC8)**. The robustness of the DNase digestion step is not considered comprehensively demonstrated although there is routine control of residual DNA impurities at the active substance level. It has been confirmed that studies to enhance the robustness of this step are ongoing and these should be reported **(REC7).** The finalised indirect filter qualification assessment, according to the applicant, already available and should be provided for evaluation **(REC6).**

Relevant hold times and transport times have been defined and were validated by appropriate studies.

The shipping qualification strategy is described in detail and considers both thermal and mechanical aspects of shipping. The shipping procedures and configuration for transport of frozen AS to the

finished product manufacturing sites were validated to maintain product temperature in the acceptable range for a defined duration.

A transport verification study is planned and results will be available in Q1/2021. The recommendation to provide shipping performance qualification data has been agreed **(REC6)**.

Manufacturing process development

Process development changes were adequately summarised. Two active substance processes have been used during the development history; Process 1 (clinical trial material) and Process 2 (commercial process). Details about process differences, justification for making changes, and results from a comparability study are provided. The major changes between active substance process versions were described in the dossier.

Batch analysis results showing comparability between non-clinical and clinical batches are provided. Additional characterization of product-related species and their relation to final product specifications will be provided as a specific obligation.

Electropherograms were presented demonstrating similarities in the peak pattern of RNA species, but some differences between Process 1 and 2 were also noted. It can therefore not be concluded that identical species are obtained by the processes. It is likely that the fragmented species will not result in expressed proteins, due to their expected poor stability and poor translational efficiency (see below). However, the lack of experimental data on the truncated RNA and expressed proteins does not permit a definitive conclusion and needs further characterisation. Therefore, additional characterisation data remain to be provided as a specific obligation **(SO1)**.

Regarding the 5′ cap end of the AS, reversed phase high performance liquid chromatography-UV and mass spectrometry (LC- UV/MS) characterisation confirmed that the 5'-capped and uncapped structures are the same but that there is a slight shift towards higher 5'-capping levels in Process 2. The reported quality attribute 'capped-intact RNA' is intended to reflect the proportion of the RNA molecules in the active substance that are a fully intact molecule and have the 5′-cap. It is noted that the capped-intact RNA is not measured, but only calculated from the results of 5′-cap and %RNA integrity tests. Therefore, this argument alone cannot fully confirm the comparability of Process 2 versus Process 1, and further characterisation data and justification of specifications were requested.

According to the Applicant, the majority of fragments are expected to be comprised of truncated transcripts including the 5′ region but lacking the 3′ region and poly(A)tail. However, the results indicating a substantial proportion of shorter/truncated mRNA with both cap and poly(A)tail are not in agreement with this statement. Therefore, the Applicant was asked to discuss and justify the obtained results and explain the apparent discrepancy. Additional characterisation data using an orthogonal method with enriched samples for fragmented species was provided. Preliminary characterization data on isolated fragmented species suggests they predominantly include the 5′-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction. The characterisation data are requested to be completed with analysis of the main peak from ion pairing RP-HPLC and analysis of other samples from Process 1 and optimised Process 2 **(SO1).** The Applicant will continue to evaluate any potential overestimation of poly(A) tail and should characterise fragments for any future AS process changes **(SO1)**.

Furthermore, the poly(A)tail of the 3′ end was characterised by LC-UV/MS. While the results were demonstrated to be comparable between Process 1 and Process 2 batches, significant differences were identified. As expected, poly(A) tail heterogeneity was observed both for Process 1 and Process 2 batches. Thus, slight differences in the poly(A)tail pattern were observed when comparing Process 1

and Process 2 AS batches. The Applicant explains that the redistribution is probably due to the use of a linearised DNA plasmid template in Process 2 instead of a PCR-derived DNA template in Process 1. For both processes, the poly(A)tail is anticipated to be sufficiently long to guarantee stability of the RNA and function in translation. This explanation is considered reasonable by the CHMP.

The overall primary sequence of BNT162b2 active substance was demonstrated to be comparable by LC/MS/MS -oligonucleotide mapping. Circular dichroism (CD) spectroscopy confirmed that the higher-order structure of Process 1 and Process 2 AS batches were comparable.

To demonstrate functionality, the protein size after in-vitro expression of BNT162b2 active substance was determined. The expressed protein sizes were demonstrated to be comparable between Process 1 and Process 2 batches. However, further clarification is requested and include correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **(SO1).**

A second comparability study was presented to assess comparability across the Process 2 manufacturing facilities, batches each from the Andover and BioNTech sites were included in the study. In addition, Process 2 batches, planned for clinical supply and for emergency supply in the US market and representative batches from Process 1 were included in the comparison.

In conclusion, the Process 2 batches manufactured at the Andover and BioNTech sites were demonstrated to be comparable with respect to identity as monitored by agarose gels and 5'Cap structure characterised by LC-UV and subsequent MS analysis. Furthermore, the primary sequence and the secondary structure was demonstrated to be comparable for all Process 1 and Process 2 batches included in the study. Poly(A) tail length and distribution was investigated by RP-HPLC and MS analysis. All process 2 batches were found comparable, while the Process 1 batches showed a somewhat different poly(A) tail pattern.

The expressed protein size after in-vitro expression of BNT162b2 active substance was determined and the results demonstrate comparability between batches. However, the identity of the bands identified by WB are not sufficiently justified and further clarification is requested **(SO1)**.

Overall, the submitted data confirm consistent and comparable quality of Process 2 batches manufactured at the Andover and BioNTech sites.

Process characterisation studies using scale-down models of individual unit operations, were performed.

It should be noted that future changes to any of the process parameters, regardless of the classification of CPP or non-CPP, should be applied for as variation to the terms of the MA.

Initially, addition volumes for ATP and CTP were identified as non-CPPs as both were supplied in theoretical excess. Following additional manufacturing campaigns and additional small-scale studies it was shown that these volumes could be limiting, and the ranges were widened at the higher end. It is noted that after the adjustment of these volumes, the percentage of RNA integrity has increased to levels more consistent with Process 1 batches. Nevertheless, since the target volumes for ATP and CTP have been increased to avoid that these nucleotides are rate-limiting in order to increase the percentage of RNA integrity, the PAR ranges need to be adjusted and the dossier updated accordingly **(REC8)**.

The acceptable ranges for CPPs will be updated in the dossier.

A safety risk assessment for potential process-related impurities included in the active substance process relative to patient safety was performed. The sources of the impurities are sufficiently addressed.

The safety risk assessment strategy involves comparison of the theoretical worst-case concentration of impurities, assuming no removal, to calculated safety concern thresholds.

The worst-case levels of residual raw materials and reagents from the BNT162b2 active substance manufacturing process were calculated to be significantly below the pre-determined safety limits. This is found acceptable.

Characterisation

Analytical characterisation was performed on BNT162b2 active substance manufactured at commercial scale. This is found acceptable.

The physico-chemical characterisation involved primary structure, 5' cap structure, poly(A)tail and higher order structure evaluation. Primary structure was confirmed by oligonucleotide mapping and the orthogonal method, RNA sequencing using Next Generation Sequencing (NGS) technology. The results confirm the RNA sequence. The 5'-cap and 3' poly A tail were confirmed by two separate LC-UV/MS-methods. It was demonstrated that the predominant form of the 5' terminus is the full-length nucleotide sequence with the 5'-Cap. The higher order structure of BNT162b2 mRNA active substance was characterised in solution using biophysical techniques.

Overall, state-of-the-art methods were applied for physico-chemical characterisation and the results confirmed the expected sequence and quality attributes. It is recommended that the applicant should comprehensively describe the capability of a specific analytical method to detect lower amounts of product related impurity in the presence of the correct form in the active substance. **(REC9)**.

An uncertainty in the characterisation section is that no biological characterisation is presented. In response to questions during the procedure, the applicant has committed to update dossier with the strategy for potency determination and to address relevant functional assays including the in vitro expression (potency) results and results from the analysis of expressed protein size for active substance lot 20Y513C101. It is recommended that the applicant should discuss the results and the assay suitability for a certain method used for biological characterization of protein expression for the active substance **(REC10)**.

As described above, the expressed protein size results are currently not sufficiently confirmed and a specific obligation is laid down in the terms of the MA requiring their adequate characterisation **(SO1)**.

Process-related and product-related impurities as well as potential contaminants are described. A number of batches were evaluated for impurities, i.e. clinical, initial emergency supply and PPQ batches from both manufacturing sites.

The sole product-related impurity addressed is double-stranded RNA, derived from the in-vitro transcription reaction. Results from the active substance batches demonstrate that the level of double stranded RNA is low, acceptable and consistent.

In addition to double stranded RNA, there are truncated RNA, also referred to as fragmented species. Truncated RNA is reflected in the AS specification in terms of RNA integrity. However, the characterisation of BNT162b2 AS is currently not found to be complete in relation to a specific parameter. This is especially important considering that the current AS and finished product acceptance criteria allow for a proportion of fragmented species. The Applicant should provide additional data to further characterise the truncated and modified mRNA species present in the finished product. Relevant protein/peptide characterization data for predominant species should be provided **(SO1)**.

Residual DNA template is a process-related impurity derived from the linearised DNA template added to the in-vitro transcription reaction. Residual DNA template is measured as defined in the active substance specification. The levels are controlled by a specification limit which is considered suitably low.

The potential contaminants described in this section are endotoxin and bioburden. Acceptable results are shown for the Proteinase K pool, UF retentate pre recovery, UF-product pool and the active substance, for all batches investigated.

Specification

The active substance specifications contain tests for appearance (clarity, coloration (Ph. Eur.)), pH (Ph. Eur.), content (RNA Concentration) (UV Spectroscopy), Identity of Encoded RNA Sequence (RT-PCR), RNA Integrity (Capillary Gel Electrophoresis), 5'- Cap (RP-HPLC), Poly(A) Tail (ddPCR), Residual DNA Template (qPCR), dsRNA (Immunoblot), Bacterial Endotoxin (Ph. Eur.) and Bioburden (Ph. Eur.).

The proposed specification for active substance is considered acceptable for authorisation with respect to the attributes chosen for routine release testing. During the procedure the specification limits for a number of attributes were tightened in response to questions.

The length of the poly(A) tails in BNT162b2 active substance is important for RNA stability and translational efficiency and even though comparable results have been reported to date, the poly(A) tail length should be included to the active substance release testing **(SO2)**.

The rationale used to establish the acceptance criteria is described in detail and based on a limited data set representative of BNT162b2 active substance manufactured at the intended commercial scale and process. From the available data, mRNA integrity, dsRNA and Poly(A) tail acceptance criteria are considered in relation with batches used in clinical studies and with the demonstrated manufacturing capability and need to be re-assessed and revised as appropriate as further data becomes available **(SO2)**.

Potency testing is not included in the control of active substance but instead is performed at the level of finished product release testing. Considering the nature of this product, the approach is endorsed by the CHMP.

Analytical methods

All analytical methods used for testing of the active substance are sufficiently described in the dossier. The following tests are performed in accordance with Ph Eur chapters; clarity (Ph Eur 2.2.1), colour (Ph Eur 2.2.2), pH (Ph Eur 2.2.3), bacterial endotoxins (Ph Eur 2.6.14) and bioburden (Ph Eur 2.6.12).

All non-compendial analytical methods are sufficiently described. These analytical methods were suitably validated against the parameters presented in ICH Q2(R1).

The technical procedure for the quantification of the poly(A) tail is considered, in general, sufficiently described but the suitability of this method for the intended purpose remains to be confirmed **(SO2)**.

Batch analysis

Batch results are presented for active substance batches used for nonclinical toxicology, clinical trials, process performance qualification (PPQ), emergency supply and stability.

In general, the results obtained using the commercial process (Process 2) demonstrate batch to batch consistency with a few exceptions.

Reference materials

The current reference standard is referred to as the Clinical Reference Material (CRM). A stability protocol is provided. The Applicant has agreed to provide additional information such as protocol on preparation and qualification on the future reference material, as requested **(REC12)**.

In future, a two-tiered system for future commercial reference material will be implemented. A primary reference material (PRM) and an initial working reference material (WRM) will be established for the active substance reference material.

Container closure

The information regarding container closure system is acceptable. Compliance with Ph. Eur. has been verified.

Stability

Based on the limited stability data presented a shelf-life at -20 ± 5°C can be approved for the active substance when stored in the commercial container closure system. The stability program is designed to follow ICH guidelines. The test methods used are stability indicating. Data from the sites Andover, Mainz, Rentschler are included.

It is noted that the Applicant states that testing is currently in progress on the clinical batches and the dossier will be updated with data for these batches, as well as any new data available for the primary process validation batches. Thermal cycling studies have been initiated and a minimum of one process validation batch will be subjected to photostability studies at a future date.

Based on the stability data presented a shelf-life at -20 ± 5°C can be approved for the active substance when stored in the commercial container closure system.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The BNT162b2 finished product (FP) is supplied as a preservative-free, 5 dose multidose concentrate to be diluted prior to intramuscular injection. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

Each vial, containing 0.45 mL of the finished product at pH 6.9 - 7.9 is designed to deliver a total of 5 doses after dilution by addition of 1.8 mL of sterile 0.9% sodium chloride solution to a total volume of 2.25 mL. Each dose contains 30 µg of RNA in 0.3 mL.

The overfill in the vial is required to ensure that the full five doses can be removed from the multi-dose vial after dilution and correctly administered, taking account of potential loss of product during these dilution and administration steps. The justification for the overfill is sufficiently discussed and considered to be acceptable. The applicant development data and finished product testing confirm that 5 doses can be consistently extracted from the vial and delivered after dilution.

The finished product is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap.

The full list of excipients is listed above in section 2.2.1; ALC-0315 and ALC-0159 (functional lipids), DSPC and cholesterol (structural lipids), potassium chloride, potassium dihydrogen phosphate, sodium

chloride and disodium phosphate dihydrate (buffer components), sucrose (cryoprotectant) and water for injections.

All excipients except the functional lipids ALC-0315 and ALC-0159 and the structural lipid DSPC comply with Ph. Eur. The functional lipid excipients ALC-0315 and ALC-0159, are classified as novel excipients. Both structural lipids DSPC and cholesterol are used in several already approved finished products. A justification was provided for why DSPC is not considered to be a novel excipient. DSPC is used as part of the LNP for the EU approved finished product Onpattro which is administered intravenously in a much higher dose than the intramuscular dose for this product. Additionally; DOPC, a structurally related lipid, is present in finished products approved in the EU for intramuscular administration. It was therefore concluded that the level of information provided for DSPC, is in line with the requirements for a known excipient are sufficient and appropriately justified.

The vial, stopper and seal components are compliant with the appropriate Ph. Eur. monographs for primary containers and closures.

Formulation development

The section on formulation development describes and justifies the chosen formulation and is sufficiently comprehensive.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described. The LNPs consists of four lipids, each has a functional or structural purpose. The formed RNA-containing LNPs are solid particles. Furthermore, the accumulated batch-data to date show consistent manufacture of lipid nanoparticles both with respect to size and polydispersity.

Lipid-related impurities have been identified in the finished product and have been characterized. An investigation has been initiated and is ongoing to assess and review potential root causes. The outcome of the investigation shall be provided (SO2).

Visual particulate matter has occasionally been observed in finished product batches. Characterization data have been presented and the control strategy has been discussed. The data demonstrates that the particles are comprised of components of the finished product formulation. A 100% visual inspection is performed during manufacturing and the automatic inspection system is updated to improve the inspection. Routine release or routine stability data indicate that the propensity of particles to form following storage is low. If particles are observed in the diluted vaccine the vial should be discarded.

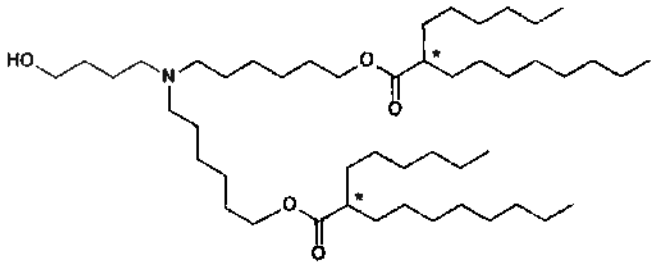
Novel excipients

Two novel excipients are included in the finished product, the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. Limited information regarding the novel excipients are provided.

ALC-0315 (cationic lipid)

The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine and two ester moieties, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate).

Figure 1 ALC-0315 structure



Asterisks (*) indicate chiral centers.

A brief description of the chemical synthesis is provided. The suppliers are defined in the dossier. A similar manufacturing process is used for ALC-0315 in clinical and commercial finished product batches.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. (**SO4**)

The proposed specification is considered acceptable based on the available data. However, additional information regarding specifications that should be provided **(SO4).**

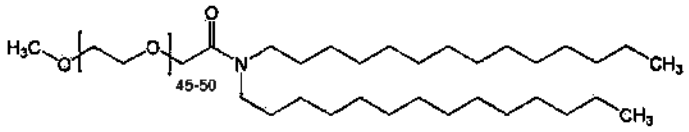
Stability data from one supplier indicate that ALC-0315 is stable when stored at the recommended storage conditions. Additionally, the excipient is stable at room temperature suitable for use in further manufacturing steps. Stability data from one supplier is considered representative for lipid from another supplier.

Lipid related impurities have been observed in some recently manufactured finished product batches, correlated with ALC-0315 lipid batches. The quality of ALC-0315 excipient is considered acceptable based on the available data on condition that specific impurities in the finished product will be further evaluated **(SO2).**

ALC-0159 (PEGylated lipid)

The ALC-0159 novel excipient is a PEGylated lipid, 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide.

Figure 2 ALC-0159 structure



A brief description of the chemical synthesis is provided.

The suppliers are defined in the dossier. The same supplier was used during development for clinical phase 1, 2 and 3 studies. The same synthetic route was used for ALC-0159 throughout development of the finished product.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant is requested to provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **(SO5)**

The proposed specification is considered acceptable based on available data. However, in order to improve impurity control strategy and to ensure batch to batch consistency of the finished product, there are additional information regarding specifications that should be provided **(SO5)**.

Stability data indicate that ALC-0159 is stable when stored at the recommended storage conditions.

Manufacturing process development

The development history of the finished product is sufficiently described. The process has been transferred to commercial facilities for manufacture of later clinical materials, emergency supply and commercial supply. A table on finished product lot genealogy and usage has been provided.

The applicant states that comparability is demonstrated in a stepwise approach through a combination of release testing and extended characterization methods. It is agreed that comparability was sufficiently demonstrated with only small differences noted.

During the present regulatory procedure, release testing results of a number of recently manufactured GMP-batches was presented. The release data for the GMP-batches are compared to the clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification and that comparability has been sufficiently demonstrated subject to the specific obligations further described, for the attributes tested and given the pandemic situation. In addition, the comparison will be further extended with additional characterization testing on future batches of finished product. The applicant has confirmed that testing will be performed according to the agreed finished product comparability testing protocol and the results will be submitted in the frame of a specific obligation (**SO3**).

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented and is agreed. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program at the commercial facility has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data (**SO3**).

The development of the manufacturing process is extensively described, and critical process parameters are defined. Process characterisation studies using scale-down models of individual unit operations, were performed.

Overall control strategy was presented but some parameters and ranges may be updated after PPQ and additional characterization studies completed. As for assessment of overall control strategy, a complete set of data and information is needed, this document will be assessed when finalised. A time-plan for the provision of the final data set has been agreed with the applicant **(SO3)**.

The analytical testing strategy of finished product has changed throughout the development and these changes have been described. Bridging studies have been performed for analytical tests that have been changed or replaced (subvisible particles, identity of encoded RNA sequence and RNA integrity). This is found acceptable.

Container closure system

The development of the container closure system is sufficiently presented. The primary packaging is composed of glass vial and rubber stopper and are compliant with the compendial requirements of Ph. Eur.

Controlled extraction studies have been performed on the bromobutyl rubber stopper. The applicant will provide the updated results from the leachables study for assessment. (**REC13**)

Microbiological attributes

Container closure integrity testing has been performed to demonstrate that the 2 mL container closure presentation is integral.

In order to improve the control strategy, the MAH should provide validation results of alternative sterility test i.e. rapid sterility test for assessment before implementation (**REC14**).

Compatibility

The studies described have been performed to assess physicochemical stability of the FP after dilution with 0.9% sodium chloride solution in the original glass vial as well with commonly used commercially available administration components and using worst-case conditions for dosage and administration in the clinical setting. The thawed hold time (in-use period) of undiluted finished product has been defined as 5 days at 2-8 °C and 2 hours at up to 30 °C.

Results presented support physicochemical stability of FP diluted in 0.9% sodium chloride solution for up to 24 hours at ambient or refrigerated temperatures (2-30°C) following an in-use thawed hold time of up to 5 days at 2-8 °C and 2 hours at 30 °C.

Compatibility with dosing components (syringes and needles) has been established for up to 6 hours. Furthermore, a microbiological in-use hold time study has been performed by a challenge test including five compendial micro-organisms. No significant growth (>0.5log10 from the start-point) was observed for any of the microorganisms within 12 hours of inoculation with storage at 20-25°C of diluted FP in 0.9% sodium chloride solution. Therefore, based on the results from the microbiological in-use hold time study, the proposed in-use period for up to 6 hours at ambient temperatures is agreed, as reflected in the product information. Furthermore, it is also stated by the applicant that the in-use period is in alignment with the WHO policy on the use of opened multi-dose vaccine vials (WHO Policy Statement: Multi-dose vial policy (MDVP) – handling of multi-dose vaccine vials after opening, rev 2014).

The compatibility of finished product is acceptably demonstrated by the dilution and administration simulation studies performed.

Manufacture of the product and process controls

The finished product is batch released by Pfizer Manufacturing Belgium NV, Puurs, Belgium or BioNTech Manufacturing GmbH, Mainz, Germany. The GMP status of the manufacturing and testing sites of the finished product have been confirmed.

The finished product manufacturing process includes the following main steps: active substance thawing and dilution, LNP formation and stabilisation, buffer exchange, concentration and filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, visual inspection, labelling, freezing and storage. Critical manufacturing steps are discussed, and relevant in-process controls are applied.

Dossier should be updated to provide more details on increase batch size including range number of AS bag and batches used, configuration of filters filter surfaces used and process controls (**REC14**). The absence of a test for residuals is considered acceptable.

Shipping validation

This section gives a summary of the qualification of the shipping process for transport of BNT162b2 finished product by passive thermal shipping containers for air and road shipments at temperature conditions of -90 to -60 °C from the finished product manufacturing and packaging site to dosing sites in the EU.

Short periods of time outside of the intended routine shipping condition of -90 to -60 °C during transport and at distribution sites have been defined.

The shipping temperature range of -90 to -60 °C is based on available stability data.

One thaw and refreeze cycle is allowed during transportation. Time during transportation out of the intended storage and shipping temperature range (-90 to -60 °C) without thaw is allowed for specified times and conditions for multiple transfers and redistribution during shipping with subsequent refreezing to -90 to -60 °C between transfers. The temperature excursion allowances are supported by data.

The selected shipping methods include shipping containers designed to maintain product temperature through a combination of insulation and dry ice. The applicant has prior experience with these passive thermal conveyances and has demonstrated that they maintain the -90 to -60 °C temperature range during product shipments, including minor shipping delays and short exposures to extreme temperatures occasionally observed during shipping and handling.

All shipments are continuously monitored using temperature data loggers.

The overall qualification strategy considered both thermal and mechanical aspects of shipping in passive thermal conveyance, supported by operational qualification and performance qualification testing. A summary of the shipping qualification strategy has been provided.

For the passive thermal conveyance, the qualification is focused on the ability of the passive system to maintain the required temperatures with specified phase change materials or dry ice when exposed to ambient temperature profiles for worst-case season. These studies are carried out in laboratory chambers to simulate the summer as worst-case ambient profiles.

A simulated distribution study demonstrated finished product and package integrity after exposure to simulated distribution hazard conditions, following the durations outlined in the worst-case extended transport lanes.

Results of thermal qualification have met specified acceptance criteria and support shipments of BNT162b2 finished product using the passive thermal conveyance shipping containers either directly or

via qualified distribution centres. Passive thermal conveyance performance qualification and the simulated shipping study finished product impact testing have been performed to complete shipping qualification assessing both thermal and mechanical aspects of shipping.

Process parameters for storage and shipping are found acceptable.

Media fills

Media fills have been performed for the filling line to validate the aseptic filling process and were run in accordance to guidelines. Results have been provided from three consecutive simulation studies and gave satisfactory results without any contaminated units. Results for the media fill cover the maximum process time for the manufacturing of finished product and simulate worst-case manufacturing conditions. The media fill validation demonstrated that aseptic conditions are maintained during the filling process. For the filling line, the maximum time will be established upon completion of media fill qualification studies. This is found acceptable.

Verification of in-process test methods

Data on verification of in-process test methods was pending at the time of the present regulatory procedure and should be provided during Q2 2021 (**REC15**).

Hold times

Hold times have been established. It is noted that any change of this section needs to be submitted to the Agency via a variation application.

Process validation plan

A FP process validation plan has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

It is described in the dossier that commercial scale PPQ-batches will be manufactured during Dec 2020 to Jan 2021 and the applicant has provided a process validation plan. In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation data, by March 2021. (**SO3**)

Filter validation

Acceptable information has been provided during the procedure for filter validation on the filters used for sterile filtration, describing the material, pore size and surface area. All study results met the predetermined acceptance criteria and the studies for microbial retention, membrane compatibility, extractable substances and integrity test determination have shown that the filters are appropriate for sterile filtration of the finished product. In addition, the applicant has clarified that the filter used for bioburden reduction is identical to the filters used for sterile filtration.

The MAH should provide the results for assessment from the filter validation as soon as they are available (**REC23**).

Control of excipients

ALC-0315 and ALC-0159 are novel excipients, not previously used in an approved finished product within EU. Additional information is provided separately in Section A.3 of the dossier.

DSPC is a non-compendial excipient sufficiently controlled by an in-house specification.

Cholesterol is sufficiently controlled according to the Ph. Eur. monograph with additional tests for residual solvents and microbial contamination.

The other excipients (sucrose, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injection) are controlled according to respective Ph. Eur. monograph.

The processing aids ethanol and citrate buffer are controlled according to Ph. Eur. standards and for HEPES and EDTA, reference is made to the active substance.

Product specification

The release and stability testing specifications for BNT162b2 finished product include tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), ALC-0315 content (HPLC-CAD), ALC-0159 content (HPLC-CAD), DSPC content (HPLC-CAD), Cholesterol content (HPLC-CAD), extractable volume (Ph. Eur.), Lipid identities (HPLC-CAD), Identity of encoded RNA sequence (RT-PCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion). For all quality attributes tested on stability except for RNA integrity, the acceptance criteria for release and stability testing throughout shelf life are the same.

The specifications document for finished product in section 3.2.P.5.1 of the dossier includes a comprehensive panel of relevant tests along with corresponding acceptance criteria.

With the exception of osmolality, volume of injections in containers, HPLC-CAD (lipid identities) and RT-PCR (identity of encoded RNA sequence), which are performed only at FP release, all other analytical procedures are conducted at release and stability studies for finished product. It is stated by the applicant that the acceptance criteria used for stability during shelf-life will be the same as the acceptance criteria used for lot release.

Several questions in relation to the acceptance criteria in the FP specifications were raised during the procedure (i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity). The acceptance criteria were tightened.

For potency, RNA integrity, RNA encapsulation, lipid content and polydispersity index, the acceptance criteria will be re-assessed during Q2 2021 in order to ensure a consistent product quality by providing additional information to enhance the control strategy. This is found acceptable subject to a specific obligation. (**SO2**)

The vial contains an overfill in order to ensure that the full required volume (5 doses) can be delivered following dilution and administration in line with the product information. The finished product specification includes a test to confirm the extractable volume from the vial provides 5 doses. During the procedure the applicant proposed to update the product information and instructions for use to indicate that up to 6 doses can be delivered from the vial. This proposed change to the product information was not considered acceptable as no supporting data were provided to demonstrate that 6 doses can be consistently extracted. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses (**REC21**).

A risk evaluation regarding the risk of N-nitrosamines impurities was provided concluding that there is no risk of the presence of nitrosamines in the finished product taking into account the active

substance, the finished product formulation and primary packaging. The risk assessment is considered acceptable.

It is recommended that a risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D **(REC17)**.

A question was raised during the procedure since no information and discussion was provided in the dossier on lipid-related impurities originating from the degradation of the LNP. It is argued by the applicant that with respect to potential lipid-related impurities originating from the degradation of LNPs, no degradation of the LNP FP has been observed in the stability studies at the recommended storage temperature (-70 to -90 °C) for the LNP as shown by specifications for size and polydispersity, RNA encapsulation, RNA and lipid content and RNA integrity quality attributes. This is acknowledged. In addition, further evaluation of lipid-related impurities in the finished product should be performed and the results submitted and discussed in the frame of a specific obligation (**SO2**).

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

The dossier includes release testing results of four recently manufactured GMP-batches. These finished product GMP batches were manufactured at the commercial FP manufacturing site. The release data for these GMP-batches are compared to min-max ranges of the small-scale clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification. Therefore, it can be concluded that comparability has been sufficiently demonstrated for the attributes tested given the pandemic situation and considering that further data is to be provided in the frame of a specific obligation. In addition, the comparison will be further extended with additional characterization testing on future PPQ-batches of finished product. The applicant has confirmed that testing will be performed according to the finished product comparability testing protocol. and the results will be provided in the frame of specific obligation **(SO3)**.

Reference materials

The finished product reference materials is the same as for active substance.

Stability of the product

A shelf-life of 6 months for the finished product is proposed when stored at the recommended storage condition of -90°C to -60°C.

The applicant has provided stability results up to 6 months at -80 to -60°C of one clinical batch and up to 6 months of a non-clinical batch of finished product. Two weeks data are also provided for two emergency supply under recommended storage conditions. In addition, there are newly initiated stability studies on the recently manufactured GMP-batches as well as plans to initiate stability studies on the future PPQ-batches.

Stability data have also been provided at accelerated (-40°C to +5°C) and stressed (+25°C to +30°C) storage conditions.

The stability studies are performed in accordance with ICH Q5C (Quality of biotechnological products: Stability testing of biotechnological/biological products) and the same or representative container-

closure system are used in these stability studies as will be used for commercial batches. The test methods used are stability indicating.

Overall, the presented stability data indicate no signs of degradation, significant trends or changes in terms of quality at the recommended storage condition (-90 to -60°C).

The applicant has provided updated reports from the ongoing stability studies and the presented data are considered sufficient and in support of the shelf-life claim since comparability has been sufficiently demonstrated between commercial scale GMP batches and the small-scale clinical batches.

In addition, the initial in-use period for the thawed, undiluted vial is 5 days at 2-8°C followed by storage at up to 30°C for not more than 2 hours. This is found acceptable.

Chemical and physical in-use stability has also been demonstrated for 6 hours at 2°C to 30°C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection.

It is described that the future PPQ-lots will be enrolled in the stability program and the stability protocol has been defined in the dossier. This is acceptable; however, the applicant should commit to provide the 6 months stability data for the PPQ-batches for assessment as soon as they are available. (**REC20**). Notwithstanding requests for further stability updates, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

It has been clarified by the applicant that results on photostability testing studies will be provided for assessment (**REC19**).

It is recommended that the applicant should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70°C to -20°C. In addition, the applicant should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8°C as well as the possibilities to extend the claims for transport conditions at 2-8°C **(REC22)**.

A shelf-life of 6 months for the finished product at -90 to -60°C is accepted.

Adventitious agents

Adventitious agents' safety evaluation has been provided for the AS manufacturing sites and for the finished product manufacturing site.

Reagents used in active substance manufacturing and in the establishment of the MCB and WCB are the only materials of animal origin used in the manufacture of BNT162b2. The applicant has identified contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents as the main theoretical risk associated with these ingredients and it is deemed of minimal risk.

Additional clarifications were requested and provided for a number of other materials.

Sufficient details on the aseptic validation filling and media fills have been provided. Furthermore, adequate testing for bioburden and endotoxin is performed at different stages of the manufacturing process. Therefore, no additional concerns are raised.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release, the comparability between clinical and commercial material and the absence of validation data on finished product manufactured at the commercial site. These issues were classified as Major Objections (MOs).

After further information was obtained from the sites and inspectors, questions regarding the manufacturing were addressed and manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing and testing sites.

Some of the proposed sites for batch control testing are currently located in the USA. The following time-limited derogation has been introduced as a condition to the MA:

'In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by the 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application'.

Additional data have been submitted by the applicant during the procedure in response to the other MOs and other questions raised.

Having considered the emergency situation and the quality documentation provided, the CHMP imposed some specific obligations (SOs) with clearly defined due dates (refer to Conclusions for details). In addition, the CHMP adopted some Recommendations (RECs) to be addressed by the Applicant.

In addition, it should be ensured that, in accordance with Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and controls (including the specifications) shall be designed to ensure product consistency and a product quality of at least shown to be safe and efficacious in clinical trials and shall introduce any subsequent changes to their manufacturing process and controls as needed.

Active substance

Overall, the information provided is satisfactory. However, certain information is still pending due to the very short time frame of product development and will either be updated in the dossier imminently or further addressed in specific obligations and other post-approval measures.

Information on the manufacturing process and process controls for the manufacturing sites Andover and BNT Mainz & Rentschler have been provided and are considered satisfactory.

Two active substance processes have been used during the development; Process 1 and 2. The major changes between AS Process 1 and 2 are: increased process scale, DNA template changed from a PCR template to linearised plasmid DNA, magnetic bead purification replaced with proteinase K digestion and UFDF steps. Based on the differences observed between batches manufactured by active substance Process 1 and 2 for the CQA mRNA integrity and lack of characterisation data, a MO was raised regarding comparability, characterisation and clinical qualification of the one proposed acceptance criteria. Biological characterisation of the active substance was limited, and additional data and discussion were requested to address functionality. Additional characterisation data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay **(SO1).**

Truncated RNA species are regarded as product-related impurities and can be expected due to the principle of the in-vitro transcription reaction (i.e. directional polymerase activity) and (theoretical) hydrolysis during manufacturing. Analysis of RNase treated samples showed that all species detected

by the capillary gel electrophoresis (CGE)-based method are composed of RNA. Manufacturing consistency with respect to fragmented species has been sufficiently demonstrated.

There were some differences in truncated RNA species level, however further analyses revealed a comparable overall fragmentation profile among Process 1 and Process 2 active substance batches. Additionally, oligonucleotide mapping data demonstrated no significant differences observed between Process 1 and Process 2 active substance batches.

The company does not expect truncated transcripts formulated in the finished product to pose a safety or efficacy concern, as in their view no protein expression is expected from truncated transcripts. Further, clinical trials with process 1 material have not revealed major safety concerns to date. Truncated BNT162b2 RNA species lacking either the 5′ cap or the poly(A) tail are expected to be rapidly targeted for degradation in the cytoplasm or would show a decrease or loss of translation efficiency. Preliminary characterization data on isolated fragment species suggest that fragment species predominantly include the 5′-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction.

However, as the overall characterisation of the truncated species is still limited, additional analysis of truncated species, additional translated protein characterisation, additional characterisation of lipid-related impurities and potential lipid-RNA species should be provided to support that they are not impacting clinical performance in terms of safety and/or efficacy. The current specification allows for a certain level of truncated mRNA species to be present however data from recent batches have shown levels of truncated species below that level. No related safety issues have been identified in the clinical studies thus far in subjects who received vaccine containing up to a certain level of truncated species. Therefore, the current specification is considered acceptable subject to the submission of additional data in the frame of a specific obligation (**SO1**).

Based on available data, the proposed specification for active substance is acceptable with respect to the attributes chosen for routine release testing. However, the length of the poly(A) tails in BNT162b2 active substance is critical for RNA stability and translational efficiency and therefore should be introduced in active substance release testing in the frame of a specific obligation (**SO2**). Moreover, the active substance specification acceptance limits should be re-assessed and revised as appropriate, as further data become available from ongoing clinical trials and in line with manufacturing process capability (**SO2**).

It is noted that the Applicant states that testing is currently in progress on the clinical batches and data for these batches, as well as any new data available for the primary process validation batches, will be provided. Based on the limited stability data presented, a shelf-life is approved for the active substance.

Finished product

The finished product is a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, intended for 5 doses. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described including studies that were performed with available active substance, representative of the mRNA platform and included in the finished product.

The development of the manufacturing process is extensively described, and critical process parameters are defined.

The manufacturing process includes lipid nanoparticle fabrication and bulk finished product formulation followed by fill and finish, and the process has been acceptably described.

Comparability between the commercial finished product and the clinical finished product has been sufficiently demonstrated for the attributes tested and will be subject to a specific obligation.

Limited data on the finished product batches manufactured at the commercial facility (entire manufacturing process at the commercial site Pfizer, Puurs, at commercial scale, active substance from process 2) were presented. A process validation plan for PPQ lots has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

Further data was requested in order to conclude on the consistency of finished product manufacturing, to assure comparability between the commercial product with the product used in clinical trials, and to support the claimed finished product shelf-life and storage conditions. A process validation plan for PPQ lots has been provided. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program, also comprising the commercial facility at Puurs, Belgium, has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data **(SO3).**

The specifications for finished product include a comprehensive panel of relevant tests along with corresponding acceptance criteria. Several issues in relation to the acceptance criteria in the finished product specifications were raised, i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity. Whilst FP specifications were subsequently amended and overall found to be acceptable, the acceptance limits should be re-assessed, and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability (**SO2**).

Two novel excipients are included in the LNP. Complete information is not provided for both the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. In order to assure comprehensive control throughout the lifecycle of the finished product and to ensure batch to batch consistency, further information needs to be submitted regarding the synthetic process and control strategy in line with specific obligations **(SO4, SO5).**

Lipid-related impurities have been observed in some recently manufactured finished product batches. For the batches with lipid-related impurities the existing quality control parameters including RNA integrity remain unchanged.

Considering the above and the emergency situation, the characterisation of the active substance and finished product is considered acceptable, and the proposed specifications for RNA Integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. These data are requested to be provided as specific obligations to the applied conditional marketing authorisation **(SO1, SO2)**.

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine from Process 1. The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities. The suitability of the analytical methods used for control of potency and poly(A) tail have not been fully demonstrated.

Data demonstrate the presence of significant amounts of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are poorly characterised, and the limited data provided for protein expression do not fully address the uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein.

The control strategy for active substance and finished product is important to guarantee acceptable quality and ensure batch to batch consistency of the finished product. Regarding the proposed control strategy, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Based on the above, the following uncertainties are considered to be of importance for the benefit-risk assessment:

- Truncated and modified RNA are present as impurities. Considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell there is a possibility that aberrant proteins will be expressed with possibilities for unwanted immunological events. The risk of this occurring is considered low based on the following observations and considerations:
    - Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
    - The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA.
    - The level of any individual aberrant mRNA species would in any way be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The amount of the protein would be expected to be too low to elicit an immune response. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the aberrant protein would be non-significant.
- Lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be sufficiently consistent and acceptable subject to the specific obligations abovementioned.

In general, physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in an acceptable way. While the characterisation data still

need to be completed, the results of tests carried out indicate consistency of product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product is expected to have a satisfactory clinical performance.

The submitted information indicate that currently manufactured product batches are of a quality that is appropriate and sufficiently comparable to that of clinical development batches. However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product a number of issues are expected to be addressed though fulfilment of specific obligations, within defined time frames.

The CHMP has identified the following specific obligations to address the identified quality development issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed below.

In addition, and in accordance with Article 16 of regulation (EC) No 726/2004, the MAH shall inform the Agency of any information which might influence the quality of the medicinal product concerned, such as any necessary tightening of the finished product specifications earlier than July 2021. This is also related to the general obligation to vary the terms of the marketing authorisation to take into account the technical and scientific progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

In the context of the conditional marketing authorisation, the applicant should fulfil the following specific obligations (SOs):

- SO1: In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data. **Due date: July 2021. Interim reports: March 2021.**
- SO2: In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications. **Due date: July 2021. Interim reports: March 2021.**
- SO3: In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data. **Due date: March 2021.**
- SO4: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. **Due date: July 2021, Interim reports: January 2021, April 2021.**
- SO5: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **Due date: July 2021, Interim reports: January 2021, April 2021.**

As regards SO1, the following data are requested in order to complete the information on the active substance and finished product characterisation.

a) Additional data is to be provided to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should further address the potential for translation into

truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterization data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated. **Due date: July 2021. Interim reports: March 2021, and on a monthly basis.**

b) The analysis of the main peak of the RNA integrity test representing the full-length RNA, should be also undertaken addressing 5'cap levels and presence of the poly (A) tail. **Due date: July 2021. Interim report: March 2021**

c) Additional data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **Due date: July 2021. Interim report: March 2021**

As regards SO2, the following data are requested to be provided in order to ensure a comprehensive control strategy, including active substance and finished product specifications:

a) The active substance and finished product specifications acceptance limits, should be re-assessed and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials. **Due date: July 2021, Interim reports March 2021, and on a monthly basis.**

b) Poly(A) tail length is considered a critical attribute, which should be controlled on each batch, even though comparable results were obtained until now. An active substance specification to control poly(A) length should be introduced. A suitable method should be developed and appropriate acceptance criteria should be set. **Due date: July 2021, Interim reports: March 2021**

c) The poly(A) tail percentage is considered a critical attribute, but uncertainties remain on the suitability of the method. Additional data should be provided to support the suitability of the method used for %poly(A) tail or an alternative suitable assay should be developed and introduced. The %poly(A) tail should be characterised following any future active substance process changes. **Due date: July 2021, Interim reports: March 2021**

d) Since mRNA integrity and polydispersity are CQAs for the efficacy of the medicinal product, the finished product acceptance criteria for these parameters should be revised as further data becomes available from ongoing clinical trials and in line with manufacturing process capability. **Due date: July 2021, Interim reports: March 2021.**

e) Additional data should be provided to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly. **Due date: July 2021, Interim reports: March 2021**

f) Lipid-related impurities should be further evaluated. An appropriate control strategy should be introduced, suitably justified and provided for assessment during Q2 2021. **Due date: July**

2021, Interim reports (LMS content in commercial FP batches, investigation results): March 2021, and on a monthly basis.

As regards SO3, the following data are requested to be provided in order to ensure batch to batch consistency and to complete the information on process validation of the finished product manufacturing process.

a) Full commercial scale finished product PPQ-batches will be manufactured at the commercial facility Pfizer Puurs, Belgium. The applicant should provide the summary report on the completed commercial scale process validation activities. **Due date: March 2021.**

b) The applicant should perform testing of future process validation-batches of finished product according to the extended comparability testing protocol and the results should be provided for assessment. **Due date: March 2021.**

As regards SO4, the data are requested to be provided regarding the synthetic process and control strategy for the excipient ALC-0315 in order to improve the impurity control strategy, assure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product.

a) A detailed description of the chemical synthesis of ALC-0315 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**

b) Differences in the manufacturing process between two suppliers should be described and possible impact on impurity profile should be discussed **by July 2021. Interim report: January 2021**

c) Information and justification of quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. **Due date: July 2021, Interim report: January 2021**

d) Information and justification on critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**

e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**

f) The specification limit for total impurities should be re-evaluated as more batch data becomes available and revised, as appropriate. **Due date: July 2021**

g) The specification limit for assay should be tightened based on the provided batch data to improve the quality control strategy of the finished product. **Due date: July 2021**

h) Detailed method validation reports for assay, impurities, and residual solvents for ALC-0315 should be provided. **Due date: July 2021**

i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

As regards SO5, the following data is requested to be provided regarding the synthetic process and control strategy for ALC-0159 in order to improve impurity control strategy, assure comprehensive control and batch-to-batch consistency throughout the lifecycle of the active product.

a) A detailed description of the chemical synthesis of ALC-0159 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**

b) Information and quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. Relevant acceptance criteria for molecular weight and polydispersity should be included in the specification for the starting material carboxy-MPEG. **Due date: July 2021, Interim report: January 2021**

c) Information and justification of critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**

d) The specification limit for assay should be tightened based on batch data in order to provide a more stringent quality control of the finished product. **Due date: July 2021, Interim report: April 2021**

e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**

f) The specification limit for total impurities should be re-evaluated as more batch data are available and revised, as appropriate. **Due date: July 2021**

g) Acceptance criteria for tetrahydrofuran should be added to the specification for ALC-0159, unless otherwise justified, as it is included as a solvent in step 2 of the synthesis. **Due date: January 2021**

h) Detailed method validation reports for assay, impurities and residual solvents for ALC-0159 should be provided. **Due date: July 2021, Interim report: April 2021**

i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

2.2.6. Recommendations for future quality development

In the context of the obligation of the Marketing Authorisation Holder (MAH) to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Active substance

1. The MAH should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials.
2. The MAH should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases.
3. The MAH should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021.
4. The MAH should reassess the specification for the linear DNA template purity and impurities. The Applicant has already agreed to supply these by Q2 2021.
5. The MAH should perform and document a gap analysis to identify any supplemental qualification needed to align the methods used for the DNA template control with ICH requirements. The gaps identified should be addressed either prior to transferring the methods to relevant sites or during the transfer activities.
6. The MAH should provide active substance process validation data regarding the finalised

indirect filter qualification assessment and the shipping validation between sites.

7. The MAH should provide the results of the studies performed to enhance the robustness of the DNase digestion step.
8. The MAH should tighten the low limits of the proven acceptable ranges for the target volumes for ATP and CTP, to the levels needed to ensure a sufficiently high mRNA integrity in the active substance manufacturing process.
9. The MAH should comprehensively describe the capability of the next generation sequencing technology platform to detect lower amounts of RNA species of alternative sequence in the presence of the correct, more abundant RNA for the active substance.
10. The MAH should discuss the results and the assay suitability for the cell-based flow cytometry and the western blot method used for biological characterization of protein expression for the active substance.
11. The MAH should provide a summary of the validation/verification status of the immunoblot analytical procedure used to detect double stranded RNA (dsRNA) in BNT162b2 active substance.
12. In order to improve the control strategy, the MAH should provide the protocol on preparation and qualification of future primary and working reference standards for the active substance.

Finished Product

13. The updated results from the finished product leachables studies should be provided for assessment.
14. In order to ensure batch to batch consistency of the finished product the MAH should expand the description of the manufacturing process with more details. (1) When the batch size is twice the original one, the range number of active substance bags and active substance batches to be thawed, and the number of mixers should be stated. (2) The MAH should confirm the configuration of filters used in finished product manufacture. (3) The surface area of the sterile filter should be adapted to the batch size, unless otherwise justified; (4) process control for RNA content prior to dilution is important, particularly if several runs of TFF are performed in parallel with batch sizes
15. Data on verification of in-process test methods should be provided for assessment during Q1 2021.
16. In order to improve the control strategy, the MAH should provide results of the validation plan phase 2 of the rapid sterility test for assessment before implementation.
17. A risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D and Ph. Eur. monograph Pharmaceutical Preparations (2619). A summary of this risk assessment should be submitted. The risk assessment should cover all relevant elements and sources in accordance with the guideline. The summary must enable a quantitative comparison of observed or predicted levels with the PDE's given in the guideline. It should contain what is necessary to evaluate the appropriateness and completeness of the risk assessment, including any assumptions, calculations etc. made. The control strategy for elemental impurities should be justified based on the risk assessment.
18. The MAH should provide the protocol on preparation and qualification of future primary and working reference materials for finished product testing.
19. In order to provide further information regarding the stability of finished product, Results from photostability testing and temperature cycling studies of the finished product should be provided for assessment in Q1 2021.
20. The applicant should provide the 6 months stability data for the finished product process performance qualification batches for assessment as soon as they are available.
21. This applicant proposed change to the product information to indicate that up to 6 doses can

be delivered from the vial was not considered acceptable as no supporting data was provided. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses.

22. The MAH should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70 °C to -20 °C. In addition, the MAH should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8 °C as well as the possibilities to extend the claims for transport conditions at 2-8 °C.
23. The MAH should provide the results for assessment from the filter validation as soon as they are available.

2.3. Non-clinical aspects

GLP inspections

The pivotal toxicological studies are stated to be GLP compliant by the Applicant. There were some issues identified during the assessment with repeat-dose toxicity study #38166 regarding the documentation which have led to a study audit GLP inspection conducted by the local German GLP Compliance Monitoring Authority at the facility where the study was performed, in November 2020. All the answers to the issues were acknowledged by the CHMP. The Applicant gave also comments on these issues. In light of all the elements provided, the issues identified were considered resolved.

With regard to repeat-dose toxicity study #20GR142 the only major concern identified was resolved with the answers from the Applicant that were considered satisfactory by the CHMP.

2.3.1. Pharmacology

The pharmacology dossier is based on initial studies of the functionality of the BNT162b2 (V9) RNA-based product and the encoded SARS-CoV-2 P2 S protein as well as on supporting studies of SARS-CoV-2 P2 S protein structure. This is followed by characterisation of the humoral and cellular immune response in mouse and nonhuman primate upon immunization with BNT162b2 (V9) and ends up with a SARS-CoV-2 challenge study of BNT162b2 (V9) immunized nonhuman primates.

No secondary pharmacodynamic, safety pharmacology or pharmacodynamic drug interaction studies have been conducted with BNT162b2 due to the nature of the RNA-based vaccine product, which is according to applicable guidelines (WHO guideline on nonclinical evaluation of vaccines, WHO Technical Report Series, No. 927, 2005).

Mechanism of action

SARS-CoV-2 infects the body by the use of the Spike protein (S) to attach to specific cell surface receptors, of which the angiotensin converting enzyme 2 (ACE2) may constitute a major part, as recently suggested. In addition to the initial attachment to a host cell, the S protein is also responsible for viral envelope fusion with the host cell membrane resulting in genome release. Due to its indispensable role, the S protein is a major target of virus neutralizing antibodies and has become a key antigen for vaccine development. By immunisation with the modified RNA (modRNA) product BNT162b2, encoding for the S protein, the intention is to trigger a strong and relatively long-lasting production of high affinity virus neutralizing antibodies, which can act through blocking the S-protein and it's receptor-binding domain (RBD) interaction with host cell receptors but also by opsonisation mediated virus clearance. In addition, the immunisation with BNT162b2 is also intended to elicit a concomitant T cell response of the Th1 type, supporting the B cells responsible for the production of S-specific antibodies and cytotoxic T cells that kill virus infected cells.

The S protein is a trimeric class I fusion protein that exists in a metastable prefusion conformation before engaging with a target cell. BNT162b2 encodes a P2 mutant (P2 S) variant of S where two consecutive proline mutations have been introduced in order to lock the RBD in the prefusion conformation. In addition, BNT162b2 is nucleoside-modified by a substitution of 1-methyl-pseudouridine for uridine and thus its inherent adjuvant activity mediated by binding to innate immune sensors such as toll-like receptors (TLRs) 7 and 8, is dampened, but not abrogated. Furthermore, the structural elements of the vector backbones of the BNT162b2 are optimised for prolonged and strong translation of the antigen-encoding RNA.

The potency of the RNA vaccine is further optimised by encapsulation of the RNA into lipid nano particles (LNPs), which protects the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (i.m.) delivery. The functional and ionizable lipid, ALC-0315, is identified as the primary driver of delivery as it allows the LNPs to have a neutral charge in a physiological environment to facilitate internalization; the endosomal environment exhibits a positive charge and therefore triggers the translocation of RNA into the cytosol (Midoux & Pichon, 2015; Hassett et al, 2019; Patel et al, 2019); ALC-0159 is included in the formulation to provide a steric barrier to: 1) facilitate the control of particle size and homogeneity during manufacturing and product storage, and 2) regulate the association of plasma and proteins with the LNP surface. The composition of the LNPs may also affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity.

Administration of LNP-formulated RNA vaccines IM results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Primary pharmacodynamic studies

Primary pharmacodynamic studies in vitro

To confirm the functionality of the BNT162b2 (V9) RNA-based product, protein expression, transfection frequency from BNT162b2 and cell surface expression of the SARS-CoV-2 P2 S protein antigen was assessed. BNT162b2 (V9) transfection of HEK293T cells indicated SARS-CoV-2 P2 S was correctly expressed on the cell surface, as indicated by flow cytometry staining of non-permeabilized cells with an anti-S1 monoclonal antibody. In addition, the cellular localisation of expressed S1 protein was investigated. The S protein co-localized with an ER marker, as detected by immunofluorescence experiments in HEK293T cells expressing BNT162b2-RNA, suggesting the S protein is processed within the ER.

In a set of supportive studies, it was investigated whether BNT162b2 RNA encodes for an amino acid sequence that authentically express the ACE2 binding site (RBD). Recombinant P2 S was expressed from DNA encoding for the same amino acid sequence as BNT162b2 RNA encodes for. Flow cytometry staining with spike protein (S) binding agents, as human ACE2 and monoclonal antibodies known to bind to authentic S-protein all indicated an authentically presented P2 S protein and ACE2 binding site. Low nanomolar affinity of P2 S binding to ACE2 PD and B38 mAb was demonstrated with the use of biolayer Interferometry.

To further structurally characterize the P2 spike protein, a cryo-electron microscopy (cryoEM) investigation of purified P2 S, expressed from DNA, was conducted. The cryoEM revealed, according to

the Applicant, a particle population closely resembling the prefusion conformation of SARS-CoV-2 spike protein. By fitting a previously published atomic model on to a processed and refined cryoEM dataset, a rebuilt model was obtained showing good agreement with reported structures of prefusion full-length wild type S and its ectodomain with P2 mutations. In the prefusion state the RBD undergo hinge-like conformational movements and can either be in an "up" position (open for receptor binding) or in a "down" position (closed for receptor binding). Three-dimensional classification of the dataset showed a class of particles that was in the conformation one RBD 'up' and two RBD 'down". This partly open conformation represented 20.4% of the trimeric molecules. The remainder were in the all RBD 'down' conformation. Although potent neutralizing epitopes have been described when the RBD is in the "heads down" closed conformation, the "heads up" receptor accessible conformation exposes a potentially greater breadth of neutralizing antibody targets. It is concluded that antibodies to both the up and down conformations will potentially be formed upon immunisation with the P2 S encoding BNT162b2.

Primary pharmacodynamic studies in vivo

The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates. The choice and relevance of the mouse for pharmacological animal model studies was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Non-human primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. The selection of rats as the toxicology test species is consistent with the World Health Organization (WHO) guidance documents on nonclinical evaluation of vaccines (WHO, 2005). The documents recommend conducting vaccine toxicity studies in a species which mounts an immune response to the vaccine. The Wistar Han (WH) rat developed an antigen-specific immune response following BNT162b2 vaccination.

Balb/c, females were immunized IM on day 0 with 0.2, 1 or 5 µg RNA/animal of BNT162b2 (V9), or with buffer alone (n=8). Blood samples were collected on Days 7, 14, 21 and 28 after immunization. The IgG antibody response to SARS-CoV-2- RBD or S1 was analysed by ELISA. Immunization with BNT162b2 induced IgGs that bound to S1 and RBD, as detected by ELISA, and on day 28 after immunization showed a binding affinity of KD 12 nM or 0.99 nM (geometric mean) respectively, as detected by surface plasmon resonance.

To further characterise the antibody response to BNT162b2 and its potential capacity to reduce SARS-CoV-2 infections, a pseudo virus type neutralization assay (pVNT) was used as a surrogate of virus neutralization since studies with authentic SARS-CoV-2 requires a BSL3 containment. The pVNT was based on a recombinant replication-deficient vesicular stomatitis virus (VSV) vector that had been pseudotyped with SARS-CoV-2 S protein according to published protocols. A dose-dependent increases in SARS-CoV-2-S VSV pseudovirus neutralizing antibodies were observed in sera from BNT162b2-immunized mice. On day 14, the difference of the group treated with 5 µg RNA compared to the buffer control was statistically significant ($p = 0.0010$). On days 21 and 28, the differences of the groups treated with 1 µg and 5 µg BNT162b2 compared to the buffer control were statistically significant. The relevance of the pseudovirus assay for authentic SARS-CoV-2 was not discussed. For technical reasons, it was not possible to determine a ratio of neutralizing to non-neutralizing antibodies.

Immunisation of mice with BNT162b2 also induced IFN-γ secreting cells of both the CD4+ and CD8+ T-cell subsets. This was shown by ELISPOT after *ex vivo* re-stimulation of splenocytes with an S-protein overlapping peptide pool Day 28 after immunization. Cytokine profiling was also carried out by Multiplex analysis of cytokine release from the Day 28 Splenocytes. High levels of the Th1 cytokines IFNγ and IL-2 but minute amounts of the Th2 cytokines IL-4, IL-5 and IL-13 were detected after re-stimulation with S but not RBD overlapping peptide mix. The much higher immune cellular responses

elicited against the S1 protein compared to the RBD domain could be explained by the presence of significantly more T cell epitopes in the larger full-length S peptide mix (in addition, S1 covers the RBD domain). It should be emphasized that cellular immune reactivity is much more important against S1 than against the RBD domain, where neutralizing antibodies are more important to the latter. In addition, an elevated secretion of TNFα, GM-CSF, IL-1β, IL-12p70 and IL-18 was recorded after re-stimulation. In order to characterize the immunophenotype of B-and T-cells appearing in lymph nodes from mice immunized with BNT162b2 (V9), B- and T-cell subsets in draining lymph node cells were quantified by flow cytometry 12 days after immunization. Higher numbers of B cells were observed in the samples from mice that received BNT162b2 compared to controls. That included plasma cells, class switched IgG1- and IgG2a-positive B cells, and germinal centre B cells. T-cell counts were elevated, particularly numbers of T follicular helper (Tfh) cells, including subsets with ICOS upregulation, which play an essential role in the formation of germinal centres (Hutloff 2015).

In the nonhuman primate (rhesus macaques) studies, BNT162b2 (V9) was shown to be immunogenic after intramuscular administration. The serum concentrations of both S1-binding and the SARS-CoV-2 neutralizing antibody titres were at least an order of magnitude higher after BNT162b2 immunization of rhesus macaques than for the panel of SARS-CoV-2 convalescent human sera. In this study, total antibody response is measured using a luminex assay and results expressed on U/ml and for the neutralization assay results are expressed in VNT 50.

Antigen specific S-reactive T-cell response after BNT162b2 immunization of the macaques was measured by ELISPOT and ICS. While S-specific T cells were low to undetectable in naïve animals, strong IFNγ but minimal IL-4 ELISpot responses were detected after the second 30 or 100 µg dose of the BNT162b2. Intra cellular staining (ICS) confirmed that BNT162b2 immunization elicited strong S-specific IFNγ producing T cell responses, including a higher frequency of CD4+ T cells that produced IFNγ, IL-2, or TNF-alpha but a lower frequency of CD4+ cells that produce IL-4. An S-specific IFNγ producing CD8+ T cell response was also recorded.

A challenge study in rhesus macaques was conducted as nonclinical proof of concept (PoC). Rhesus macaques share a 100% homology with the human ACE2 sequence that interacts with the RBD of the S protein. BNT162b2 (V9) immunized macaques were challenged with SARS-CoV-2 intra nasally and intratracheally 55 days after the second immunization with BNT162b2. Rhesus macaques were immunized on days 0 and 21, in order to align with the clinical vaccination regimen. Some other COVID-19 vaccine candidates have different prime-boost intervals, such as 4 weeks for both ChAdOx1 (Graham et al., 2020) and mRNA-1273 (Corbett et al., 2020). At the time of challenge, SARS-CoV-2 neutralising titres ranged from 260 to 1,004 in the BNT162b2 (V9)-immunized animals. Neutralising titres were undetectable in animals from the control-immunized and sentinel groups. The presence of SARS-CoV-2 RNA was monitored by nasal and oropharyngeal (OP) swabs and bronchoalveolar lavage (BAL). Viral RNA was detected in BAL fluid from 2 of the 3 control-immunized macaques on Day 3 after challenge and from 1 of 3, on Day 6. At no time point sampled was viral RNA detected in BAL fluid from the BNT162b2 (V9)-immunized and SARS-CoV-2 challenged macaques. The difference in viral RNA detection in BAL fluid between BNT162b2-immunized and control-immunized rhesus macaques after challenge is statistically significant (p=0.0014). From control-immunized macaques, viral RNA was detected in nasal swabs obtained on Days 1, 3, and 6 after SARS-CoV-2 challenge; from BNT162b2 (V9)-immunized macaques, viral RNA was detected only in nasal swabs obtained on Day 1 after challenge and not in swabs obtained on Day 3 or subsequently. The pattern of viral RNA detection from OP swabs was similar to that for nasal swabs. No signs of viral RNA detected vaccine-elicited disease enhancement were observed. The viral RNA levels between control-immunized and BNT162b2-immunized animals after challenge were compared by a non-parametric analysis (Friedman's test), and the p-values are 0.0014 for BAL fluid, 0.2622 for nasal swabs, and 0.0007 for OP swabs.

Despite the presence of viral RNA in BAL fluid from challenged control animals, none of the challenged animals, immunized or control, showed clinical signs of illness (weight change, body temperature change, blood oxygen saturation and heart rate). The Applicant concluded, the absence of clinical signs in any of the challenged animals, immunised or control, despite the presence of viral RNA in BAL fluid from challenged control animals, indicates that the 2-4 year old male rhesus monkey challenge model appears to be an infection model, but not a clinical disease model. However, a further investigation by lung radiograph and computerized tomography (CT) was conducted. Radiographic evidence of pulmonary abnormality was observed in challenged controls but not in unchallenged sentinels nor in challenged BNT162b2-immunized animals except for a CT-score signal in 1 of 6 pre infection and 2 out of six at Day 10/EOP in BNT162b immunised animals. The CT score signal was at the same level as the control at Day 10/EOP. No radiographic evidence of vaccine-elicited enhanced disease was observed.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted with BNT162b2, which is acceptable to the CHMP.

Safety pharmacology studies

No safety pharmacology studies were conducted with BNT162b2. The Applicant refers to that they are not considered necessary according to the WHO guideline (WHO, 2005). In addition, no findings on vital organ functions have been recorded in the repeat dose toxicology studies. Thus, the absence of safety pharmacology studies is endorsed by the CHMP.

Pharmacodynamic drug interactions studies

No pharmacodynamics drug interaction studies were conducted with BNT162b2. This is agreeable to the CHMP.

2.3.2. Pharmacokinetics

The applicant has determined the pharmacokinetics of the two novel LNP excipients ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) in plasma and liver as well as their elimination and metabolism in rats. Furthermore, the Applicant has studied the biodistribution of the two novel lipids (in rats) and the biodistribution of a LNP-formulated surrogate luciferase RNA in mice (IV), as well as the biodistribution of a [^{3}H]-Labelled Lipid Nanoparticle-mRNA Formulation in rats (IM).

No traditional pharmacokinetic or biodistribution studies have been performed with the vaccine candidate BNT162b2.

In study PF-07302048_06Jul20_072424, the applicant has used a qualified LC-MS/MS method to support quantitation of the two novel LNP excipients. The bioanalysis methods appear to be adequately characterized and validated for use in the GLP studies.

PK studies with the two novel LNP-excipients ALC-0315 and ALC-0159:

Wistar Han rats were IV bolus injected with LNP formulated luciferase-encoding RNA at 1 mg/kg and ALC-0315 and ALC-0159 concentrations at 15,3 mg/kg and 1,96 mg/kg respectively. ALC-0315 and ALC-0159 levels in plasma, liver, urine and faeces were analysed by LC-MS/MS at different time-points up to 2-weeks.

ALC-0315 and ALC-0159 were rapidly cleared from plasma during the first 24 hours with an initial t½ of 1.62 and 1.72 h, respectively. 24 hours post-dosing, less than 1% of the maximum plasma concentrations remained. A slower clearance rate was observed after 24 hours with ALC-0315 and ALC-0159 terminal elimination t½ of 139 and 72.7 h, respectively.

Following plasma clearance, the liver appears to be to major organ to which ALC-0315 and ALC-0159 distribute. The applicant has estimated the percent of dose distributed to the liver to be ~60% for ALC-0315 and ~20% for ALC-0159. The observed liver distribution is consistent with the observations from the biodistribution study and the repeat-dose toxicology, both using IM administration.

For ALC-0315 (aminolipid), the maximum detected concentration in the liver (294 µg/g liver) was reached 3 hours after IV injection. ALC-0315 was eliminated slowly from the liver and after 2-weeks the concentration of ALC-0315 was still ~25% of the maximum concentration indicating that ALC-0315 would be eliminated from rat liver in approximately 6-weeks. For ALC-0159 (PEG-lipid), the maximum detected concentration in the liver (15.2 µg/g liver) was reached 30 minutes following IV injection. ALC-0159, was eliminated from the liver faster than ALC-0315 and after 2-weeks the concentration of ALC-0159 was only ~0,04% of the maximum detected concentration. The applicant was asked to discuss the long half-life of ALC-0315 and its effect, discussion on the comparison with patisiran, as well as the impact on the boosts and post treatment contraception duration. The applicant considered that there were no non-clinical safety issues based on the repeat dose toxicity studies at doses (on a mg/kg basis) much greater than administered to humans; this was acceptable to the CHMP.

Both patisaran lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives. According to the applicant, it is difficult to further contextualize the pharmacokinetic data and therefore to understand the safety of these molecules, beyond consideration of dose. There is a large dose differential between the human BNT162b2 dose and the dose used in the toxicity studies (300-1000x) which provides an acceptable safety margin.

Moreover, according to the Applicant given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. Finally, the applicant is of the opinion that these results support no requirements for contraception. The CHMP found this position agreeable.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159.

Biodistribution of a LNP-formulated luciferase surrogate reporter:

To determine the biodistribution of the LNP-formulated modRNA, the applicant did study distribution of the modRNA in two different non-GLP studies, in mice and rats, determined the biodistribution of a surrogate luciferase modRNA formulated with a LNP with identical lipid composition used in BNT162b2 (mouse study) or the biodistribution of a [3H]-Labelled Lipid Nanoparticle-mRNA Formulation (rat study).

The mouse study used three female BALB-c mice per group and luciferase protein expression was determined by *in vivo* bioluminescence readouts using an *In Vivo* Imaging System (IVIS) following injection of the luciferase substrate luciferine. The readouts were performed at 6h, 24h, 48h, 72h, 6d and 9d post IM injection (intended clinical route) in the right and left hind leg with each 1 µg (total of 2µg) of LNP-formulated luciferase RNA.

In vivo luciferase expression was detected at different timepoints at the injection sites and in the liver region indicating drainage to the liver. As expected with an mRNA product, the luciferase expression was transient and decreased over time. Luciferase signals at the injection sites, most likely reflecting distribution to the lymph nodes draining the injection sites, peaked 6h post injection with signals of

approximately 10 000 times of buffer control animals. The signal decreased slowly during the first 72 hours and after 6 and 9 days the signals were further weakened to approximately levels of 18 and 7 times the signals obtained from animals injected with buffer control.

The signals from the liver region peaked 6h post injection and decreased to background levels 48h after injection. The liver expression is also supportive of the data from the rat PK study and the findings in the rat repeat-dose toxicological study showing reversible liver vacuolation and increased γGGT levels.

The biodistribution was also studied in rats using radiolabeled LNP and luciferase modRNA (study 185350). The radiolabeling data, measuring distribution to blood, plasma and selected tissues, of IM injection of a single dose of 50 µg mRNA over a 48-hour period is considered more sensitive than the bioluminescence method and indicate a broader biodistribution pattern than was observed with bioluminescence. Over 48 hours, distribution from the injection site to most tissues occurred, with the majority of tissues exhibiting low levels of radioactivity.

Radioactivity was detected in most tissues from the first time point (0.25 h) and results support that injections site and the liver are the major sites of distribution. The greatest mean concentration was found remaining in the injection site at each time point in both sexes. Low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, distribution was mainly observed to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of radiolabeled LNP+modRNA outside the injection site was greatest in the liver (up to 21.5%) and was much less in spleen (≤1.1%), adrenal glands (≤0.1%) and ovaries (≤0.1%). The mean concentrations and tissue distribution pattern were broadly similar between the sexes. No evidence of vaccine-related macroscopic or microscopic findings were found in the ovaries in the repeat-dose toxicity studies (Study 38166 and Study 20GR142) and no effects on fertility were identified in the DART study.

Immunogenicity of a LNP formulated luciferase modRNA:

Activation of the innate immune system following IM injection of a LNP-formulated luciferase reporter RNA into mice was assessed in a Luminex-based multiplex assay were serum samples (day -1 (pre), 6 h and day 9) were tested for levels of the following chemokines and cytokines: MCP-1, MIP-1β, TNF-α, IFN-α, IFN- γ, IL-2, Il-6, IL-10, IL1-β, IP-10. The applicant tested 3 different LNPs, all formulated together with luciferase RNA. The results suggest that the LNP formulation used in BNT162b2 (LNP8) slightly increased levels of MCP-1, IL-6, and IP-10 at 6h post immunisation. All chemokine/cytokine levels dropped to background levels at day 9.

In addition to innate immune activation, LNP formulated luciferase modRNA was able to induce IFN-γ T-cell responses (when challenged with MHC I-specific luciferase peptide pools) measured in splenocytes isolated from the mice at day 9.The LNP formulated luciferase modRNA did not induce the formation of luciferase-specific IgGs as measured by ELISA.

In an additional hPBMC study (R-20-0357), overall, low levels of pro-inflammatory cytokines (TNF, IL-6, IFNγ, IL-1β) and low or medium levels of chemokines (IP-10, MIP-1β, MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. IP-10, MIP-1b, MCP-1 were seen to be increased among donors, because of transfection of antigen presenting cells after infection.

Metabolism of the two novel LNP-excipients ALC-0315 and ALC-0159:

Metabolism studies were conducted to evaluate the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid). No metabolic studies were performed with the modRNA or the other two lipids of the LNP. Overall, it seems as both ALC-0159 and ALC-0315 are metabolised by hydrolytic

metabolism of the amide or ester functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

The metabolism of the novel excipients, ALC-0159 and ALC-0315, were examined *in vitro* using blood, liver S9 fractions and hepatocytes, all from mouse, rat, monkey and human. The *in vivo* metabolism was examined in rat plasma, urine, faeces, and liver from a rat pharmacokinetics study where a luciferase-encoding modRNA formulated in an LNP was used.

Metabolism of ALC-0315 appears to occur via two sequential ester hydrolysis reactions, first yielding the monoester metabolite followed by the doubly de-esterified metabolite. The monoester metabolite was observed *in vitro* in rat blood, monkey S9 fraction, and *in vivo* in rat plasma and rat liver. The doubly de-esterified metabolite was observed *in vitro* in mouse and rat blood; monkey liver S9 fraction; and *in vivo* in rat plasma, urine, faeces and liver. Subsequent metabolism of the doubly de-esterified metabolite resulted in a glucuronide metabolite which was observed in urine only from the rat pharmacokinetics study. Additionally, 6-hexyldecanoic acid, the acid product of both hydrolysis reactions of ALC-0315, was identified *in vitro* in mouse and rat blood; mouse, rat, monkey and human hepatocytes; mouse, rat and human liver S9 fractions; and *in vivo* in rat plasma.

ALC-0315 was stable over 120 min (>93% remaining) in liver microsomes and S9 fractions and over 240 min (>93% remaining) in hepatocytes in all species and test systems.

The primary route of metabolism for ALC-0159 appears to involve amide bond hydrolysis yielding *N,N*-ditetradecylamine. This metabolite was identified in mouse and rat blood as well as hepatocytes and liver S9 from mouse, rat, monkey and human.

ALC-0159 was stable over 120 min (>82% remaining) in liver microsomes and S9 fractions and over 240 min (>87% remaining) in hepatocytes in all species and test systems.

Excretion of the two novel LNP-excipients ALC-0315 and ALC-0159:

Excretion of the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) was studied in the rat PK study. No excretion studies were performed with the modRNA or the other two lipids of the LNP which is considered acceptable by the CHMP.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159. Since almost no unchanged ALC-3015 was detected in urine or faeces, metabolism may play a bigger role in the elimination of ALC-0315 than ALC-0159.

2.3.3. Toxicology

The toxicological dossier for BNT162b2 is based on a total of three pivotal toxicological experimental studies; two repeat-dose toxicity rat studies and one DART fertility-EFD rat study. The test substance in the repeat-dose toxicity studies is BNT162b2 (100 µg of variant 8 in one study (study 38166) and 30 µg of the clinically relevant variant 9 in the second study (study 20GR142)), which consists of a modified RNA in a lipid nanoparticle (LNP) formulation. The differences between the variants are due to codon optimization. The LNP contains four excipients whereof two are considered novel (ALC-0315 and ALC-0159).

Repeat dose toxicity

The two general/repeat-dose toxicity studies involved IM exposure of Han Wistar rats to BNT162b2 for a total of 17 days (three weekly administrations) followed by three weeks of recovery. Overall, the

study designs only included a single experimental group each with a variant of BNT162b2 (V8 or V9 variant), with no dose-response assessment or specific experimental groups for the LNP alone or its novel excipients. No test substance-linked mortality or clinical signs were observed (except a slight increase [<1C] in body temperature). No ophthalmological and auditory effects were found. The animal model of choice, the rat, has not been assessed in the pharmacological dossier but a limited absorption/distribution study has been conducted in pharmacokinetics dossier. Immunogenicity was assessed in the toxicology studies.

Body weight and food intake: Exposure generated a slight reduction of absolute BW statistically significant at D9 (-6.8% to -11.3%; BNT162b2 V8) alternatively a weak body weight increase reduction [BNT162b2 v9]. No changes in food intake were observed.

Gross pathology and organ weights: At 100ug BNT162b2 V8 and 30ug BNT162b2 V9, the tissue at the injection site was thickened/enlarged with oedema and erythema at the end of exposure in a reversible manner. The spleen was enlarged (reversible) with up to 60% for both vaccine variants and doses. There was also an enlargement of the draining and inguinal lymph nodes at 100ug (BNT162b2 V8). Overall, there were signs of a significant immune response which is likely linked to the test substance. There was a trend of slightly enlarged liver in females at 100ug (BNT162b2 V8) but not at 30ug (BNT162b2 V9).

Histopathology: At 100ug BNT162b2 V8, there were observations of various inflammatory signs at the injection site (e.g. fibrosis, myofiber degeneration, oedema, subcutis inflammation and epidermis hyperplasia). Also, there was inflammation of the perineural tissue of the sciatic nerve and surrounding bone in most rats at d17. The bone marrow demonstrated increased cellularity and the lymph nodes showed plasmacytosis, inflammation and increased cellularity. The spleen demonstrated increased haematopoiesis in half the animals at d17. The liver showed hepatocellular periportal vacuolation at d17 (fully reversed during recovery) which may be related to hepatic clearance of ALC0315. Histopathology assessment of 30ug BNT162b2 V9 generated similar results as 100ug BNT162b2 V8 although not on as extensive level (possibly due to a lesser dose). Minimal to moderate inflammation and oedema was observed at the injection site (usually resolved after ~3d). There was minimal to moderate increased plasma cell cellularity in the lymph nodes and germinal center cellularity plus hematopoietic cell cellularity in the spleen at d17 (reversible at end of recovery). There was minimal increase cellularity in the bone marrow. Reversible vacuolisation in the liver was also observed.

The Applicant explained that peri-portal liver vacuolization was observed in both pivotal studies but are not related to any microscopic evidence of liver/biliary injury in animals (cellular hypertrophy, inflammation) nor any clinical data from Phase 1 study. Vacuoles are considered by the Applicant to be a result of ALC-0315 accumulation in liver and not PEG.

A novel finding at 30ug was minimal extra-capsular inflammation in the joints at d17.

Moreover, increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells does not provide additional information. The CHMP found this agreeable.

Immunogenicity: Treatment of rats with 100 ug BNT162b2 V8 generated SARS-CoV-2 neutralizing titers (based on a vesicular stomatitis virus (VSV)-based pseudovirus neutralization assay) and IgG antibodies against the S1 fragment and the RBD (based on ELISA) in serum samples. Treatment of

rats with 30 ug BNT162b2 V9 generated SARS-CoV-2 neutralizing antibodies (not a pseudovirus neutralization assay).

Haematology: At 30ug BNT162b2 V9 and 100ug BNT162b2 V8, there was a moderate to strong reduction of reticulocytes (48-74%, not specified for V9) coupled to lowered red cell mass parameters (RBC, HGB, and HCT). There was a moderate to strong increase (>100%) in large unclassified cells [LUC], neutrophils, eosinophils, basophils and fibrinogen that may be related to the inflammatory/immune response. The changes were reversible. No effects on coagulation were observed for V8 whereas a slight increase in fibrinogen was observed with V8 and V9.

Clinical pathology: A very strong but reversible increase (>100%) in pro-inflammatory acute phase proteins in the blood (A1AGP, A2M) was seen with both 30ug BNT162b2 V9 and 100ug BNT162b2 V8. Also, indicative of pro-inflammation, a slight to moderate reduced albumin/globulin ratio was seen for both variants. V8 (100ug) exposure generated increased levels of γGT (>200%) and increased γGT enzyme activity and increased AST levels (+ ~19%). V9 (30ug) exposure led to slight to moderate increases in AST and ALP levels (+20-100%), possible indicative of liver effects but no changes in γGT levels. There were no changes in cytokine levels (IFNγ, TNFalpha, Il-1b, Il6, Il-10) after 100ug V8 exposure (not measured for V9). For 100ug V8, there were no changes measured in urine whereas there was a slight-moderate reduction in pH for 30ug V9.

Genotoxicity

No genotoxicity studies have been provided. This is acceptable as the components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

Reproduction Toxicity

In the DART study, the test substances used were BNT162b1, BNT162b2 and BNT162b3, which were given to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day). The test substances were administered intramuscularly (IM) to F0 female Wistar rats 21 and 14 days before the start of mating (M-21 and M-14, respectively) and then on Gestation Day (GD) 9 and GD20, for a total of 4 doses. A subgroup was terminated at GD21 and another (litter) group was terminated at PND21. SARS-CoV-2 neutralizing antibody titers were found in the majority of females just prior to mating (M-14), in most females and foetuses at the end of gestation (GD21), and in most offspring at the end of lactation (PND21). There was transient reduced body weight gain and food consumption after each dose. No effects on the estrous cycle or fertility index were observed. There was an increase (~2x) of pre-implantation loss (9.77%, compared to control 4.09%) although this was within historical control data range (5.1%-11.5%). Among foetuses (from a total of n=21 dams/litters), there was a very low incidence of gastroschisis, mouth/jaw malformations, right sided aortic arch, and cervical vertebrae abnormalities, although these findings were within historical control data. Regarding skeletal findings, the exposed group had comparable to control group levels of presacral vertebral arches supernumerary lumbar ribs, supernumerary lumbar short ribs, caudal vertebrae number < 5). There were no signs of adverse effects on the postnatal

pups (terminated at PND21). It is noted that there is currently no available data on the placental transfer of BNT162b2. This information is reflected in section 5.3 of the SmPC.

Local Tolerance

No dedicated local tolerance studies have been conducted; however the assessment of local tolerance was performed in repeat-dose toxicity studies. At 100ug BNT162b2 V8, there was mostly slight to moderate oedemas but in some cases severe oedema. The severity increased with the 2nd and 3rd injections. The data for 30ug BNT162b2 V9 exposure indicated less severe but similar effects.

2.3.4. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100 Corr 2), due to their nature vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this Application for Marketing Authorisation, which is considered acceptable.

2.3.5. Discussion on non-clinical aspects

Pharmacology

The proposed medicinal product is composed of a modRNA formulated with functional and structural lipids forming lipid nano particles (LNPs), the latter having the purpose to protect the modRNA from degradation and enable transfection of the modRNA into host cells after IM injection. The composition of the LNPs is likely to affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity (see also toxicology below).

The general immune activating mode of action of LNP-formulated RNA vaccines have been described in the literature. The administration of LNP-formulated RNA results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Whether other cells than professional APCs may transiently express the vaccine derived spike protein and therefore from a theoretical point of view, as compared to SARS-CoV-2 infected cells, also could potentially be targets for previously primed spike protein reactive cytotoxic T cells, if present, is not known. However, no overt signs of such adverse pharmacological responses have been recorded in the repeat dose toxicity study or in the clinical trials. In the clinical trial, a second dose was administered to patients who had been immunologically primed by the first dose. Moreover, in the clinical trials it appeared around 270 patients that was shown to have been seropositive for SARS-COV-2 before vaccination. In these cases, the expression of the spike protein on host cells occurred in the presence of a primed immune response to the spike protein but no overt adverse pharmacological response has been observed. The low amount of vaccine product in a single dose may limit the distribution of modRNA/LNP mainly to the injection site and to migrating APCs. Due to the transient expression of the modRNA, no persistent expression is expected.

Regarding the structural and biophysical characterization of the modRNA, a schematic description shows that 5 different sequences are included in the BNT162b2, of which two being coding sequences.

Concerning the protein expression obtained from the V8 and V9 variants, specific immune responses (total IgG binding Ab + neutralizing Ab) were obtained at significant levels against the Spike S protein in animals with both variants (in mice and rats), indicating the efficiency of the *in vivo* expression of Spike S protein. An additional study was provided (R-20-0360) further demonstrating *in vitro* protein expression. Transfection efficiency, expression rate and cellular viability were analysed in HEK293T cells, upon transfection with different constructs (saRNA, uRNA, modRNA V8 and V9). HEK293T cells were efficiently transfected by both modRNA V8 and modRNA V9 with higher transfection rate for V9, but quite similar the expression rate by V8 and V9.

Although some of the structural and biophysical characterization of P2 S as a vaccine antigen has been provided, it was investigated in supportive studies based on P2S expressed from DNA and not the product modRNA. While it is not considered to be of critical importance for the assessment in this procedure, it still provides a scientific understanding supporting the nonclinical key studies of humoral and cellular immune response, including SARS-CoV-2 neutralizing antibodies, as well as SARS-CoV-2 challenge nonclinical PoC.

In-vivo pharmacodynamics: The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates and was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Nonhuman primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. This is accepted but a more in-depth discussion on the suitability of these pharmacological animal models have not been provided (e.g. susceptibility for SARS-CoV-2 infection and similarity to COVID 19 disease; potential bias for Th1- or Th2-skewed responses has been well characterized for certain mice strains). Only single immunisation was conducted in mice, as compared to the clinical 2-dose regimen, which was adequate since only characterization of the immune response, but no challenge study was carried out in mice. Also, no or limited attention to the induction of long-term memory responses nor immunogenicity and protection in aged animals has been paid. That being said, the induction of virus neutralizing antibodies in both mice (VSV-SARS-CoV-2 S) and primates (SARS-CoV-2) indicated that BNT162b2 immunization has the potential to induce neutralizing antibodies also in humans. Thus, vaccination with modRNA is expected to induce robust neutralising antibodies and a concomitant T cell response to achieve protective immunity.

In mice, the immune response was assessed by single immunization only. Taking the phenotyping of B and T cells in aggregate, the data indicates a concurrent induction of SARS-CoV-2 S-specific neutralizing antibody titers and a Th1-driven T-cell response by immunization with BNT162b2 (this was also seen in nonhuman primates).

Concerning the nonhuman primate (rhesus macaques) studies, the applicant considers the human convalescent serum panel as an assessable benchmark to judge the quality of the immune response to the vaccine; this is accepted by the CHMP.

Concerning the characterization of the T cell responses, the Applicant suggests the S-specific IFNγ producing T cell responses, including a high frequency of CD4+ T cells that produced IFNγ, IL-2, or TNF-α but a low frequency of CD4+ cells that produce IL-4, indicates a Th1-biased response occurred after the BNT162b2 (V9) immunization. This reasoning appears acceptable to the CHMP. The role of such a Th1 biased response was put in the context of antigen-specific T-cell responses playing an important role in generation of antigen-specific antibody response as well as in elimination of infected cells to mediate protection against disease.

When immunised macaques were challenged with SARS-CoV-2, a clear and statistically significant effect was observed on reduced presence of viral RNA in bronchoalveolar lavage (BAL) and oropharyngeal (OP) swabs. A clear effect was also recorded by blinded X ray scoring of the lungs. A

protective effect is also evident in the CT score Day 3 after challenge, however at Day 10/EOP, there was a CT signal in 2 out of six BNT162b immunized monkeys at the same level as observed in the control group. That signal is of unclear significance since also in 1 out of 6 pre infection BNT162b immunized animals a similar CT-score signal was observed. During this time period the SARS-CoV-2 neutralizing GMT in the BNT162b2-immunised rhesus macaques continued to decrease but remained above the GMT of a human convalescent serum panel.

In conclusion of the preclinical pharmacology, the presented data, including immunogenicity, triggering of neutralizing antibodies and Th1 response and reduced presence of viral RNA in challenged animals as well as radiological lung parameters, provide support for the vaccination approach. Due to species differences in the immune system between animal model species and humans, the conclusion whether this candidate vaccine will be sufficiently effective in humans needs to be established in clinical studies.

Pharmacokinetic

Pharmacokinetic (regarding the two novel LNP excipients): The two novel lipid excipients play different roles in the formulation and have different pharmacokinetics. It is worth to notice that the lipid displaying a persistent kinetic over time in liver is ALC-0315.

ALC-0159 is comprised of a polyethylene glycol (PEG) headgroup (~2000 M.Wt.) attached to hydrophobic carbon chains (ie, the lipid anchor). ALC-0159 is present in BNT162 at a low mol% (<2 mol%), and therefore dose, relative to the other lipids. PEGylated lipid can exchange out of the LNP after administration, thus allowing the desired binding of endogenous proteins (eg, Apolipoprotein E) and removing the steric barrier that would otherwise restrict interactions of the LNP with target cells and proteins.

ALC-0315 is an ionizable aminolipid in BNT162b2 and is the most important lipid component for efficient self-assembly and encapsulation of the mRNA within the LNP, and for providing successful delivery of mRNA into target cells.

The PEG-lipid (ALC-0159) is designed to largely exchange out of the LNP after administration and before uptake into target cells, whereas the aminolipid (ALC-0315) is critical to the efficient intracellular delivery of the mRNA through endosomal uptake and release and must remain with the LNP.

ALC-0159 is much more hydrophilic, in large part due to the presence of the PEG molecule which is known to be a strongly hydrophilic molecule (Ma et al, 1990). Due to the more hydrophilic and essential neutral nature of this molecule, ALC-0159 has a much lower affinity for tissues and relative to ALC-0315 there will be freer compound available for redistribution from tissue to plasma; thus, elimination will be more rapid.

The Applicant pointed out that during the course of the 2-week pharmacokinetic study, liver concentrations of ALC-0315 fell 4-fold from their maximum value indicating that 75% of the material delivered to the liver was eliminated over this two-week period.

ALC-0315 has no known biology. In the absence of this 'biological relevance' the applicant used an estimation of >95% elimination of ALC-0315 to represent the essential elimination from the body. The elimination half-life of ALC-0315 in the liver following IV administration in the rat is approximately 6-8 days. These data indicate that 95% elimination of ALC-0315 will occur approx. 30-40 days following final administration in the rat.

Based on the understanding of the process involved in the terminal half-life, redistribution from tissues into which the lipid nanoparticle is delivered, a similar half-life and time to 95% elimination in human is expected (Mahmood et al, 2010). Examination of the scaling of the comparable lipids (PEG2000-C-DMG, DLin-MC3-DMA) in patisiran indicates that the half-life of these lipids appears to scale with a value approaching the typically used exponent for half-life (0.25). If this is the case for ALC-0315 we may

expect a half-life approximating 20-30 days in human for ALC-0315 and 4-5 months for 95% elimination of the lipid (Mahmood et al, 2010).

Both lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives.

Given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. This is noted by the CHMP.

Biodistribution: Several literature reports indicate that LNP-formulated RNAs can distribute rather non-specifically to several organs such as spleen, heart, kidney, lung and brain.

In line with this, results from the newly transmitted study 185350, indicate a broader biodistribution pattern with low and measurable radioactivity in the ovaries and testes. Given the current absence of toxicity in the DART data, the absence of toxicological findings in gonads in the repeat-dose studies and that the radioactivity in the gonads were low (below 0,1% of total dose), the current data does not indicate it to be a safety concern. The relative high dose used in the rats (500x margin to human dose based on weight) also supports a low risk from distribution to the gonads in humans.

RNA stability and kinetics are not expected to be the same for all RNAs and are influenced by the nucleosides of the RNA and although expression of the full-length spike (S) protein is expected to follow similar kinetics of that of the luciferase with a transient expression fading over time, it cannot be excluded that differences in stability/persistence of the signal could differ between the luciferase protein and the spike (S) protein.

In an additional hPBMC study (R-20-0357), low levels of pro-inflammatory cytokines (TNF, IL-6, IFNγ, IL-1β) and low or medium levels of chemokines (IP-10, MIP-1β, MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. The Applicant underlines that no specific general trend in cytokine secretion can be observed, given variability among donors and based on the low numbers of donors in the experiment.

Toxicology

Although no extensive pharmacological assessment has been conducted in rat (only in mouse and non-human primate), the rat was used as a toxicological animal model in the repeat-dose toxicity studies. The positive neutralization assay results in the repeat-dose toxicity studies demonstrate that V8 and V9 generate an immune response in this species (i.e. SARS-CoV-2 antibodies), partially supporting the use of the rat as an animal model. Other SARS-CoV-2 immune responses in rat remain unclear. The immune responses, especially at the injection sites (e.g. oedema, erythema), seem to increase with each injection in the studies (n=3). There was a marked increase in acute phase proteins, fibrinogen and reduced albumin-globulin ratio (but no increase in cytokines with V8, unclear for V9). There was also a general increase in immune cells (LUC, neutrophils, eosinophils, basophils) and a decrease in red blood cell parameters (reticulocytes, RGB, HGB, HCT). The spleen was enlarged at both 30ug V9 and 100ug V9 and the draining and inguinal lymph nodes were enlarged mostly at 100ug (V8) but also in a few animals at 30ug (V9).

Systemic complement activation (which sometimes may be induced by liposomal drugs and biologicals and potentially result in hypersensitivity reactions) was not investigated as no signs indicative of such clinical manifestations were detected. An absence of dose-response designs in the studies increases the difficulty to interpret the effects. Overall, the V8 and V9 test substances invoked a strong but mostly reversible immune-linked response in rats after 17d exposure. Increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the

inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The Applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells would not provide additional information. The CHMP agreed with this position.

With regards to the vaccine components, only the whole formulation (modified RNA in LNPs) were used, so there is no toxicological data on the LNP alone or its specific novel excipients. The novel LNP components, these are not considered primarily as adjuvant substances.

No genotoxicity nor carcinogenicity studies have been provided. The components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

As the pharmacokinetic distribution studies in rat demonstrated that a relatively large proportion - second to the levels at the injection site - of the total dose distributes to the liver (up to 18%, and far more than levels seen in spleen [<1.1%], adrenal glands [<0.1%] and ovaries [<0.1%]). While there was no severe pathogenesis in liver, there were some reversible functional hepatic and/or biliary effects with V8 and V9 (enlarged liver, vacuolation, strongly increased γGT levels at >200% and activity, minor-moderate increase in levels of AST and ALP) which may be linked to the LNP. The γGT changes were not observed with 30ug V9, which may be due to variant differences and/or, more likely, a lower dose. The applicant is of the view that the vacuoles are a result of primarily ALC-0315 accumulation in liver. It can be noted that ALC-0159 needs to be lost from the surface of the LNP to facilitate efficient uptake into target cells. At the same time, ALC-0315 is present in the LNP at a high mol% (50 mol%) relative to the other lipids in the BNT162 vaccine, suggesting that this lipid is more likely to be present within the cells (and possibly in the vacuoles).

The assessment of the data available as regards to the DART study shows that there is no clear adverse signs on fertility and early embryogenesis effects. There were no effects on the oestrous cycle in dams but there was an ~2x increase in pre-implantation loss (~9.77% vs 4.1% in controls) but these effects are within historical control data (5.1% to 11.5%) so these findings do not raise any specific concern. It can be noted that the choice of rat as an DART animal model is supported by means of the repeat-dose toxicity rat studies which demonstrates an immune response to the vaccine candidates [V8 and V9] and the publication of Bowman et al (2013; PUBMED ID [PMID] 24391099) that reports that foetal-maternal IgG ratios are relatively low during organogenesis but that these ratios approach 1 by the end of gestation in both rat and human.

2.3.6. Conclusion on the non-clinical aspects

The applicant sufficiently addressed other concerns raised to be granted MA from a non-clinical perspective.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

Some rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher exposure in rats due to body weight differences) developed some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) which is consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible. These findings are described in SmPC section 5.3.

As per guidance, no genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential. This is acceptable to the CHMP.

Finally, the combined fertility and developmental toxicity study showed that SARS-CoV-2 neutralising antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, gestation, or embryo-foetal or offspring development up to weaning. The CHMP noted that no data are available on vaccine placental transfer or excretion in milk.

2.4. Clinical aspects

2.4.1. Introduction

Pfizer and BioNTech have developed a vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a FIH study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study.

Phase 1/2 Study BNT162-01

Study BNT162-01 is the ongoing, FIH, Phase 1 dose level-finding study, in which healthy adults 18 to 55 years of age all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. The protocol was later amended to allow inclusion of older adult participants up to 85 years of age. The available Phase 1 safety and immunogenicity data for adults 18 to 55 years of age are reported in this application. Multiple vaccine candidates are being evaluated in this study. For each vaccine candidate, participants received escalating dose levels (N=12 per dose level) with progression to subsequent dose levels based on recommendation from a Sponsor Safety Review Committee (SRC).

Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 pivotal study for registration. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study planning to enrol ~44,000 participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. In Phase 1, two age groups were studied separately, younger participants (18 to 55 years of age) and older participants (65 to 85 years of age). The study population includes male and female participants deemed healthy as determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with high risk of exposure to SARS-CoV-2 infection due to exposure in the workplace and/or medical conditions that represent risk factors, clinically important prior illness or laboratory abnormalities, serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by polymerase chain reaction (PCR).

GCP

The Applicant claimed that the Clinical trials included in the application were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In addition, to seek further reassurance of the GCP compliance of the studies included in this dossier, in the context of the COVID-19 pandemic, EMA gathered additional information as indicated below from EU and non-EU regulatory authorities, and shared them with the CHMP to be considered in the assessment:

- a full inspection report from GCP inspection by Regierungspräsidium Karlsruhe and Paul-Ehrlich-Institut conducted at one of the investigator sites and at a CRO in Germany for the study BNT 162-01;
- Establishment Inspection Reports from GCP inspection by Food and Drug Administrations (USA Regulatory Authority) of six investigator sites in USA for study C4591001 (BNT 162-02);
- A full inspection Report and the summaries of the outcome from two GCP inspections by the National Administration of Drugs, Foods and Medical Devices (Argentinian Regulatory Authority) conducted at the single site located in Argentina for the study C4591001(BNT 162-02).

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

- Tabular overview of clinical studies

Table 1 Overview of the Clinical Development

Sponsor	Study Number (Status)	Phase Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech	BNT162-01 (ongoing)	Phase 1/2 randomized, open-label, dose-escalation, first-in-human	BNT162b2 (1, 3, 10, 20, 30 µg)	Phase 1: 60	Adults (18-55 years of age)
BioNTech (Pfizer)	C4591001 (ongoing)	Phase 1/2/3 randomized, observer-blind, placebo-control	Phase 1: BNT162b2 (10, 20, 30 µg) Placebo	Phase 1: 90 randomized 4:1 (within each dose/age group)	Phase 1: Adults (18-55 years of age, 65-85 years of age)
			Phase 2: BNT162b2 (30 µg) Placebo	Phase 2: 360 randomized 1:1	Phase 2: Adults (18-55 years of age, 65-85 years of age)
			Phase 3: BNT162b2 (30 µg) Placebo	Phase 3: ~44,000 randomized 1:1 (includes 360 in Phase 2)	Phase 3: Adolescents, Adults (12-15 years of age, 16-55 years of age, >55 years of age)

Note: study information relevant to the scope of data presented in this application are summarized in this table.

Table 2 Overview of the pivotal phase 3 study

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Diagnosis Incl. criteria	Primary Endpoint
C4591001	131 United States 9 Turkey 6 Germany 4 South Africa 2 Brazil 1 Argentina.	randomized, multinational, placebo-controlled, observer-blind,	2 doses of 30 µg given 21 days apart	Primary: To evaluate the efficacy of BNT162b2 against confirmed severe COVID-19 occurring from 7 and 14 days after the 2nd dose in participants with and without evidence of infection before vaccination	Healthy volunteers at risk of COVID-19	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection

2.4.2. Pharmacokinetics

Not applicable.

2.4.3. Pharmacodynamics

Mechanism of action

The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Immunogenicity studies

For vaccines, pharmacodynamics relates to investigation of immunogenicity. The available data were generated from the phase 1/2 study BNT162-01 conducted in Germany, and from the phase 1 and 2 parts of the phase 1/2/3 study C4591001, conducted in the USA (later phases were multinational). Both studies were designed to choose the optimal vaccine candidate and an appropriate dose and schedule for further studies. Among the four prophylactic SARS-CoV-2 RNA vaccines initially tested the following two candidates were selected for further development:

BNT162b1: RNA-lipid nanoparticle (LNP) vaccine containing nucleoside-modified messenger ribonucleic acid (modRNA) that encodes the RBD (receptor-binding domain)

BNT162b2: RNA-LNP vaccine containing modRNA that encodes SARS-CoV-2 full-length, P2 mutant (see section 2.2.2), prefusion spike glycoprotein (P2 S).

Key features of the two studies are summarised in the below table.

Study Id	BNT162-01	C4591001
Title	A multi-site, Phase 1/2, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using	A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine

	different dosing regimens in healthy adults	Candidates Against COVID-19 in Healthy Individuals
Design	This is an open-label, multi-site, Phase 1/2, 2-part, dose-escalation study. Part A of the study includes the first in human dose and dose ranging groups in healthy adults (aged 18 to 85yrs).	This is a Phase 1/2/3, randomized, multinational, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in healthy individuals. The study consists of 2 parts: Phase 1 to identify preferred vaccine candidate(s) and dose level(s); and Phase 2/3 as an expanded cohort and efficacy part.
Immunogenicity objectives	To describe the immune response in healthy adults after dose 1 only or after both dose 1 and dose 2 measured by a functional antibody titre	To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses
Study population	Healthy adults aged 18 to 55yrs BNT162b1: N=84 (12/group) BNT162b2: N=60 (12/group) Healthy adults aged 56-85 yrs BNT162b1: N=36 (12/group) BNT162b2: N=36 (12/group)	Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive Phase 1 comprised 15 participants (randomization ratio of 4:1 so that 12 received active vaccine and 3 received placebo) per group; 13 vaccine groups were studied, corresponding to a total of 195 participants (the 100 µg dose was only used in the younger adult cohort)
IMP and dose level	BNT162b1: 1µg, 3µg, 10µg, 20µg, 30µg, 50µg, and 60µg. BNT162b2: 1µg, 3µg, 10µg, 20µg, 30µg	BNT162b1: 10 µg, 20 µg, 30µg, 100 µg BNT162b2: 10µg, 20µg, 30µg Placebo: normal saline
Dosing frequency	Two injections ~21d apart	Two injections ~21d apart
Immunogenicity endpoints	Virus neutralization test (VNT). Antibody binding assay, CMI assays, e.g. ELISpot and intracellular cytokine staining (ICS).	SARS-CoV-2 neutralization assay S1-binding IgG level assay RBD-binding IgG level assay N- binding antibody assay

Endpoints and Assays used to evaluate immunogenicity

In Study BNT162-01, immunogenicity was evaluated in Phase 1 using a SARS-CoV-2 serum neutralization assay to determine neutralizing titres and the fold rise in SARS-CoV-2 serum neutralizing titres. Immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1 (Day 8); and at Day 22 (before Dose 2) and 7 days, 14 days, and 21 days after Dose 2. Only qualified assays were used. In addition, T cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from

whole blood samples of vaccinated Phase 1 participants were evaluated by enzyme-linked immunospot (ELISPOT) and intracellular cytokine staining visualized with fluorescence activated cell sorting (FACS). Blood samples were collected from study participants prior to the first vaccine dose and on Day 29 (7 days) after the second vaccine dose. Assessments included cytokines associated with Th1 responses such as IFNγ and IL-2 and those associated with Th2 responses such as IL-4, to analyse the induction of balanced versus Th1-dominant or Th2-dominant immune responses.

In Study C4591001, immunogenicity was evaluated in Phase 1 and Phase 2 using a SARS-CoV-2 serum neutralization assay to determine titres and a SARS-CoV-2 RBD- or S1-binding IgG direct Luminex immunoassay to determine antibody binding levels. Fold rises were assessed also. Only qualified assays were used. In Phase 1, immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1; and at Day 21 (before Dose 2) and 7 days, 14 days, and 1 month after Dose 2. Data were summarized for each dose level and age group. In Phase 2, immunogenicity was assessed at Day 1 (before Dose 1) and 1 month after Dose 2. Data were summarized for each age strata group and by evidence of prior SARS-CoV-2 infection at baseline per NAAT (PCR) or N-binding IgG assay. To facilitate interpretation of immunogenicity data generated in Study C4591001, a human convalescent serum (HCS) panel was obtained from Sanguine Biosciences (Sherman Oaks, CA), MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY). The 38 sera in the panel were collected from SARS-CoV-2 infected or COVID-19 diagnosed individuals 18 to 83 years of age ≥14 days after PCR-confirmed diagnosis at a time when they were asymptomatic. The serum donors had predominantly had symptomatic infections (35 of 38) including 1 who had been hospitalized. In Phase 3, exploratory immunogenicity assessments are planned at time points up to 24 months, to be reported at a later time.

These are the immunogenicity assays that were used in clinical trials:

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 S1-binding IgG in Human Serum

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 RBD-binding IgG in Human Serum

Roche Elecsys SARS-CoV-2 N Binding Antibody Assay

mNeonGreen SARS-CoV-2 Microneutralization Assay

ELISpot Assay

Intracellular Cytokine Staining (ICS) for BNT162b1 and BNT162b2

The SARS-CoV-2 Wuhan-Hu-1 isolate spike glycoprotein (GenBank accession # QHD43416.1) is the reference sequence for the recombinant S1 and RBD proteins used in the Luminex assays. The SARS-CoV-2 neutralisation assay used a previously described strain of SARS-CoV-2 (USA_WA1/2020).

Study BNT162-01

Immunogenicity - functional antibody responses (secondary objectives)

Functional antibody titre data are available up until Day 43 for younger adults (18 to 55 yrs) dosed with 1, 10, 30, 50, and 60 µg BNT162b1 on Days 1 (all dose levels) and 22 (all dose levels except 60 µg) (n=12 per group). Data are available for the 10 and 30 µg up until Day 50 for younger adults dosed with 1, 10, 20, and 30 µg BNT162b2 on Days 1 and 22 (dose level 1 µg, n=9; dose levels 10, 20, and 30 µg, n=12).

Virus neutralizing antibody GMTs for participants aged 18 to 55 years after dosing with BNT162b1, are shown in Figure 3. On Day 22, at 21 d after the first dose, virus neutralizing antibody GMTs had increased in a dose-dependent manner for all dose groups. At 7 d after the second dose (Day 29), neutralizing GMTs showed a strong, dose level dependent booster response. In the 60 µg dose group,

which was only dosed once, neutralizing GMTs remained at a lower level, indicating that a booster dose is necessary to increase functional antibody titres.

On Day 43 (21 d after the second dose of BNT162b1), neutralizing GMTs decreased (with exception of the 1 µg dose level). Day 43 virus neutralizing GMTs were 0.7-fold (1 µg) to 3.6-fold (50 µg) those of a COVID-19 HCS panel.

The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs at least 14 d after confirmed diagnosis and at a time when the individuals were asymptomatic.

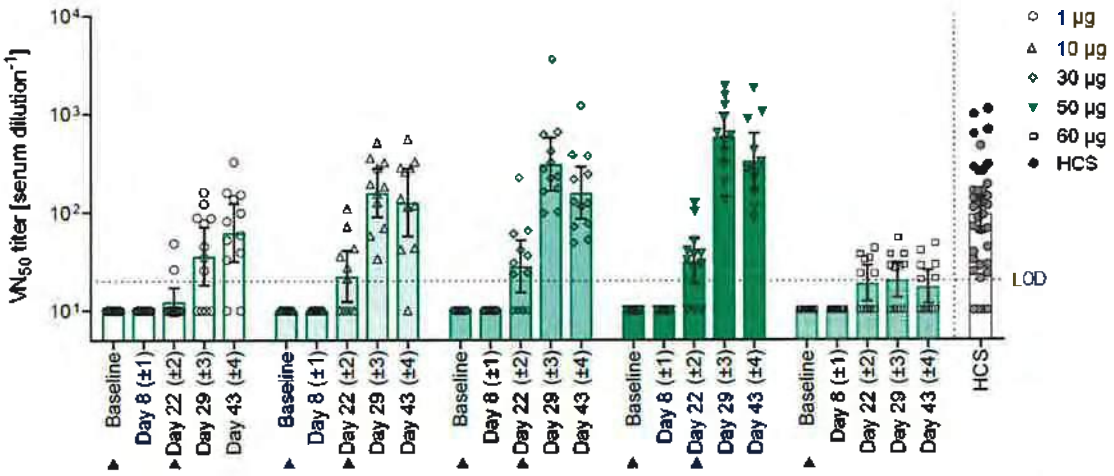


Figure 3: BNT162b1 – Functional 50% SARS-CoV-2 neutralizing antibody titers (VN50) – IMM

VN_{50} titers with 95% confidence intervals are shown for younger participants (aged 18 to 55 years) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the LOD. IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum

For virus neutralizing antibody GMTs for participants aged 18 to 55 yrs after dosing with BNT162b2, see Figure 4. Participants dosed with BNT162b2 showed a strong IMP-induced antibody response. Virus neutralizing GMTs were detected at 21 d after Dose 1 (Day 22) and had increased substantially in younger participants (aged 18 to 55 yrs) immunized with ≥3 µg BNT162b2, and older participants (aged 56 to 85 yrs) immunized with 20 µg BNT162b2 by 7 d after Dose 2 (Day 29). Day 29 virus neutralizing GMTs were comparable between the younger and older adult in the 20 µg dose level cohorts. The lowest tested dose of 1 µg BNT162b2 elicited only a minimal neutralizing response in participants aged 18 to 55 yrs.

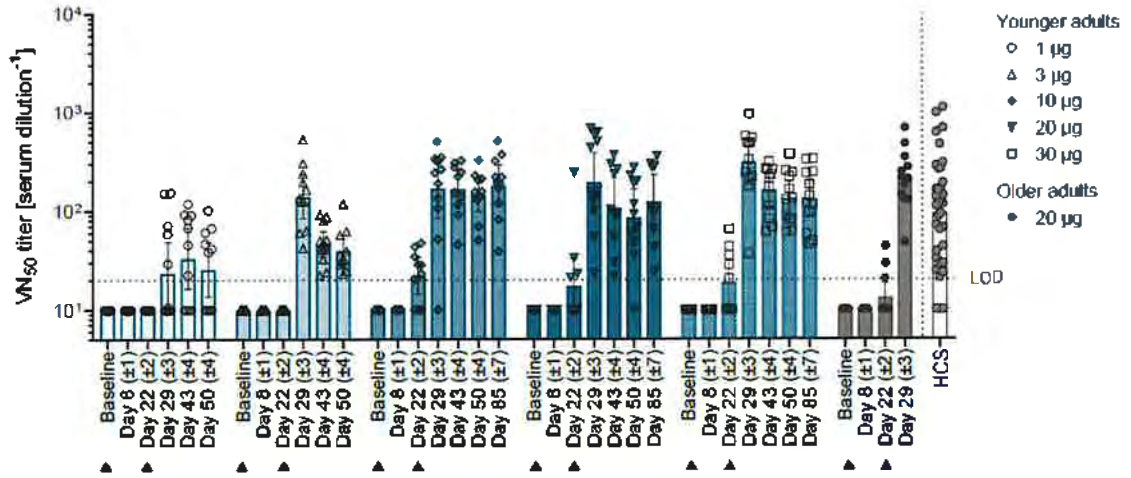
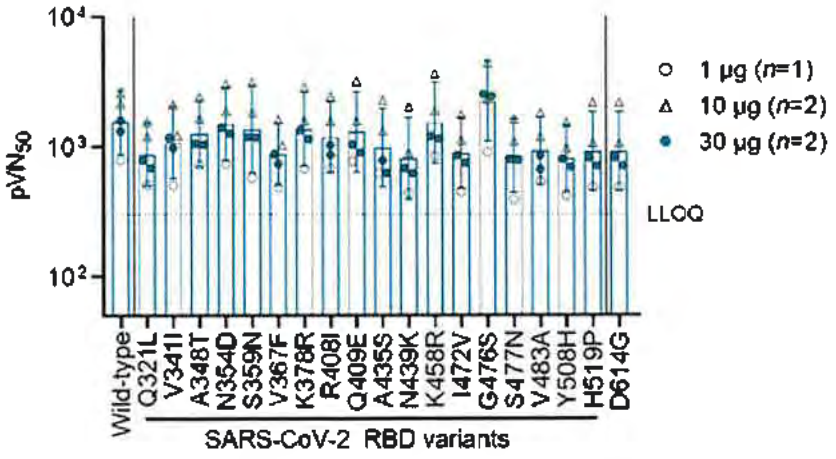


Figure 4: BNT162b2 – Functional 50% SARS-CoV-2 neutralizing antibody titres (VN50) – IMM
VN50 titres with 95% confidence intervals are shown for younger adults (aged 18 to 55 years) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and older adults (aged 56 to 85 yrs) immunized with 20 µg BNT162b2. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the LOD.
IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum.

Neutralisation of different spike protein mutants

Different pseudoviruses including RBD sequence variants have been tested in a pseudovirus neutralization assay with sera from BNT162b1-and BNT162b2-immunized participants in the BNT162-01 study. Efficient neutralization of spike protein mutants was observed with sera from BNT162b1- and BNT162b2-immunized participants demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies.



BNT162b2-induced virus neutralization titers with pseudovirus 50% neutralization titers (pVNT50) across a pseudovirus panel with 19 SARS-CoV-2 spike protein variants including 18 RBD mutants and the dominant spike protein variant D614G. LLOQ = Lower level of quantification (at 300). Data shown as group (total n=5) GMT with 95% CI.

Cell mediated immunity (CMI)

CMI were measured in terms of IFNγ- producing CD4+ and CD8+ T cells by ELISpot. Both vaccine candidates elicited clear responses (baseline vs post-dose 2). Further characterisation was determined using intracellular cytokine staining for Th1 cytokines (IFNγ, IL-2) and Th2 cytokines (IL-4). Both vaccine candidates stimulated predominantly Th1 responses, both in CD4 and CD8 T cells.

Study C4591001

Methods

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations. Phase 1 and Phase 2 data were reported as the following, for SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-binding and RBD-binding IgG concentrations:

- geometric mean titers/concentrations (GMTs/GMCs)
- geometric mean-fold rise (GMFR)
- geometric mean ratio (GMR) (for Phase 1 only)
- proportions of participants with ≥4-fold rise (for Phase 1 only)
- antibody titers/levels at defined thresholds (for Phase 2 only)

For immunogenicity results of SARS-CoV-2 serum neutralizing titers and S1- or RBD-binding IgG concentrations, GMTs or GMCs were computed with associated 95% CIs.

The GMFR was calculated by exponentiating the mean of the difference of logarithm transformed assay results: (later time point) – (earlier time point) with two-sided CIs. The GMR was calculated as the mean of the difference of logarithm transformed assay results: (SARS-CoV-2 serum neutralizing titers) – (SARS-CoV-2 anti-S binding antibody) for each participant, then exponentiating the mean, with two-sided CIs.

Results

The study set out to evaluate 2 SARS-CoV-2 RNA vaccine candidates, as a 2-dose (separated by 21 days) schedule, at different dose levels (BNT162b1: 10, 20, 30, and 100 µg, BNT162b2: 10, 20, and 30 µg) and in different age groups (18 55 y; 65-85 y), to select a vaccine and dose level for further testing in Phase 2/3. Cut-off date: 24-Aug-2020 (1 month post-dose 2 = D52).

Immunogenicity results are available for both adult age groups up to 1 month post-Dose 2 for the BNT162b1 and BNT162b2 vaccine candidates at the 10-µg, 20-µg, and 30-µg dose levels, and up to 7 weeks after Dose 1 of BNT162b1 at the 100-µg dose level (younger age group only).

Results for the 7 days after Dose 1 time point are only analysed and presented in the younger age group (18 to 55 years of age) for 10 µg and 30 µg BNT162b1.

Immunogenicity results SARS-CoV-2 Neutralizing Titres

BNT162b1

In the younger age group, SARS-CoV-2 50% neutralizing GMTs modestly increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b1 (Figure 5).

Generally similar trends were observed in the older age group, with higher GMTs observed in the 20-µg and 30-µg dose groups of BNT162b1 compared to the 10-µg dose group (Figure 6). In the older age

group, the SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.

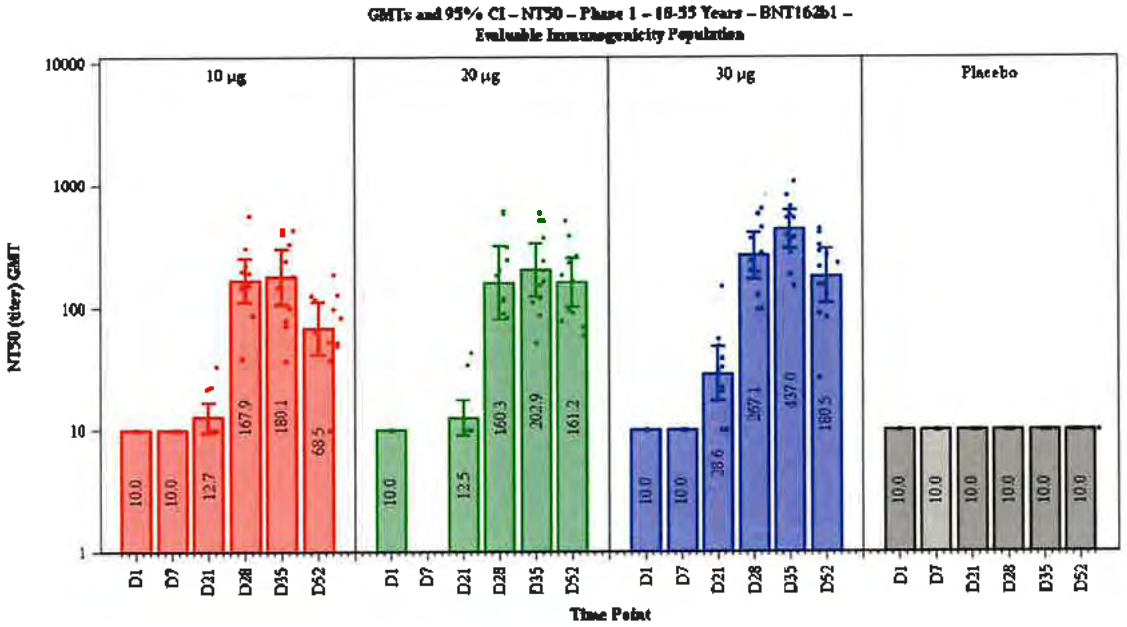


Figure 5. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

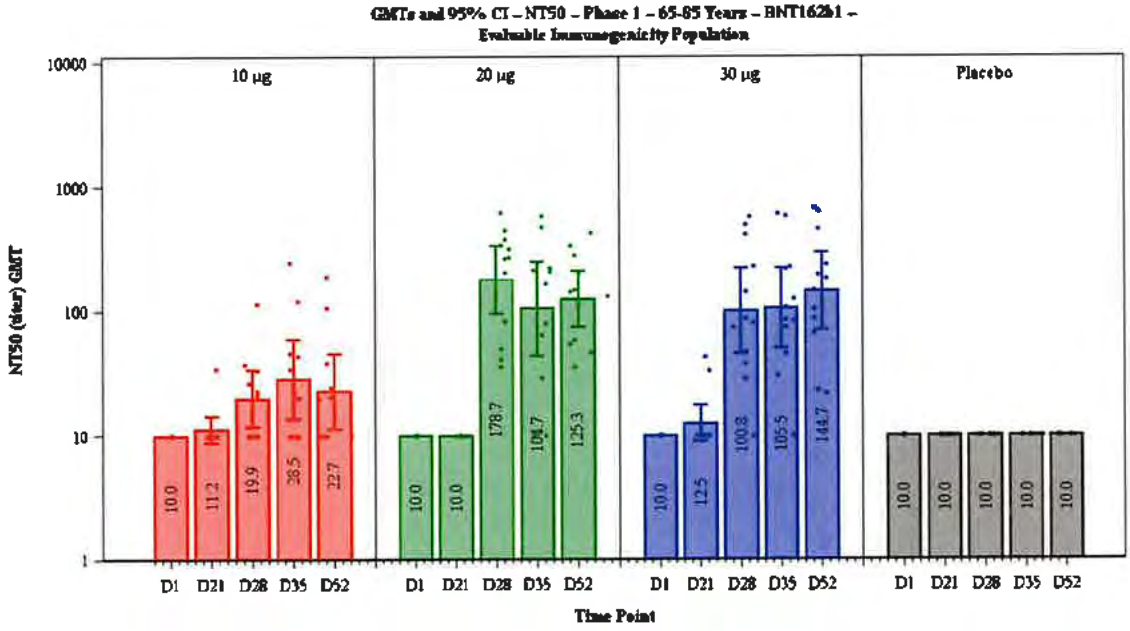
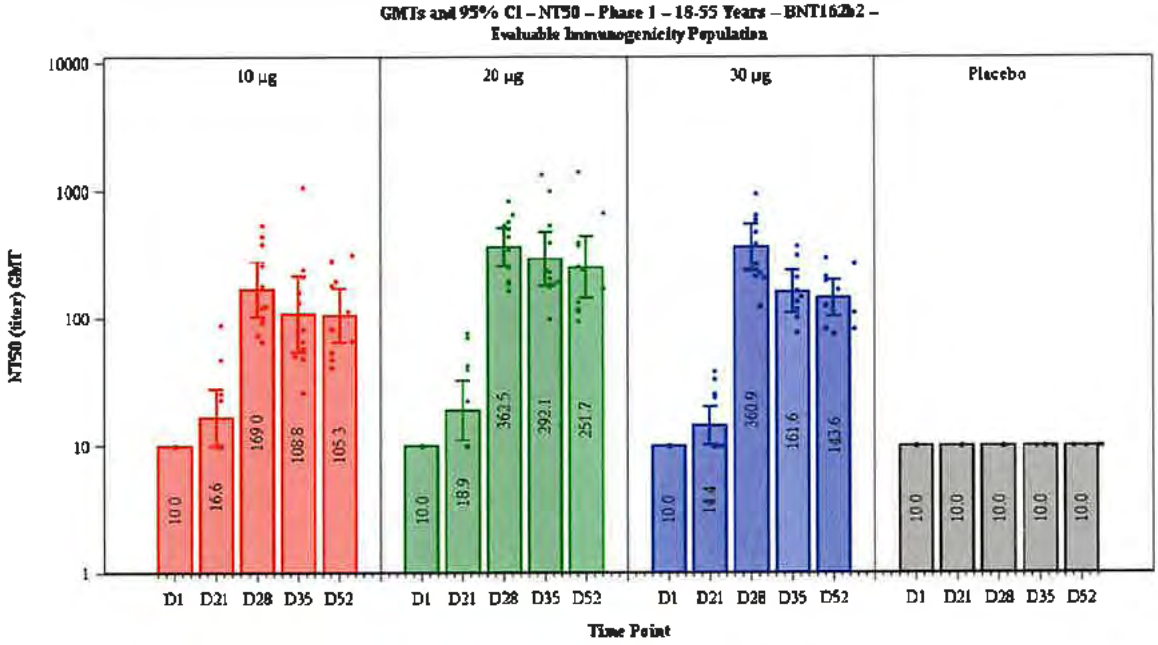


Figure 6. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart– 65-85 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

BNT162b2

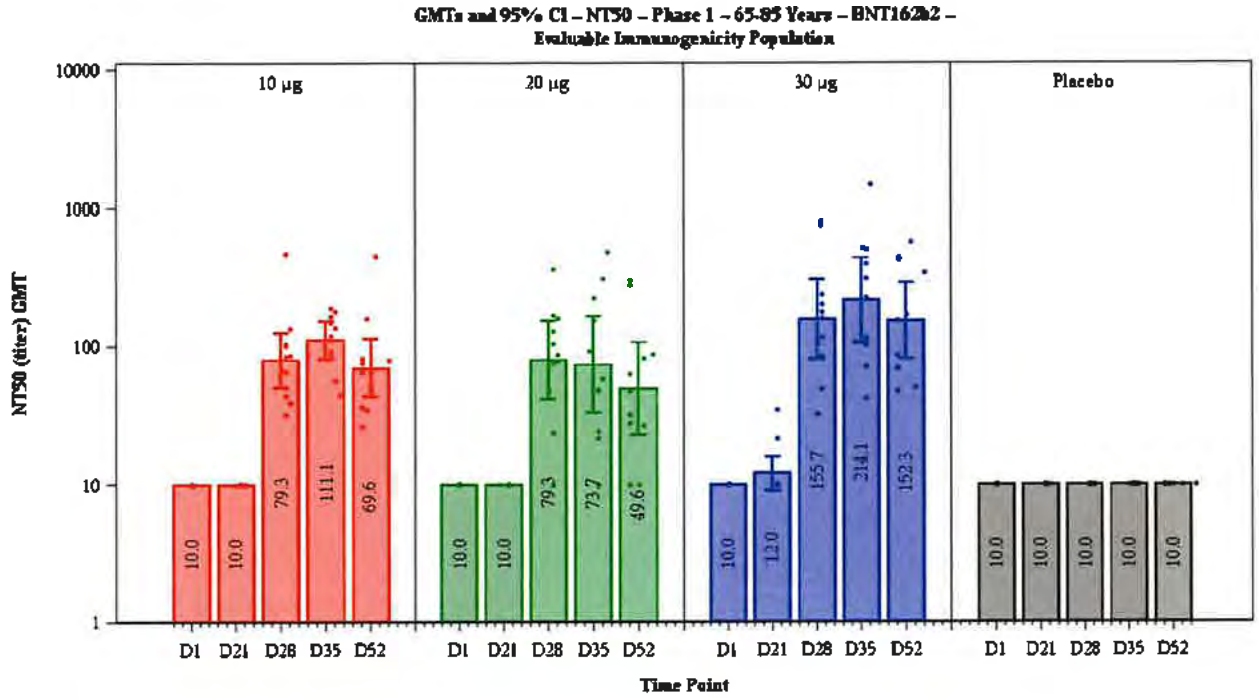
In the younger age group, SARS-CoV-2 50% neutralizing GMTs increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b2 (Figure 7).

Similar trends were generally observed in the older age group, with higher GMTs observed in the 30-µg dose groups compared to the 20-µg and 10-µg dose groups (Figure 8). In the older age group, SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
Note: Dots present individual antibody levels
Note: Number within each bar denotes geometric mean
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: advs Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nde3/C4591001_IA_P1_Serology/advs_f002_sars_50_18_b2_p1

Figure 7. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
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(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001_IA_P1_Serology/adva_f002_sars_50_65_b2_p1

Figure 8. Geometric Mean Titres and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Evaluable Immunogenicity Population

2.4.4. Discussion on clinical pharmacology

The choice and dose of vaccine candidate was based on the results of two clinical phase I studies. Immune responses and safety of the two candidates were studied in both studies. The immune responses in terms of neutralising antibody responses clearly demonstrated that two doses resulted in increased geometric mean titres (GMTs) compared to responses after only the first dose. Thus, in the absence of a serological correlate of protection, these data supported that two doses would be needed in adults. The responses were numerically higher in higher dose groups compared to lower doses but did not substantially differ between 10ug and 30ug. The neutralising antibody responses between the two vaccine candidates are considered similar although no formal comparison was made. The responses to the vaccines were higher compared to a pool of human convalescent sera in study BNT162-001. In both studies subjects 55 years of age and older were included as well as younger adults. The responses in elderly were lower compared to younger adults, but the difference is likely of no clinical relevance, also considering the delayed peak.

For BNT162b1 and BNT162b2, the S1- and RBD-binding IgG kinetics were comparable to the kinetics of neutralizing antibodies, with lower IgG concentrations in older age group than in younger age group.

Further evaluation of antibody persistence is ongoing. Neutralizing antibody titres will be followed until the end of 162 days post-dose 2 for study BNT162-01 and up to 2-years for study C459001. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation).

Immune responses induced by the vaccine against emerging circulating strains of SARS-CoV-2 will be also be investigated. Effectiveness studies included in the RMP will be important to understand the performance of the vaccine in case of e.g. mutating variants.

Efficient neutralization of spike protein mutants including RBD sequence variants was observed with sera from vaccine-immunized study BNT162-01 participants, demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies. This may be important to consider when facing emerging variants with mutations in the spike proteins, e.g. the UK variant, as the vaccine might still be able to confer sufficient cross-neutralisation.

Further characterisation of immune responses was included in study BNT162-001. Cellular immune responses were demonstrated in terms of IFNγ-producing CD4 and CD8 T cells. In addition, a clear Th1-polarised response, i.e. IFNγ/IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED. For the 30 µg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults, whereas for the 30 µg dose cohort vaccinated with BNT162b1, RBD-specific IL-2 producing CD4+ and CD8+ T cells were reduced in older adults.

2.4.5. Conclusions on clinical pharmacology

The immune response data overall support the choice of vaccine candidate, BNT162b2, and the choice of a 2-dose schedule of 30 µg. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation), including data on persistence of immune responses.

2.5. Clinical efficacy

2.5.1. Dose response study

See section 2.4.3.

2.5.2. Main study

Title of study

Study C4951001: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Methods

Study Participants

Main Inclusion criteria:

- Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥12 years (Phase 2/3) at randomization.
- Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks

before enrolment, could be included. Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfil the criteria specified in the protocol.

- Phase 2/3 only: Participants who, in the judgment of the investigator, were at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).
- Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent

Exclusion criteria:

- Other medical or psychiatric condition including recent or active suicidal ideation/behaviour or laboratory abnormality that increased the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention.
- Receipt of medications intended to prevent COVID-19.
- Previous clinical or microbiological diagnosis of COVID-19.
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding.
- Previous vaccination with any coronavirus vaccine.
- Individuals who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids were administered short term (<14 days) for treatment of an acute illness, participants should not have been enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.
- Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation
- Previous participation in other studies involving study intervention containing lipid nanoparticles.

Treatments

The vaccine candidate selected for Phase 2/3 evaluation was BNT162b2 at a dose of 30 µg. In phase 2/3 the participants were randomized 1:1 to receive vaccine or placebo, normal saline (0.9% sodium chloride solution for injection). The injection was intramuscular for both vaccine and the placebo.

Available safety, efficacy and immunogenicity data pertain to vaccine made according with the manufacturing process employed for clinical trial batches.

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply (commercial process) will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. Data are expected in February 2021. See the Quality section regarding comparability of clinical lots and commercial lots.

Objectives

The outcomes of the primary efficacy objectives were included in the Clinical Study Report submitted in this application. Results of the secondary objectives are expected during 2021.

Primary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination

Primary safety objectives

- To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)
- To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3
- To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3

Secondary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination

- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination.

Secondary immunogenicity objectives

- To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age (data not included in this report)

Exploratory objectives

- To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination
- To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study
- To describe the serological responses to the BNT vaccine candidate in cases of:
  - Confirmed COVID-19
  - Confirmed severe COVID-19
  - SARS-CoV-2 infection without confirmed COVID-19
- To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease
- To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by two different manufacturing processes (see under Treatment).

Outcomes/endpoints

Immunogenicity

See pharmacodynamics section for description of immunological methods used in phase 1 and 2 of this study. The same methods are used also in phase 3, but results are not yet available.

Primary Efficacy Endpoints

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.

Secondary Efficacy Endpoints

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2.

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

COVID-19 Case Definitions

Participants who developed any potential COVID-19 symptoms were to contact the site immediately and, if confirmed, to participate in an in-person or telehealth visit as soon as possible (within 3 days of symptom onset and at the latest 4 days after symptom resolution). At the visit (or prior to the visit, if a self-swab was used), investigators were to collect clinical information and results from local standard-of-care tests sufficient to confirm a COVID-19 diagnosis. Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a validated reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA) to detect SARS-CoV-2. If the evaluation was conducted by telehealth, the participant was to self-collect a nasal swab and ship for assessment at the central laboratory. A local nucleic acid amplification test (NAAT) result was only acceptable if it met protocol specified criteria and if a central laboratory result was not available.

Two definitions of SARS-CoV-2 related cases, and SARS-CoV-2 related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

Confirmed COVID-19 (defined for FDA guidance): presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhoea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC:

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2<300mm Hg);

- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

In addition, evidence of prior infection was determined by virological testing via NAAT on mid-turbinate swab and serological testing for IgG to the SARS-CoV-2 N-antigen. A serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result.

In addition, prior infection with SARS-CoV-2 was assessed also at Dose 2 (NAAT) and is being evaluated for up to 24 months. The purpose is to assess persistence of efficacy, explore efficacy against asymptomatic SARS-CoV-2 infections, and ensure safety in both seronegative and seropositive participants.

Sample size

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

Randomisation and Blinding (masking)

Allocation of participants to vaccine groups were performed through the use of an IRT system (IWR). Participants were randomised 1:1 to active vaccine or placebo.

The trial included participants ≥12 years of age, stratified as follows: 12 to 15, 16 to 55 years or >56 years. It was intended that a minimum of 40% of participants were to be enrolled in the >56-year stratum.

The study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments.

Exceptions to blinding for e.g. DMC activities were described and found acceptable.

Efficacy Analysis Methods

During Phase 2/3, interim analyses were pre-specified in the protocol to be conducted after accrual of at least 62, 92, and 120 evaluable COVID-19 cases, where overwhelming efficacy could be declared if the primary endpoint was met with a posterior probability that the true VE is >30% (i.e., Pr[VE >30%|data] >99.5% at an interim analysis or >98.6% at the final analysis). The success threshold for each interim analysis was calibrated to protect overall type I error at 2.5%. Futility was also assessed, and the study could be stopped for lack of benefit if the predicted probability of demonstrating vaccine efficacy at the final analysis was <5% at any of the first 2 planned interim analyses. Efficacy and futility boundaries were applied in a nonbinding way. The calculation of posterior probability and the credible interval were adjusted for surveillance time. For subgroup analyses of the primary efficacy endpoint, a 2-sided 95% confidence interval (CI) was calculated. VE is defined as 100% × (1 – IRR), where illness rate ratio (IRR) is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. VE is demonstrated if there is convincing evidence (i.e., posterior probability greater than 99.5% at an interim analysis or greater than 98.6% at the final analysis) that the true VE of BNT162b2 is >30% using a beta-binomial model, where VE represents efficacy for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior SARS-CoV-2 infection before and during the vaccination regimen. Participants with positive or unknown NAAT results at any illness visit prior to 7 days after Dose 2 were not included in the evaluation for VE. Cases were counted from 7 days after Dose 2.

The interim analysis was performed for the first primary efficacy endpoint only. Other efficacy data analysed for the interim analysis were summarized with descriptive summary statistics, including COVID-19 case counts in the BNT162b2 and placebo groups on the basis of:

- evidence of prior SARS-CoV-2 infection at baseline per NAAT or N-antigen binding assay
- subgroup status (i.e., age, sex, race, ethnicity baseline SARS-CoV-2 status)
- COVID-19 cases meeting protocol criteria as severe after the first and second doses.

Overwhelming efficacy success criteria were met at the first interim analysis, so further formal interim analyses would not be conducted. The final analysis of all protocol specified primary and secondary efficacy endpoints was pre-specified in the protocol to be conducted after accrual of the final number of COVID-19 cases (at least 164 cases). Subgroup analyses of VE were performed for the primary endpoints and secondary endpoint of severe COVID-19 cases. Additional post hoc analyses of subgroups defined by comorbidity risk assessment were performed. Secondary efficacy was analysed in the same manner as primary efficacy (Section 2.5.4.1.2.2), using the cases definitions for severe COVID-19 and CDC criteria for COVID-19

Statistical methods

The estimands to evaluate the efficacy objectives were based on evaluable populations for efficacy. These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE was also analysed by all-available efficacy population.

The evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized, with Dose 2 received within the predefined window (19-42 days after Dose 1),and had no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2. This was the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy populations, including all randomized participants who completed 1 and 2 vaccination doses respectively, were also performed.

The two primary endpoints were tested hierarchically. Key secondary efficacy endpoints were evaluated sequentially in a prespecified order after the primary endpoints were met. Missing data were not imputed for the primary or secondary analyses. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with MNAR assumption.

VE was estimated as follows: 100 × (1 − IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose.

A Bayesian approach was used for the primary and secondary endpoints. A beta prior, beta (0.700102, 1), was used for θ = (1-VE)/(2-VE). The prior was centred at θ = 0.4118 (VE=30%). The 95% interval for θ is (0.005, 0.964) and the corresponding prior 95% interval for VE is (-26.2, 0.995). The Bayesian approach was not used for the point estimate for VE. At final analysis, efficacy was to be declared if the posterior probability of VE greater than or equal to 30% ("p") > 98.60%.

During Phase 2/3, 4 interim analyses (IAs) were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. The final analysis was to be performed when 164 cases were observed. However, only one interim analysis was performed, at 94 cases. The final analysis was performed with 170 cases. At the time of the IAs, futility and VE with respect to the first primary endpoint were planned to be assessed. The IA that was performed was successful, as was the final analysis, and results were consistent with the IA.

The success threshold for each interim analysis was to be calibrated to protect overall type I error at 2.5%. The risk of falsely concluding the VE to be above 30% (the type I error rate) with the proposed Bayesian model and over the interim analyses and final analysis under assumption of 30% vaccine efficacy is 0.021 (one sided). Hence the type I error rate for the primary endpoint is controlled. Although only one interim analysis was performed, the overall Type I error (overall probability of success when true VE=30%) was controlled at 0.025 with the originally proposed success/futility boundaries.

Although Bayesian analysis are not usually accepted as confirmatory evidence in pivotal trials, the magnitude of the effect in this study, makes this concern redundant. Hence, the conclusions of the inference are considered robust.

Results

Disposition of All Randomised Subjects – ~38000 Subjects for Phase 2/3 Analysis

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) (N[a]=18904) n[b] (%)	Placebo (N[a]=18892) n[b] (%)	Total (N[a]=37796) n[b] (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Not vaccinated	46 (0.2)	43 (0.2)	89 (0.2)
Vaccinated			
Dose 1	18858 (99.8)	18849 (99.8)	37707 (99.8)
Dose 2	18555 (98.2)	18533 (98.1)	37088 (98.1)
Completed 1-month post–Dose 2 visit (vaccination period)	16902 (89.4)	16804 (88.9)	33706 (89.2)
Discontinued from vaccination period but continue in the study	121 (0.6)	111 (0.6)	232 (0.6)
Discontinued after Dose 1 and before Dose 2	121 (0.6)	107 (0.6)	228 (0.6)

Discontinued after Dose 2 and before 1-month post–Dose			
Reason for discontinuation from vaccination period			
riter	48 (0.3)		129 (0.3)
Withdrawal by subject	45 (0.2)		54 (0.1)
Adve	20 (0.1)		32 (0.1)
	4 (0.0)		8 (0.0)
Phys	2 (0.0)		3 (0.0)
	0		2 (0.0)
ithou	0		1 (0.0)
ther	2 (0.0)		3 (0.0)
ithdra	180 (1.0)		
afte	132 (0.7)		
Withdrawn after Dose 2 and before 1-month post–Dose 2	44 (0.2)		
Withdrawn after 1-month post–Dose 2 visit		11 (0.1)	
draw			
Withdrawal by subject			241 (0.6)
w-up			166 (0.4)
dve			13 (0.0)
			5 (0.0)
			3 (0.0)
eets eligibili			3 (0.0)
			1 (0.0)
Refused further study procedures			1 (0.0)
			6 (0.0)

Note : 1 subject was randomised but did not sign informed consent and is not included in any analysis population
Note: because of a dosing error, 2 subjects received an additional dose of BNT162b2 (30µg) and one dose of placebo
Note: HIV-positive subjects are included in this summary but not included in the analysis of the overall study objectives.
a. N=number of randomised subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations
b. n=number of subjects with the specific characteristics

Recruitment

This study is ongoing, and participants are continuing to be enrolled and evaluated in Phase 3.

Subject First Visit: 29 April 2020

Data Cut-off dates:

- 24 August 2020 (Phase 1 safety and immunogenicity data through 1 month after Dose 2)
- 02 September 2020 (Phase 2 safety data 7 days after Dose 2 only)
- 06 October 2020 (Phase 2/3 safety data 1 month after Dose 2 for the first 6610 participants, and available safety data for all 36,855 participants)
- 04 November 2020 (Phase 2/3 first interim analysis for efficacy at 94 cases)

As a result, 44,822 subjects have been enrolled and 43,386 subjects have been randomised at 153 centres, in 6 countries worldwide, including: United States (131 centres, 33,068 subjects), Argentina (1 site, 5,776 subjects), Brazil (2 sites, 2,900 subjects), Turkey (9 sites, 342 subjects), South Africa (4 sites, 800 subjects) and Germany (6 sites, 500 subjects).

Conduct of the study

This study has gone through extensive changes or amendments. The amendments of the phase 1 of the study are deemed acceptable for a dose-finding design. Protocol amendments concerning the phase 3 of the study are overall adequately motivated and acceptable, since they are not expected to affect the conclusions on efficacy. Main Amendments have allowed to include adolescents from 12 to 15 years in the study and added corresponding objectives. Furthermore, secondary efficacy endpoints to include COVID-19 cases that occurred from 14 days after the second dose were added. The SAP was amended twice in line with protocol amendments.

Baseline data

Overall, demographic characteristics were well balanced between study groups.

Demographics (population for the primary efficacy endpoint)[a]

	Comirnaty (N=18,242) n (%)	**Placebo (N=18,379) n (%)**
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥12 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
75 through 85 years	799 (4.4)	807 (4.4)
>85 years	5 (0.0)	5 (0.0)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other[b]	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities[c]		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

a. All eligible randomised participants who receive all vaccination(s) as randomised within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.

c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
   - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
   - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
   - Obesity (body mass index ≥ 30 kg/m^2)
   - Diabetes (Type 1, Type 2 or gestational)
   - Liver disease
   - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

Baseline comorbidities - safety population 38,000 subjects- at final analysis:

Table 3. Baseline Charlson Comorbidities ~ 3800 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
Charlson Comorbidity Index Category	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Subjects with any Charlson comorbidity	3934 (20.9)	3809 (20.2)	7743 (20.5)
AIDS/HIV	59 (0.3)	62 (0.3)	121 (0.3)
Any Malignancy	733 (3.9)	662 (3.5)	1395 (3.7)
Cerebrovascular Disease	195 (1.0)	166 (0.9)	361 (1.0)
Chronic Pulmonary Disease	1478 (7.8)	1453 (7.7)	2931 (7.8)
Congestive Heart Failure	88 (0.5)	83 (0.4)	171 (0.5)
Dementia	7 (0.0)	11 (0.1)	18 (0.0)
Diabetes With Chronic Complication	99 (0.5)	113 (0.6)	212 (0.6)
Diabetes Without Chronic Complication	1473 (7.8)	1478 (7.8)	2951 (7.8)
Hemiplegia or Paraplegia	13 (0.1)	21 (0.1)	34 (0.1)
Leukemia	12 (0.1)	10 (0.1)	22 (0.1)
Lymphoma	22 (0.1)	32 (0.2)	54 (0.1)
Metastatic Solid Tumor	4 (0.0)	3 (0.0)	7 (0.0)
Mild Liver Disease	125 (0.7)	89 (0.5)	214 (0.6)
Moderate or Severe Liver Disease	1 (0.0)	2 (0.0)	3 (0.0)
Myocardial Infarction	194 (1.0)	188 (1.0)	382 (1.0)
Peptic Ulcer Disease	52 (0.3)	71 (0.4)	123 (0.3)
Peripheral Vascular Disease	124 (0.7)	117 (0.6)	241 (0.6)
Renal Disease	123 (0.7)	133 (0.7)	256 (0.7)
Rheumatic Disease	62 (0.3)	56 (0.3)	118 (0.3)

Note: MedDRA (v23.1) coding dictionary applied.

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of subjects with the specified characteristic. Subjects with multiple occurrences within each category are counted only once. For 'Subjects with any Charlson comorbidity', n = number of subjects reporting at least 1 occurrence of any Charl

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The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease

not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Numbers analysed

The disposition of the efficacy populations is described in the Table below. There was an imbalance between the two study groups on the number of subjects excluded from the evaluable efficacy population. The two reasons responsible for this imbalance were "Dosing/administration error, subject did not receive correct dose of vaccine" (n=105 in vaccines and n=3 in placebo) and "IP administered that was deemed not suitable for use by Almac" (n=144 in vaccines and n=0 in placebo). There may be several explanations for this imbalance as listed below:

- As the placebo was a fixed volume of saline, with no dilution required, the likelihood of a dosing error in the placebo group was lower compared to vaccine, which did required dilution.
- An isolated dosing/administrative error event in one clinical centre affecting a higher number of participants receiving BNT162b2 (n=52 participants) has contributed to this imbalance.
- Almac was responsible for determining suitability for use of investigational product that was subject to a temperature excursion. Due to the differences in the required storage conditions (ambient for the placebo versus ultracold for the BNT162b2), temperature excursions were not an issue for the placebo but were for BNT162b2.

The protocol design was such that, if a participant experienced any of the specified trigger symptoms that could indicate COVID-19, a potential COVID-19 illness visit should occur, including obtaining a swab for the central laboratory.

Table 4 Efficacy Populations

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Subjects without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Subjects excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			

Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Subjects without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Subjects without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Subjects excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Subjects without evidence of infection prior to 7 days after Dose 2	18242 (83.6)	18379 (84.2)	36621 (83.9)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Subjects without evidence of infection prior to 14 days after Dose 2	18219 (83.5)	18315 (83.9)	36534 (83.7)
Subjects excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Subjects excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. n = Number of subjects with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Subjects may have been excluded for more than 1 reason.

Outcomes and estimation

Primary Efficacy Endpoints – Final Analysis

The result for the first primary efficacy analysis is shown in Table 5. VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 95.2%, with 8 and 165 cases in the BNT162b2 and placebo group.

Table 5 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 =severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details

For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with or without evidence of prior SARS-CoV-2 infection through 7 days after Dose 2. Cases were counted from 7 days after Dose 2 (Table 6). VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 94.8%, with and 9 and 172 cases in the BNT162b2 and placebo group, respectively.

Table 6 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.9, 97.3)	>0.9999

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

However the seropositive subjects were not many: among 38,000 subjects there were 407 individuals seropositive in the vaccine group and 436 in the placebo group in the age strata 16-55 YOA, and 150 individual seropositive in the vaccine group and 152 in the placebo group in the >55 YOA age strata.

All Confirmed Cases of COVID-19 After Dose 1

An analysis of the cases occurring from dose 1 and until dose 2 or 1 week after dose 2 provides information on onset of protection.

All reports of COVID-19 with onset at any time after Dose 1 are accounted for in Table 7, which provides a summary of cases for all participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group (Table 7). Notably, in the BNT162b2 group, most cases occurred before Dose 2.

Figure 9 displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy (modified intention-to-treat) population. Disease onset appears to track together for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group. From table 7 and figure 9 it is evident that the first dose offers partial protection, while few cases occur after the second dose.

Table 7 Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All- Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
≥10 days after Dose 1 to before Dose 2	6		45		86.7	(68.6, 95.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

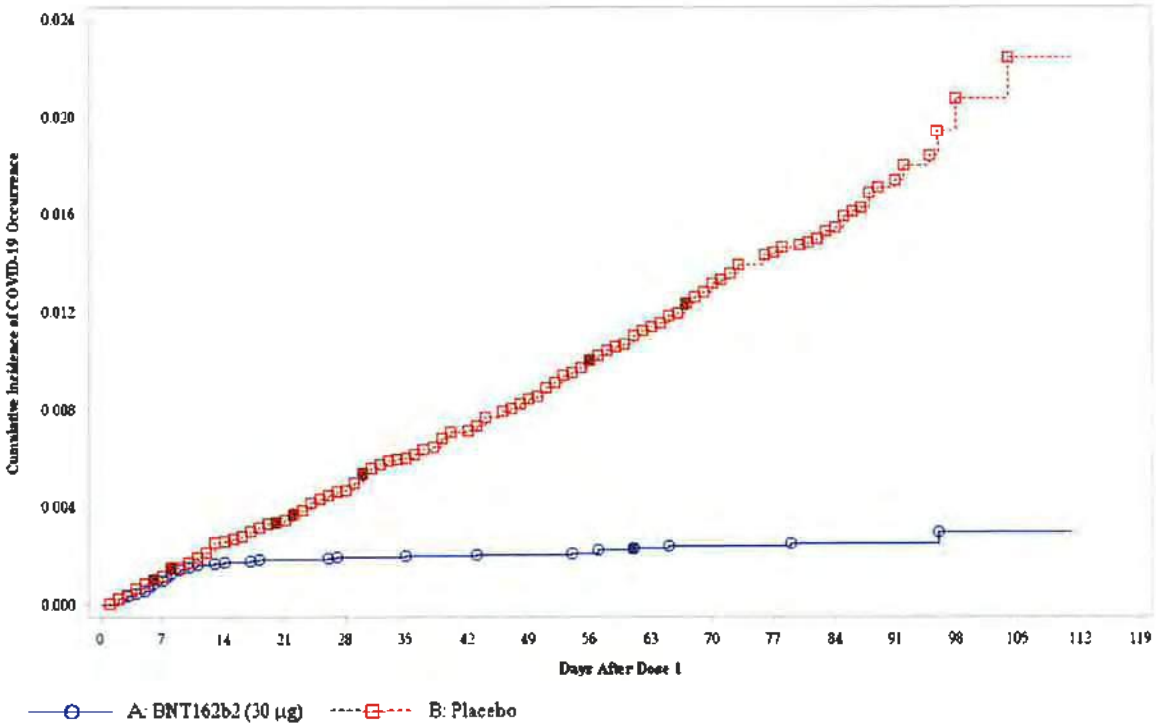


Figure 9. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Immunogenicity results

The immunogenicity part of study C4591001 are presented in this section and aimed to confirm the conclusions on safety and immunogenicity from phase 1. These are the only immunogenicity results from a larger study population available at this stage, and further results from phase 3 are expected post approval. In addition, any data generated in attempts to establish a serological correlate of protection are expected to be reported when available.

The results of the immunogenicity analyses here reported are generated from the Dose 2 evaluable immunogenicity population; baseline positive participants (by N-binding antibody or positive NAAT at Visit 1) were not excluded from these analyses.

SARS-CoV-2 Neutralizing Titres and S1-Binding IgG Concentrations GMTs/GMCs

At 1 month after Dose 2 (Day 52) of BNT162b2, there were substantial increases in SARS-CoV-2 50% neutralizing GMTs (Figure 10) and S1-binding IgG concentrations (GMCs) (Figure 11). GMTs/GMCs were higher in younger participants (18 to 55 years of age) than in older participants (56 to 85 years of age). Similar trends were observed for the SARS-CoV-2 90% neutralizing GMTs (data not shown in this report).

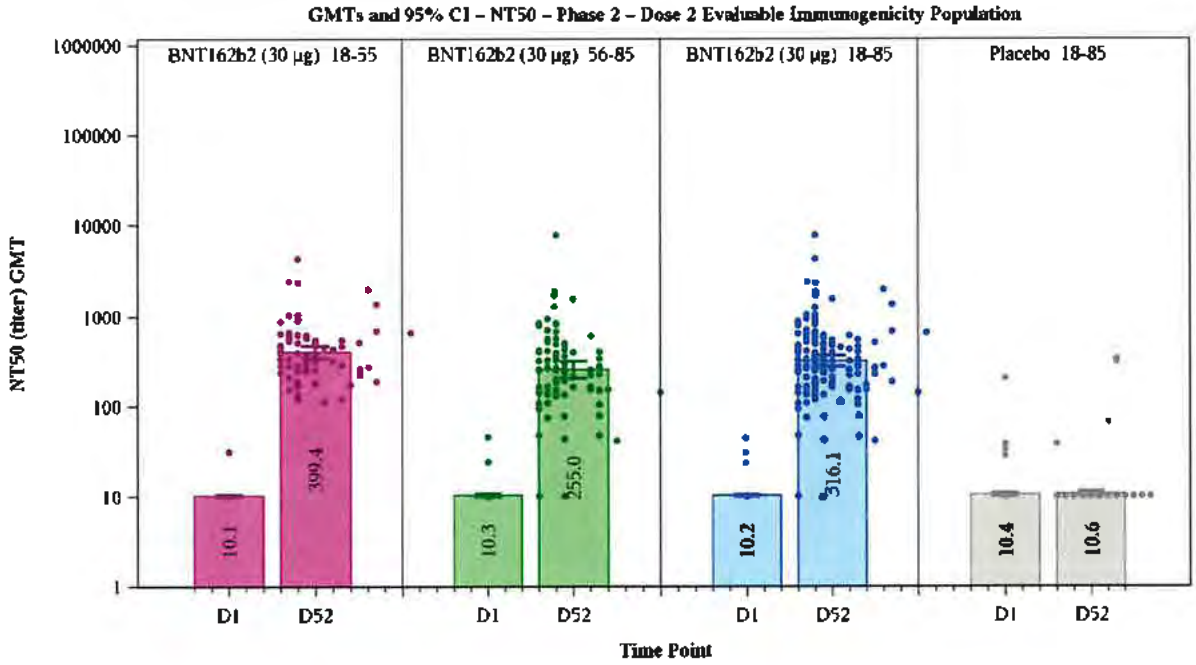


Figure 10. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay – NT50 – Phase 2 – Dose 2 Evaluable Immunogenicity Population

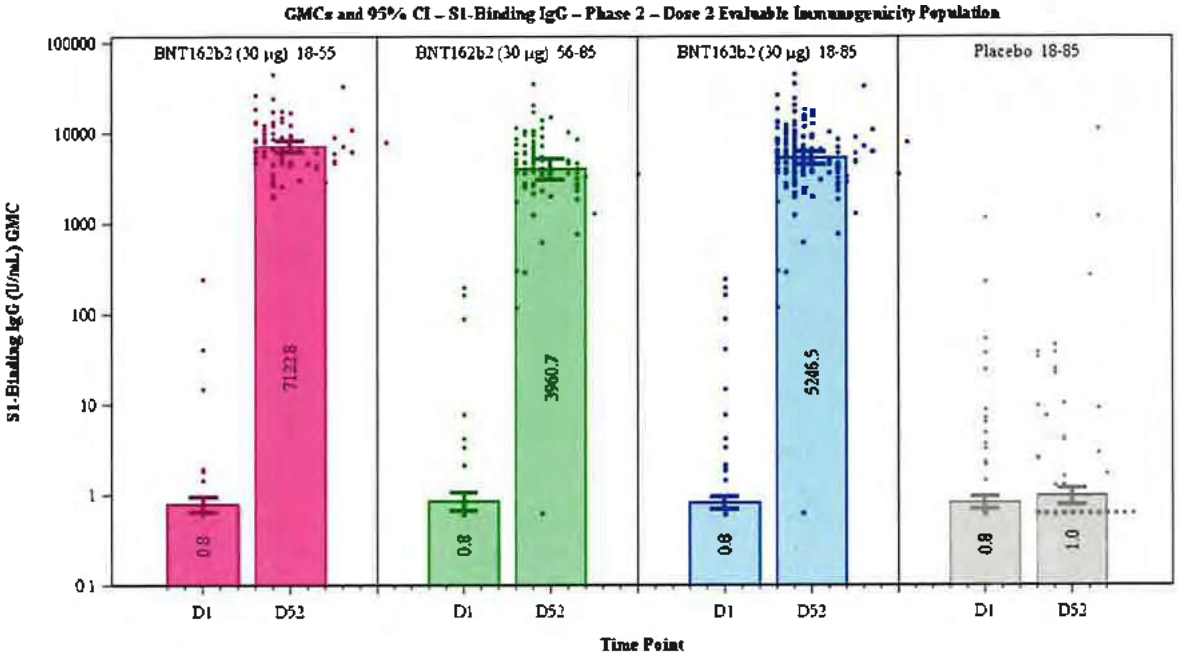


Figure 11. Geometric Mean Concentrations and 95% CI: S1-Binding IgG Level Assay – Phase 2 Dose 2 Evaluable Immunogenicity Population

A few participants in the Dose 2 evaluable immunogenicity population had a positive baseline SARS-CoV-2 status. These SARS-CoV-2 status positive participants were analysed separately from the baseline negative participants. In general, at 1 month after Dose 2 among BNT162b2 recipients, SARS-CoV-2 50% neutralizing GMTs and S1-binding IgG GMCs in participants with a positive baseline SARS-CoV-2 status (n=3) were numerically higher than those observed in participants with a negative baseline SARS-CoV-2 status (n=163).

Ancillary analyses

Vaccine Efficacy by Subgroup

For both primary endpoints, VE was also evaluated for subgroups of participants by age, sex race/ethnicity, and country, without evidence of prior infection (Table 8). Results for additional age groups are shown in Table 9.

Post hoc analyses of efficacy by risk status were performed. For these analyses, at-risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese (defined as BMI ≥30 kg/m2) (table 11). Results for the all-available population were similar; no clinically meaningful differences were observed in VE on the basis of subgroup.

These subgroup analyses are considered of importance. There is no evidence of significantly reduced efficacy in older age groups, i.e. >90% vaccine efficacy even in over 75-year-old subjects, although not statistically significant as there were only few cases in this age stratum. There were no cases in the 16-17-year-old age stratum, but efficacy is not anticipated to be lower in younger age groups compared to the overall study population. Additionally, it is reassuring that other factors, e.g. ethnicity/race, gender did not impact efficacy. Efficacy was not demonstrated in subjects who were

seropositive at baseline, but the subgroup was very small and results are considered inconclusive rather than negative at this stage.

Table 8 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
16 to 55	5	1.234 (9897)	114	1.239 (9955)	95.6	(89.4, 98.6)
>55	3	0.980 (7500)	48	0.983 (7543)	93.7	(80.6, 98.8)
≥65	1	0.508 (3848)	19	0.511 (3880)	94.7	(66.7, 99.9)
Sex						
Male	3	1.124 (8875)	81	1.108 (8762)	96.4	(88.9, 99.3)
Female	5	1.090 (8536)	81	1.114 (8749)	93.7	(84.7, 98.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
All others[f]	1	0.160 (1405)	9	0.155 (1355)	89.3	(22.6, 99.8)
Ethnicity						
Hispanic/Latino	3	0.605 (4764)	53	0.600 (4746)	94.4	(82.7, 98.9)
Non-Hispanic/non-Latino	5	1.596 (12548)	109	1.608 (12661)	95.4	(88.9, 98.5)
Country						
Argentina	1	0.351 (2545)	35	0.346 (2521)	97.2	(83.3, 99.9)
Brazil	1	0.119 (1129)	8	0.117 (1121)	87.7	(8.1, 99.7)
USA	6	1.732 (13359)	119	1.747 (13506)	94.9	(88.6, 98.2)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 9 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=19965)		Placebo (N[a]=20172)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.6, 97.6)
Age group (years)						
16 to 55	6	1.309 (10653)	120	1.317 (10738)	95.0	(88.7, 98.2)
>55	3	1.022 (7892)	49	1.028 (7956)	93.8	(80.9, 98.8)
≥65	1	0.530 (4044)	19	0.532 (4067)	94.7	(66.8, 99.9)
Sex						
Male	4	1.183 (9457)	85	1.170 (9342)	95.3	(87.6, 98.8)
Female	5	1.149 (9102)	84	1.176 (9366)	93.9	(85.2, 98.1)
Race						
White	7	1.975 (15294)	153	1.990 (15473)	95.4	(90.3, 98.2)
Black or African American	0	0.187 (1758)	7	0.188 (1758)	100.0	(30.4, 100.0)
All others[f]	2	0.170 (1507)	9	0.167 (1477)	78.2	(-5.4, 97.7)
Ethnicity						
Hispanic/Latino	3	0.637 (5074)	55	0.638 (5090)	94.5	(83.2, 98.9)
Non-Hispanic/non-Latino	6	1.681 (13380)	114	1.693 (13509)	94.7	(88.1, 98.1)
Country						
Argentina	1	0.366 (2664)	36	0.367 (2684)	97.2	(83.5, 99.9)
Brazil	2	0.134 (1274)	8	0.132 (1257)	75.4	(-23.5, 97.5)
USA	6	1.816 (14141)	124	1.830 (14287)	95.1	(89.1, 98.2)
South Africa	0	0.015 (362)	1	0.015 (363)	100.0	(-3818.9, 100.0)
Prior SARS-CoV-2 Status						
Positive at baseline[g]	1	0.056 (526)	1	0.060 (567)	-7.1	(-8309.9, 98.6)
Negative at baseline but positive prior to 7 days after Dose 2[h]	0	0.003 (27)	1	0.004 (34)	100.0	(-6004.9, 100.0)
Negative prior to 7 days after Dose 2[i]	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Unknown	0	0.059 (595)	5	0.060 (596)	100.0	(-9.6, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; VE= vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.
g. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
h. Negative N-binding antibody result and negative NAAT result at Visit 1, positive NAAT result at Visit 2 or at unscheduled visit, if any, prior to 7 days after Dose 2.

i. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1 and Visit 2, and negative NAAT result at unscheduled visit, if any, prior to 7 days after Dose 2.

Table 10 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Requested Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
12 to 15	0	0.000 (14)	0	0.000 (13)	NE	(NE, NE)
16 to 17	0	0.002 (52)	0	0.003 (55)	NE	(NE, NE)
18 to 64	7	1.703 (13497)	143	1.708 (13563)	95.1	(89.6, 98.1)
65 to 74	1	0.406 (3074)	14	0.406 (3095)	92.9	(53.1, 99.8)
≥75	0	0.102 (774)	5	0.106 (785)	100.0	(-13.1, 100.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
American Indian or Alaska native	0	0.011 (100)	1	0.010 (96)	100.0	(-3429.0, 100.0)
Asian	1	0.092 (764)	4	0.093 (769)	74.6	(-156.6, 99.5)
Native Hawaiian or other Pacific Islander	0	0.006 (46)	1	0.003 (29)	100.0	(-2266.9, 100.0)
Multiracial	0	0.042 (414)	1	0.036 (359)	100.0	(-3231.3, 100.0)
Not reported	0	0.010 (81)	2	0.012 (102)	100.0	(-563.3, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Table 11 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
At risk[f]						
Yes	4	1.025 (8030)	86	1.025 (8029)	95.3	(87.7, 98.8)
No	4	1.189 (9381)	76	1.197 (9482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7671)	69	0.964 (7701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5878)	74	0.746 (5917)	95.9	(87.6, 99.2)
≥65 and not at risk	0	0.227 (1701)	7	0.233 (1771)	100.0	(29.0, 100.0)
≥65 and at risk	1	0.281 (2147)	12	0.279 (2109)	91.7	(44.2, 99.8)
Obese[g]						
Yes	3	0.763 (6000)	67	0.782 (6103)	95.4	(86.0, 99.1)
No	5	1.451 (11406)	95	1.439 (11404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8811)	83	1.101 (8825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4734)	60	0.609 (4789)	94.9	(84.4, 99.0)
≥65 and not obese	1	0.343 (2582)	12	0.338 (2567)	91.8	(44.5, 99.8)
≥65 and obese	0	0.165 (1265)	7	0.173 (1313)	100.0	(27.1, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
f. At risk is defined as having at least one of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m^2).
g. Obese is defined as BMI ≥30 kg/m^2.

Vaccine efficacy by different age subgroup is shown below in line with the information included in the SmPC.

Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection and participants with or without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COVID-19 mRNA Vaccine N[a]=18,198 Cases n1[b] Surveillance time[c] (n2[d])**	**Placebo N[a]=18,325 Cases n1[b] Surveillance time[c] (n2[d])**	**Vaccine efficacy % (95% CI)[f]**
All subjects[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. No confirmed cases were identified in participants 12 to 15 years of age.
f. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Vaccine efficacy for Severe COVID-19 cases, Final analysis

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, the estimated VE against severe COVID-19 occurring at least 7 days after Dose 2 was 66.4%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively (Table 12). The posterior probability for the true vaccine efficacy greater than 30% is 74.29%, which did not meet the prespecified success criterion of >98.6% for this endpoint due to the small number of severe cases observed after Dose 2 in the study.

Consequently, statistical testing of subsequent secondary endpoints (i.e., the additional secondary endpoints related to severe disease with pre-specified control of overall type 1 error) ended. However, descriptive summaries for the additional endpoints were provided.

Table 12 Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days AfterDose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial C4591001

Title: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer- Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals		
Study identifier	C4591001	
Design	Phase 1/2/3 randomized, observer-blind, placebo-controlled	
	Follow-up for efficacy	Until nov 14, 2020
	Follow-up for safety	At least 1 month, median 2 months
Hypothesis	Superiority of vaccine vs placebo for vaccine efficacy	
Treatments groups	Active arm	BNT162b2 (30 µg), 2 doses, 21 days apart, randomized 22 000

	Control arm		Saline placebo, 2 doses, 21 days apart, randomized 22 000
Endpoints and definitions	First Primary endpoint	VE-7d-no-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2
	Second Primary endpoint	VE-7d-no/yes-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2.
	Secondary Endpoint	VE-14d-no-no/yes-SARS-Cov-2	COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2
	Secondary Endpoint	VE-7d/14d-no-no/yes-SARS-Cov-2-Severe	Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2
Database lock	November 14, 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population	Per protocol, Evaluable Efficacy population		
Effect estimate per comparison VE=100x (1- IRR) IRR= caseN/groupN Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time., Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.	Primary endpoint	VE-7d-no-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=8/18198 Cases in Placebo arm N= 162/18325
		Vaccine Efficacy VE %	95.0
		95% Credible Interval	90.3, 97.6
		Pr (VE >30% |data)	>0.9999
	Co-Primary	VE-7d-no/yes-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=9/18559 Cases in Placebo arm N= 169/18708
		Vaccine Efficacy VE %	94.6
		95% Credible Interval	89.9, 97.3

		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-14d-no- SARS-CoV-2	Cases in Active arm N=8/18175 Cases in Placebo arm N= 139/18261
		Vaccine Efficacy VE %	94.2
		95% Credible Interval	88.7, 97.2
		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-14d-no/yes-SARS-CoV-2	Cases in Active arm N=8/19965 Cases in Placebo arm N= 144/20171
		Vaccine Efficacy VE %	94.4
		95% Credible Interval	89.1, 97.3
		Pr (VE >30% |data)	>0.9999
	Secondary endpoint	VE-7d-no-SARS-CoV-2-Severe	Cases in Active arm N=1/18198 Cases in Placebo arm N= 3/18325
		Vaccine Efficacy VE %	66.4
		95% Credible Interval	-124.8, 96.3
		Pr (VE >30% |data)	0.7429
Notes	Subgroup analyses support the overall results, e.g. elderly and patients with risk factors appear to be protected as well.		

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the selected vaccine BNT162b2 was investigated in one pivotal trial, BNT162-02 study. This is a phase 1/2/3, multicentre, multinational, randomized, placebo-controlled, observer blind, dose finding, vaccine candidate efficacy and safety study in subjects that are healthy or have clinically stable comorbidities. Safety and immunogenicity data generated during the phase 1 portion of this study supported the selection of BNT162b2 at 30 µg, as a prime/boost regimen (separated by 21 days) as the vaccine candidate to proceed into Phase 2/3.

Phase 2/3 was designed to evaluate the efficacy of BNT162b2, and to provide additional safety and immunogenicity data in a larger population. The study design for the pivotal phase 3 study is overall acceptable and in line with applicable guidelines. In the Phase 2/3 portion, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for

up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. It is an observer-blind study, which is considered acceptable as placebo and vaccine differed in appearance. Randomisation and blinding were considered acceptable.

Overall inclusion and exclusion criteria are acceptable and the study population is considered representative of the target population for vaccination, including subjects at higher risk of severe disease, i.e. age above 65 years (>20% with no upper age limit) and relevant underlying diseases (46%, e.g. obesity, chronic pulmonary diseases, diabetes, hypertension, and cardiovascular disease). Immunocompromised subjects and pregnant or breastfeeding women were excluded from the study. Subjects with known stable infection with HIV, HBV, HCV could be enrolled. Further, individuals who had previous clinical or microbiological diagnosis of COVID-19 were excluded, since the natural infection would affect the immunogenicity of the vaccine.

The study mainly recruited in the USA, but other sites worldwide were also included.

The primary endpoint (laboratory confirmed symptomatic COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection up to 7 days after receipt of the second dose, and then in all participants regardless of serostatus) is considered relevant for the purpose of establishing vaccine efficacy.

SARS-CoV-2 genomic RNA has been detected in nasal swab samples using Cepheid Xpert Xpress SARS-CoV-2 PCR assay on the GeneXpert Molecular Diagnostic System. This method detects 2 structural genes of SARS-CoV-2: E and N2. A validation of this method was performed, and in addition the test was issued a EUA by FDA. In order to assess the analytical detection limit, live virus and commercial control (AccuPlexTM SARS-CoV-2) were used. Clinical sensitivity and specificity were evaluated in comparison with results obtained using another FDA authorised real-time RT-PCR method with positive or negative clinical specimens and pre-pandemic samples. Results showed that Cepheid Xpert Xpress PCR assay is a sensitive and specific method for the detection of SARS-CoV-2 RNA in nasal swabs. The positive rate of self-swab is similar to site-swab, 3.7% and 4.7% positive from self-swab and site-swab respectively in the BNT162b2 group.

The third main secondary endpoint evaluated vaccine efficacy against severe cases of the disease (defined as confirmed COVID-19 with the presence of at least one of pre-defined severity criteria), to determine whether the vaccine decreased the incidence of confirmed severe COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection, 7 to 14 days after the second dose. Prevention of severe disease is an important endpoint, but the relative rarity of severe cases would require either a very large study population and/or a very long study duration to be certain to achieve sufficient statistical power. Therefore, it is acceptable as a secondary endpoint.

The immunogenicity secondary and exploratory endpoints are considered acceptable.

This is an event-driven study. This case-driven approach is deemed appropriate as the rate of accumulation of cases was not certain which could allow a rapid assessment of efficacy in case of a high attack rate. With assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. The randomisation procedure is considered appropriate to control confounding factors.

The statistical methods are overall acceptable. The Bayesian approach used is not expected to affect the decisions from the hypothesis testing procedure. For consistency and ease of interpretation, the Clopper Pearson confidence intervals will be included in the SmPC rather than the Bayesian credible intervals. Of the four pre-planned interim analyses only one was performed, and the final analysis was also submitted. These analyses give highly consistent results with VE far from the null hypothesis limit

of 30%. Confidence intervals were not adjusted for multiplicity, which is considered acceptable in this context.

While it could be argued that alpha could be allocated according to a group sequential design, since no failed interim analysis has been performed, the alpha allocated to the interim analysis may be recycled to the final analysis. Hence the final analysis could have been performed at full alpha level and the coverage probability of the "naïve" confidence interval is therefor considered correct.

The interim and final analyses are conducted in an evaluable efficacy population of participants who receive the two doses within the predefined window and excluding subjects with other major protocol deviation, in order to obtain a best-case estimate of vaccine efficacy. However, this approach could result in bias due to exclusion of subjects. For this reason, sensitivity analyses assessing VE based on all laboratory-confirmed cases with symptom onset at any time after the first dose (dose 1 all-available efficacy population) and 7 days after the second dose (dose 2 all-available efficacy population) have been performed without excluding participants with major protocol deviations.

Overall, the study report including the final analysis is considered adequate. This is not the final report for the study, as the study is expected to continue for a total of 24 months.

Baseline data

At the cut-off date of 14 November 2020, the disposition of the 38,000 participants were similar in the BNT162b2 and placebo groups. Overall, 0.2% of participants did not receive study vaccine. A small percentage of participants discontinued study vaccine after Dose 1 and before Dose 2 (0.6%). The reasons for discontinuation were also balanced. The most frequently reported reasons for discontinuation included: no longer meets eligibility criteria (0.3% BNT162b2; 0.4% placebo; the most common reason was previous clinical or microbiological diagnosis of COVID-19), withdrawal by participant, and AEs (0.1% in both treatment groups).

The distribution of demographics and other baseline characteristics was similar between both arms among participants without evidence of infection up to 7 days after dose 2 in the final analysis evaluable efficacy population. Overall, most participants were White (82.8%) and non-Hispanic/non-Latino (72.7%) (26.8% of Hispanic/latino ethnicity), median age was 52.0 years, and approximately 49% were female. There were 42.6% of participants in the older age group (>50 years), 26% of participants over 65 years of age and 0.7% (112 subjects) of participants adolescents (12-17 years). In 75-85 years and >85 years age groups, 837 and 5 participants respectively had been vaccinated with BNT162b2 (Dose 2 all-available efficacy).

Across both treatment groups, 20.5% had any comorbidity (per the Charlson comorbidity index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%) and were reported at similar frequencies in each group. Obese participants made up 35.1% of the safety population. Overall, 120 subjects were HIV-positive and were evenly distributed between treatment groups.

Efficacy data and additional analyses

The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

The first interim analysis for vaccine efficacy (VE) was conducted on 08-Nov-2020 by an IDMC. The data cut-off date was 04-Nov-2020, when a total of 94 confirmed COVID-19 cases were accrued. There were 4 COVID-19 cases in the BNT162b2 group compared to 90 COVID-19 cases reported in the

placebo group. These data gave a vaccine efficacy of 95.5% (95%CI: 88.8%, 97.5%) among participants without evidence of infection up to 7 days after Dose 2, and a >99.99% posterior probability for the true vaccine efficacy greater than 30% conditioning on available data. Participants included in the first interim analysis were also included in the final analysis.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued.

The protective efficacy in subjects without prior evidence of SARS-CoV-2 infection from 7 days after dose 2 was high, 95.0% (95% CI: 90.0; 97.9) in the primary efficacy population (8 cases and 162 cases in the BNT162b2 and placebo groups, respectively). The posterior probability of >99.99% for the true VE greater than 30% met the pre-specified success criterion of >98.6% for this endpoint.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after dose 2 was 94.2%, 95%CI (88.7%, 97.2%) (8 and 139 cases in the BNT162b2 and placebo groups respectively) with a posterior probability (VE≥30%/data) of >99.99%.

Slightly more subjects in the placebo group had symptoms of COVID-19 without being a confirmed case by PCR. This is also reflected in slightly more subjects in the placebo arm with result not available from the swab. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with the available data, assuming a higher than the observed case rate when imputing missing efficacy endpoints from participants in the BNT162b2 group only, to reflect potentially unknowable missing not at random (MNAR) effects that are unfavourable for efficacy results of the study. 500 imputations were performed that were generated using SAS PROC MI Fully Conditional Specification (FCS) method. Each imputation filled in the missing laboratory results based on a logistic regression model at the subject level. VE after imputation was over 80% also with up to 15-fold increase of positivity rate applied to the BNT162b2 group. Hence, there is no concern that this slight imbalance has introduced any significant bias to the results presented below.

The 2-dose schedule is considered justified both based on immune responses and on the actual efficacy results. In dose 1 all-available efficacy (mITT) population, regardless of evidence of infection before or during the vaccination regimen, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group (n=21,314 subjects) compared to 275 cases in the placebo group (n=21,258 subjects). Notably, in the BNT162b2 group, most cases (36/(50)) occurred before Dose 2. The estimated VE against confirmed COVID-19 occurring after dose 1 was 82% (2-sided 95% CI: 75.6 %, 86.9%), with an estimated VE of 52.4% (2-sided 95% CI: 29.5%, 68.4%) against confirmed COVID-19 occurring after dose 1 but before dose 2.

The cumulative incidence curves for the first COVID-19 occurrence after dose 1 (all-available efficacy population) showed that COVID-19 disease onset seems to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, then cumulative curves diverge with more cases accumulating in the placebo group than in the BNT162b2 group. During the follow-up time of approximately 2 months post-dose 2, the BNT162b2 cumulative curve is stable which would not suggest waning protection. A longer follow-up is necessary to investigate the duration of the efficacy of the vaccine in protecting against the disease.

For both primary endpoints, no clinically meaningful differences in VE by subgroup were observed by age group, country, ethnicity, sex, or race in the dose 2 evaluable efficacy population, with VE estimates that ranged from 91.2% to 100.0%. Efficacy was consistent across relevant subgroups.

The results in elderly are of great importance, as increasing age is an identified risk factor for severe disease and death. The results from this study are therefore reassuring suggesting a high protective efficacy in subjects ≥65 years of age (95%, 95% CI: 66.8; 99.9). There was no indication of

decreasing efficacy in subjects ≥75 years although the number of cases was small (0 in the vaccine group and 5 in placebo). In addition, the number of subjects >85YOA is very limited (5 subjects) hence the impact of immunosenescence on vaccine efficacy in these very old individuals remain uncertain.

Among participants without prior evidence of SARS-CoV-2 infection before and during vaccination regimen, VE for participants at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, obese with body mass index (BMI) ≥30 kg/m2, chronic pulmonary disease, diabetes mellitus, hypertension) was 95.3%, as compared with 94.7% for those not at risk. VE for participants ≥65 years of age and at risk was 91.7%, as compared with 100% for those ≥65 years of age and not at risk. VE was similar in obese (95.4%) and non-obese (94.8%) participants. The VE by comorbidity status are as follows: cardiovascular (VE 100.0 (-0.8, 100.0)), Chronic pulmonary disease (93.0 (54.1, 99.8)), diabetes (94.7 (66.8, 99.9)), Hypertension (95.4 (82.6, 99.5)).

Severe disease cases were uncommon in the study: 1 case in the vaccine group and 4 cases in the placebo group (one case in the all evaluable population) after 7 days post second vaccination. None of the severe cases were baseline positive for SARS-CoV-2.

In the evaluable efficacy population, subjects without evidence of prior SARS-CoV-2 infection, the estimated VE against severe COVID-19 occurring at least 7 days after dose 2 was 66.4% (95% CI: -124.8%: 96.3%). The posterior probability for the true VE greater than 30% is 74.29% (7 days) and 74.32% (14 days), which did not meet the pre-specified success criterion for this endpoint, therefore no reliable conclusion can be drawn at this stage. While data on severe COVID-19 are limited, the experience with other vaccines (rotavirus and influenza vaccines with known efficacy against mild disease but better efficacy against severe disease) coupled with the high observed vaccine efficacy observed for BNT162b2 on all COVID-19 cases in populations with any comorbidity gives reassurance that the vaccine is likely to prevent severe disease. However, a precise estimate of its protective effect is presently lacking. The final study report may include additional data to the extent that the study is continued in a randomised fashion with a placebo group.

The second primary endpoint -VE in participants with and without prior evidence of SARS-CoV-2 infection- yielded similar results as the one in the population excluding those without evidence of prior infection. However, analysis is largely driven by events in subjects without evidence of prior infection, and therefore does not provide additional information.

It is not possible to conclude on vaccine efficacy in subjects with prior COVID-19, or signs of infection with SARS-CoV2 because only a small number of subjects were found to be seropositive at baseline (approximately 550 in each vaccine and placebo group), and only 2 cases of disease were reported in this subset (1 in each group). Further data may become available as the trial proceeds, but it is unlikely that the study will be able to deliver conclusive evidence for a number of reasons (e.g. it is very likely that the number of subjects seropositive will remain limited, and that there will be a lower incidence of disease in seropositive placebo recipients compared to seronegative placebo recipients due to existing partial protection). The extent of additional protection in seropositive subjects is presently uncertain. Effectiveness studies may give us some information on this regard.

Genome sequencing of the SARS-CoV-2 strains in the BNT162b2 vaccine and placebo groups has not been performed. However, this work is planned by the Applicant.

The primary analysis of efficacy was conducted when the pre-defined number of 164 COVID-19 cases had occurred. This correspond to about 1.5 months of median follow-up time duration after completion of the full vaccination regimen. Therefore, available efficacy data are limited in term of follow-up duration, and the efficacy of the vaccine over longer-time remains unknown. Data are expected to become available post-authorisation.

Immune responses in terms of neutralising antibodies were measured in the phase 1 and 2 part of the study. Overall, the immune responses measured in the phase 1 and 2 part of the pivotal study are consistent and in line with the phase 1 study BNT162-01 results. As expected, both neutralising antibody levels and S-protein binding antibody levels were higher in the youngest age stratum compared to the older age stratum. Serum titres in vaccinated subjects were numerically higher compared to human convalescent sera, up to 1 month after dose 2. There is presently no established correlate of protection.

Very limited results by baseline serostatus were provided, but updated immunogenicity data is expected to become available.

Cell mediated immune responses were demonstrated in the phase 1 part of the study as well as in the other phase 1/2 study BNT162-01, but in a small cohort of subjects only. A clear Th1-polarised response, i.e. IFNγ/IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED.

In total 14 adolescents aged 12-15 years were included in the vaccine group and 13 in the placebo group, and 52 adolescents aged 16-17 years in the vaccine and 55 in the placebo group. Vaccine efficacy could not be estimated for these subjects as no cases of disease were reported. No immune response data are available. However extrapolation of efficacy is possible from young adults because, from an immune system perspective, adolescents do not differ from young adults, thus there are no reasons to believe that the vaccine will not be as efficacious at least in the age subgroup proposed for the current indication (>16 years).

At cut-off date (14-Nov-2020), 120 subjects HIV positive were vaccinated with BNT162b2. Immunogenicity and efficacy data are not available at this time but will be provided post-authorisation.

Additional efficacy data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.5.4. Conclusions on clinical efficacy

Excellent vaccine efficacy (preventing symptomatic COVID-19) was shown in subjects without evidence of prior SARS-Cov2 infection (VE 95.0% (95% CI: 90.3%, 97.6%), which was consistent across relevant subgroups. It is likely that the vaccine also protects against severe COVID-19, though these events were rare in the study, and statistically certain conclusion cannot be drawn. It is presently not known if the vaccine protects against asymptomatic infection, or its impact on viral transmission. The duration of protection is not known.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- The final clinical study report will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA. This will provide long-term data.

Regarding missing data to confirm efficacy in subpopulations that were not studied or whose data are limited please refer to sections 2.7 and 3.3.

2.6. Clinical safety

The candidate vaccine BNT162b2 at 30 µg given twice 21 days apart was assessed a first-in-human (FIH) study in April 2020 in Germany (BNT162-01) and a Phase 1/2/3 study (C4591001) was initiated shortly afterwards in the United States (US). Hence, the safety data base for BNT162b2 constitutes of two Phase 1 studies (BNT162-01 and C4591001) and one Phase 2/3 study still ongoing (C4591001).

The cut-off for safety data included in this assessment is 14 November 2020.

The two Phase 1 trials (BNT162-01 and C4591001) are described in previous sections. Study C4591001 was initially started as a Phase 1/2 study in the USA and was then amended to expand to a global Phase 3 study.

Phase 2/3 of Study C4591001 included subjects that were stratified into two age groups: 18-55 years and >55-85 years. The Phase 3 part however was subsequently amended (6 Sept 2020 protocol amendment) to include subjects from 16 years of age in the younger age group (and then from 12 years of age) and subjects >85 years of age in the older age group.

AEs were collected during the Phase 2/3 study from the signing of the informed consensus document through and including 1 month after Dose 2 (visit no. 3). In addition, in all follow-up visits where blood samples for immunogenicity data are taken, any AEs and SAEs as appropriate occurring up to 48 hours were recorded after each visit. Immunogenicity follow-up is planned to occur during that period with visits 1-month, 6-months, 12-months and 24-months post the first vaccination. AEs are categorized by frequency, maximum severity, seriousness, and relationship to study intervention using SOC and PT according to MedDRA. SAEs are recorded for up to 6 months after Dose 2 (ongoing at the time of this submission). In addition, any potential COVID-19 illness will lead to extra visits followed by convalescent visits. At the cut-off date 14-Nov-20, the longest follow-up time available was 12-13 weeks after Dose 2 (N=780: N=382 BNT162b2 and N=398 placebo).

Overall the study enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up.

The assessment is based on the following safety data (cut-off date 14 Nov 2020):

- Phase 1: i) Study C4591001 (N=72 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=18); ii) Study BNT162-01 (N=60 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=0).
- Phase 2/3 participants with a follow-up ≥ 2 months after Dose 2 (N=19,037) of either BNT162b2 (N=9531) or placebo (N=9536). This subset constitutes the core safety data set in this assessment.
- All enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up. In this population, the total number of subjects 16-17 years were 283 (N=138 BNT162b; N=145 placebo) and 100 participants were 12 to 15 years of age (N=100; 49 in the BNT162b2 group and 51 in the placebo group).
- Phase 2/3 participants (N=37,706) randomised before 9 October 2020 who received BNT162b2 (N=18,860) or placebo (N=18,846). These subjects had a median follow-up time of 2 months after Dose 2 (at least 1 month after dose 2). Among these, 1,148 subjects had a positive SARS-CoV-2 baseline status (vaccinated N=558; placebo N=590).
- Reactogenicity was evaluated based on a subset of subjects in the Phase 2/3 study, i.e. 8,183 (N=4,093 BNT162b2; N=4,090 placebo), who reported on local reactions, systemic events,

and antipyretic/pain medication usage for 7 days after each dose by using an e-diary. Eight subjects aged 16-17 years were included in this subset (BNT162b2 N=5; placebo N=3).

2.6.1. Patient exposure

Distribution and Exposure were presented for the population with median follow up of 2 months and for the whole population. Of the 37,796 subjects in the group with median follow up of 2 months who were randomized in the study before 9 October 2020, 90 participants (0.2%) were excluded from the safety population (89 did not receive study intervention and 1 did not provide informed consent).

		BNT162b2 N = 18904	**Placebo N = 18892**
		N (%)	**N (%)**
Median follow up 2 months (at least one month after dose 2)	Randomized	18904 (100%)	18892 (100%)
	Vaccinated with Dose 1	18858 (99.8%)	18849 (99.8%)
	Vaccinated with Dose 2	18553 (98.1)	18534 (98.1%)
HIV positive		59	61
Follow up ≥ 2months after dose 2		9531 (50.5%)	9536 (50.6%)
Follow up ≥ 10 to < 12 weeks after dose 2		2853 (15.1%)	2809 (14.9%)
Follow up ≥ 12 to < 14 weeks after dose 2		382 (2.0%)	398 (2.1%)

For Dose 1, three participants randomized to the placebo group received BNT162b2, and two participants randomized to the BNT162b2 group received placebo. For Dose 2, four participants randomized to the placebo group received BNT162b2, and five participants randomized to the BNT162b2 group received placebo.

The majority of participants received Dose 2 between 19 to 23 days after Dose 1 in the BNT162b2 (93.1%) and placebo (92.9%) groups.

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. Note that HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition but did not have safety data available to contribute to the safety analyses at the time of the data cut-off.

In total 1145 individuals of the safety population were SARS-CoV-2 seropositive at baseline.

A high exposure rate of 99.8% to the first dose was reached in both vaccine and control arm and a small number of individuals were withdrawn after the first dose, leading to a high rate of exposure to the second dose in both study arms (98.2% and 98.1%). Reasons for withdrawals (1.0% and 1.4%, respectively) were in most cases withdrawals by the participant, or loss to follow-up.

There were no clinically meaningful differences in the safety population by age group, baseline SARS-CoV-2 status, ethnicity, race, or sex.

Table 14 Safety Population, by Baseline SARS-CoV-2 Status – ~38000 Subjects for Phase 2/3 Analysis

		Vaccine Group (as Administered)		
Baseline SARS-CoV-2 Status		BNT162b2 (30 µg) n[a]	Placebo n[a]	Total n[a] (%)
Positive	Randomized[b]			1148
	Vaccinated	557	588	1145 (99.7)
	Safety population	557	588	1145 (99.7)
	HIV-positive	12	8	20 (1.7)
	Excluded from safety population			3 (0.3)
	Reason for exclusion			
	Subject did not receive study vaccine			3 (0.3)
Negative	Randomized[b]			35764
	Vaccinated	17885	17858	35743 (99.9)
	Safety population	17884	17858	35742 (99.9)
	HIV-positive	43	50	93 (0.3)
	Excluded from safety population			22 (0.1)
	Reason for exclusion			
	Subject did not receive study vaccine			21 (0.1)
	Did not provide informed consent			1 (0.0)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. n = Number of subjects with the specified characteristic, or the total sample.
b. This value is the denominator for the percentage calculations.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 18NOV2020 (07:27)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adsl s003 saf pop bs p3

The disposition, exposure and withdrawal profile of the whole study population was comparable to the group that was randomised before 9 October 2020 with median follow up of 2 months.

Among the 37,706 subjects with a median follow-up of 2 months, 50.6% had ≥2 months duration of follow-up after Dose 2 and 91.6% had a duration of follow-up time of ≥1 month after Dose 2. Around 3000 individuals have already a follow of at least 10 weeks after dose 2. Updates, including additional safety data as well as assessment of the differences in safety profile in the longer follow-up compared to the initial safety dataset, if any, shall be provided when more mature data will be available.

Six-months post Dose 2 follow-up data from the first ~6000 subjects are expected by the end of February 2021 and this will allow a relevant discussion on the safety profile versus the initial dataset.

Based on the population with a median follow up of 2 months, demographic characteristics are considered well balanced between vaccine and placebo arm. Most included subjects were white (83%), with a median age of 52 years. A balanced distribution is seen regarding gender (51% male, 49%

female). The younger and older age groups were 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Of note, 35% of individuals were obese in both study arms. Across both treatment groups, 20.7% had any comorbidity.

The number of subjects with any Charlson co-morbidity diagnoses was balanced in both study arms (20%). Most prevalent were the diagnoses diabetes mellitus (7.8%) and COPD (7.8%) followed by subjects showing any type of malignant disease (3.9% in vaccine and 3.5% in placebo group). Other diagnoses were abundant with ≤ 1% in both study arms (population with a median follow up of 2 months). In the population with a follow-up ≥2 months, Charlson co-morbidity diagnoses was similar.

The demographic distribution was somewhat different when comparing seropositive and seronegative individuals, observing a median age of 43 years in seropositive and of 52 years in seronegative individuals. Furthermore, the seropositive group covered a higher proportion of obese individuals (42.2% versus 34.7%). Demographic characteristics in the whole population were comparable to those seen in the population with a median follow up time of 2 months.

2.6.2. Reactogenicity

Reactogenicity was evaluated in a subset of the Phase 2/3 study of 8,183 subjects (BNT162b2 n=4093; placebo n=4090) from both age groups (16 to 55 and >55 years of age) that received BNT162b2 or vaccine according to the proposed dosing regimen. Of note, the number of subjects aged 16-17 years included in this subset was limited (n=8; BNT162b2 n=5; placebo n=3). After each dose, the subjects reported any local reactions, systemic events, including antipyretic/pain medication usage for 7 days, by using an e-diary (cut-off date 14 Nov 20).

Local reactions

The most commonly reported local reaction among the subject that received BNT162b2 was pain at the injection site, which occurred slightly more common among subjects 16-55 years (N=2291 [83.1%] post Dose 1; N=2098 [77.8%] post Dose 2) compared to those >55 years of age (N=1802 [71.1%] post Dose 1; N=1660 [66.1%] post Dose 2). In the placebo group, pain at the injection site after Doses 1 and 2 was reported at a lower frequency (16-55 [14.0% and 11.7%]; >55 [9.3% vs 7.7%]).

There was no difference in frequency of redness and swelling at injection site after the two doses of BNT162b2. Redness occurred in about 5-7% in both age groups (16-55 [4.5% after Dose 1, 5.9% after Dose 2]; >55 [4.7% after Dose 1, 7.2% after Dose 2]). Swelling was reported also in about 5-7% of the subjects in both age groups (16-55 [5.8% after Dose 1, 6.3% after Dose 2]; >55 [6.5% after Dose 1, 7.5% after Dose 2]). In the placebo group, redness and swelling were reported infrequently in both age groups (≤1.2%).

Overall, the majority of local reactions were mild or moderate in severity, no Grade 4 reactions were reported. Severe local reactions (≤0.7%) were reported infrequently in the BNT162b2 group after either dose and was more commonly reported in the younger group. Across age groups, local reactions for the BNT162b2 group after either dose had a median onset between 1-3 days (Day 1 was the day of vaccination), with a median duration of 1-2 days.

No clinically meaningful differences in local reactions were observed by baseline SARS-CoV-2 status subgroups. However, since the baseline SARS-CoV-2 positive subgroup included very few participants (vaccinated n=154; placebo n=164), these results should be interpreted with caution.

Systemic reactions

Table 15 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group 16-55 Years – Reactogenicity Subset for Phase 2/3 Analysis– Safety Population

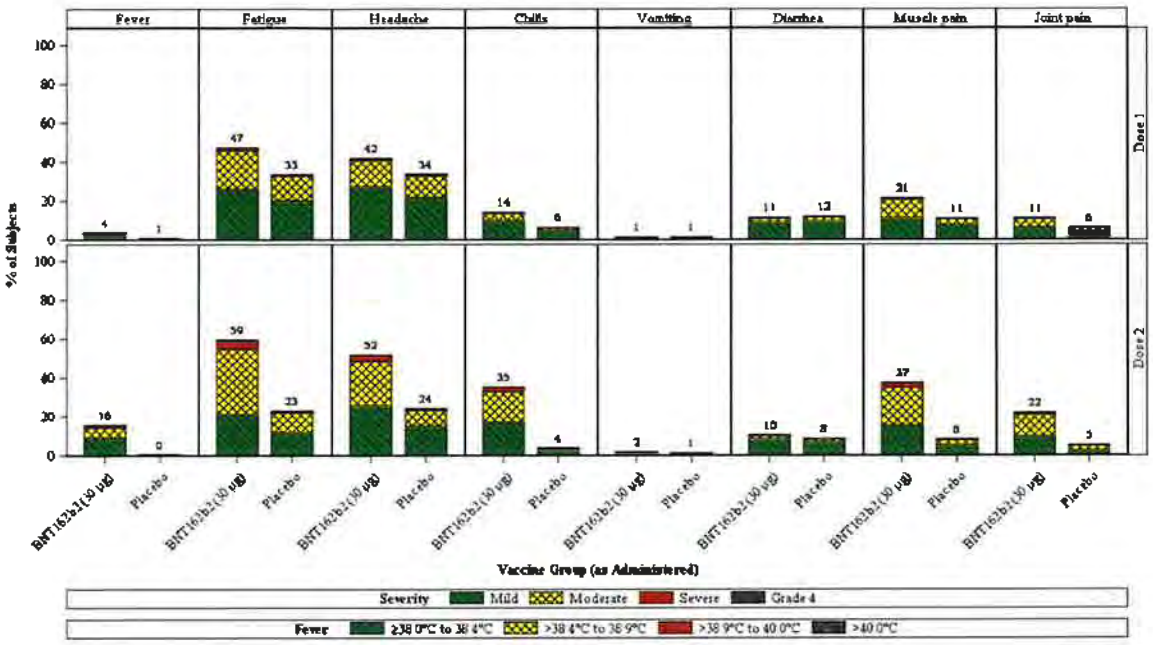
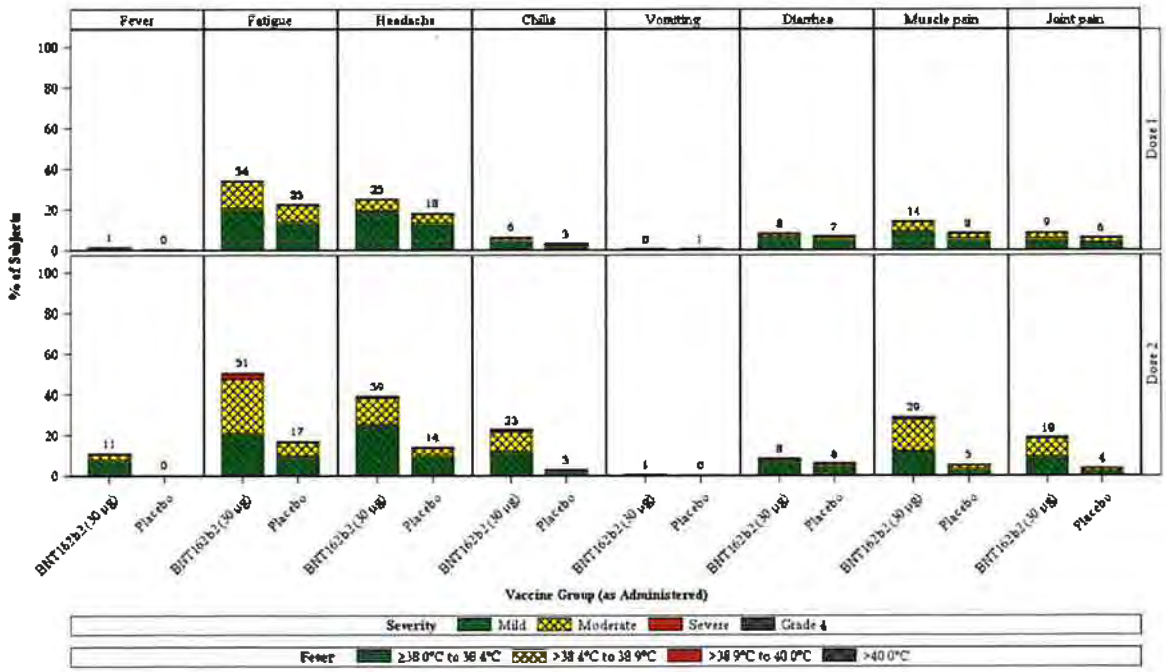


Table 16 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group >55 Years – Reactogenicity Subset for Phase 2/3 Analysis–Safety Population



Systemic events were generally reported more frequently in the BNT162b2 group than in the placebo group, for both age groups and doses. Across age groups, median onset day for all systemic events after either dose of BNT162b2 was 2-3 days, with a median duration of 1 day.

Systemic events were generally increased in frequency and severity in the younger age group compared with the older age group, with frequencies and severity increasing with number of doses (Dose 1 *vs* Dose 2). Vomiting and diarrhoea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhoea reported at similar incidences after each dose. Systemic events in the younger group compared with the older group, with frequencies increasing with number of doses (Dose 1 vs Dose 2), were: fatigue, headache, muscle pain, chills, joint pain and, fever.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.9% vs 37.7%) than in the younger age group (27.8% vs 45.0%). Of note, medication use increased in both age groups after Dose 2 as compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (ranging from 9.8% to 22.0%).

No clinically meaningful differences in systemic reactions were observed by baseline SARS-CoV-2 status subgroups, however as mentioned data in baseline SARS-CoV-2 positive subjects are limited.

Overall, the reported reactogenicity is in line with what can be expected from any vaccine. The local and systemic reactions were transient and of short duration, the majority were mild to moderate at intensity and the reactions were milder among older subjects (>55 years).

2.6.3. Adverse events

In the subset of participants randomised before 9 October 2020 with Median 2 Months of Follow-Up After Dose 2 (N= 37,586; from Dose 1 to 1 month after dose 2) and the subset of participants with at least 2 Months of Follow-Up After Dose 2 (N=19,067; from dose 1 to data cut off 14 November 2020), the numbers of overall participants who reported at least 1 AE and at least 1 related AE were higher in the BNT162b2 group as compared with the placebo group. This trend continued to be seen through the data cut-off date for all enrolled participants (N=43,252; from dose 1 to data cut-off 14 November 2020). Overall, AEs reported from Dose 1 to 7 days after Dose 1 and from Dose 2 to 7 days after Dose 2 were largely attributable to reactogenicity events (see above). This observation provides a reasonable explanation for the greater rates of AEs observed overall in the BNT162b2 group (26.7%) compared with the placebo group (12.2%).

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn because of AEs.

Table 17 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to date cutoff date (14 Nov 2020) – Subjects with 2 months follow-up time after dose 2 for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=9531)	Placebo (N[a]=9536)	Total (N[a]=19067)
Adverse Event	n[b] (%)	n[b] (%)	n[b] (%)
Any event	2044 (21.4)	1197 (12.6)	3241 (17.0)
Related[c]	1297 (13.6)	343 (3.6)	1640 (8.6)
Severe	105 (1.1)	69 (0.7)	174 (0.9)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any serious adverse event	57 (0.6)	53 (0.6)	110 (0.6)
Related[c]	2 (0.0)	0	2 (0.0)
Severe	32 (0.3)	33 (0.3)	65 (0.3)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any adverse event leading to withdrawal	1 (0.0)	0	1 (0.0)
Related[c]	0	0	0
Severe	0	0	0
Life-threatening	1 (0.0)	0	1 (0.0)
Death	1 (0.0)	0	1 (0.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16.28)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_all_2mpd2_p23_saf

Overall, in participants with 2 months follow up after dose 2, 21.4% / 12.6% (vaccine/placebo) and 13.6%/3.6% experienced at least 1 AE and 1 related AE, respectively. It is noted that the frequency of AEs and related AEs is lower compared to individuals with a median follow up of 2 months (27%/12.5% and 20.8%/5.1%).

The frequency of individuals experiencing AEs were slightly higher in the younger compared to older individuals (29.3% and 23.8% vaccine arm; 13.2% and 11.7% placebo arm). SAEs and deaths were however balanced in both study arms in both age groups.

The frequency of immediate AEs after dose 1 was low in participants with median 2 months of follow-up after Dose 2 (0.4%) and the whole population (≤0.5%), belonging mostly to the SOC general disorders and administration site conditions, primarily injection site reactions. No participant reported an immediate allergic reaction to vaccine.

Severe AEs, SAEs, AEs leading to discontinuation, and deaths were reported by ≤1.1%, 0.6%, 0.0%, and 0.0%, i.e. low and equally distributed in both study arms. No differences vs. the whole population were seen according to age groups.

The rate of AEs and related AEs was slightly higher in the SARS-CoV-2 negative group compared to SARS-CoV-2-positive individuals. Stratification according to serostatus in the safety group median follow up 2 months reveals overall very low numbers of severe AEs, SAEs and deaths.

Table 18 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to 1 Month after Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subject for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Positive

	Vaccine Group (as Administered)	
Adverse Event	BNT162b2 (30 µg) (N[a]=545) n[b] (%)	Placebo (N[a]=580) n[b] (%)
Any event	120 (22.0)	57 (9.8)
Related[c]	90 (16.5)	26 (4.5)
Severe	8 (1.5)	2 (0.3)
Life-threatening	2 (0.4)	0
Any serious adverse event	4 (0.7)	1 (0.2)
Related[c]	0	0
Severe	2 (0.4)	1 (0.2)
Life-threatening	2 (0.4)	0
Any adverse event leading to withdrawal	2 (0.4)	1 (0.2)
Related[c]	0	0
Severe	0	0
Life-threatening	1 (0.2)	0
Death	1 (0.2)	0

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis

Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.

c. Assessed by the investigator as related to investigational product.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2 unblinded/C4591001 IA P3 2MPD2/adae s091 pd2 bs p3 saf

Table 19 Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Negative

	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N[a]=17841)	Placebo (N[a]=17808)
Adverse Event	n[b] (%)	n[b] (%)
Any event	4837 (27.1)	2253 (12.7)
Related[c]	3742 (21.0)	911 (5.1)
Severe	205 (1.1)	105 (0.6)
Life-threatening	16 (0.1)	20 (0.1)
Any serious adverse event	97 (0.5)	80 (0.4)
Related[c]	3 (0.0)	0
Severe	54 (0.3)	47 (0.3)
Life-threatening	16 (0.1)	19 (0.1)
Any adverse event leading to withdrawal	31 (0.2)	24 (0.1)
Related[c]	13 (0.1)	7 (0.0)
Severe	13 (0.1)	7 (0.0)
Life-threatening	1 (0.0)	4 (0.0)
Death	0	2 (0.0)

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_pd2_bs_p3_saf

There were 19,067 participants with at least 2 months follow-up time after Dose 2, and similar to the 37,586 participants randomised before 9 October 2020 with a median of 2 months of safety follow up after Dose 2, most AEs reported after Dose 1 up to the safety data cut-off date were reactogenicity, in SOCs of:

- general disorders and administration site conditions (11.9% BNT162b2 vs 2.9% placebo)
- musculoskeletal and connective tissue disorders (5.5% BNT162b2 vs 2.1% placebo)
- nervous system disorders (4.2% BNT162b2 vs 2.1% placebo)
- infections and infestations (1.9% BNT162b2 vs 1.6% placebo)
- gastrointestinal disorders (2.6% BNT162b2 vs 1.8% placebo).

In the younger versus older BNT162b2 age groups, AE SOCs were:

- general disorders and administration site conditions (13.1% vs 10.4%)
- musculoskeletal and connective tissue disorders (6.0% vs 4.9%)

- nervous system disorders (4.8% vs 3.5%)
- infections and infestations (1.9% vs 1.9%)
- gastrointestinal disorders (2.7% vs 2.5%)

Most often occurring events by PT comprised vaccine typical reactions such as injection site pain, fever, fatigue as well as myalgia and arthralgia. Lymphadenopathy and nausea occurred respectively in 0.4% and 0.6% more cases in the vaccine compared to placebo arm.

Related AEs belonged overall to the same SOCs as described above, i.e. general disorders and administration site conditions (3426 cases, 20.8%), musculoskeletal reactions (1148 cases, 6.1%), and nervous system disorders (979 cases, 5.2%) and occurred overall more often in the vaccine than in the placebo arm (median follow up 2 months). Severe AEs occurred more often in the vaccine arm (1.2% vs. 0.6%) in the subset with a median follow up time of 2 months, reflecting a similar SOC pattern.

The following specific observations are made based on PTs:

Numerical disbalances are observed for several hypersensitivity terms ((drug)hypersensitivity/ immunisation events; 5/3 cases ≥ 2 months group, 13/6 cases whole population, 6/1 cases deemed related in the whole population, 4 cases deemed severe (whole population), in the SOC immune system disorders).

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study, 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and, among those, two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. The participant who received BNT162b2 had a history of allergy to tree pollen. This participant reported Drug hypersensitivity and Urticaria on the day of Dose 1. Both AEs were of moderate severity and lasted one day. The participant did not receive Dose 2 of the vaccine. The participant who received placebo had an allergy to shellfish and iodine. This participant reported Allergy to vaccine and Pharyngeal swelling 1 day after Dose 1. Both events were of moderate severity and lasted 13 days and 10 days, respectively. This participant did not receive Dose 2 of study intervention.

In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine.

Four cases of facial paralysis were observed in the vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole population). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days had no previous history of Bell´s palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole population)). However, none of the cases considered related to study drug treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm, which where however balanced in frequency between vaccine and placebo arm.

An imbalance in PT connected to sleep disturbances was noted in the whole population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus the placebo arm).

A slight imbalance of hyperhidrosis/night sweats was noted in the whole population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole population).

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole population).

Stratification according to age did not reveal meaningful differences in the types of AEs.

A stratification according to serostatus was performed in individuals with a follow up of at least one month (median FUP 2 months) and ≥2 months. Most abundant SOCs are similar to the SOCs identified in the general population with ≥2 months follow-up. No additional safety concerns are detected when stratifying according to serostatus.

2.6.4. Serious adverse event/deaths/other significant events

SAEs

This section presents the SAEs reported up to the data cut-off (14-nov-20).

Among the 19,067 subjects (BNT162b2 n=9531; placebo n= 9536) with ≥2 months of follow-up post Dose 2, small percentages of subjects in the 30 µg BNT162b2 group (56 [0.6%]) and the placebo group (53 [0.6%]) reported any SAEs. Subjects in both the BNT162b2 group and placebo group, respectively, reported SAEs at similar rates for the observed SOCs. A similar frequency was observed for the entire study population and no clinically meaningful differences in SAEs were observed by age, baseline SARS-CoV-2 status, ethnicity, race or sex subgroups.

Among all included subjects (BNT162b2 n=21720; placebo n=21728) three SAEs were reported in the SOC immune system disorders. One SAE of anaphylactic reaction (related to bee sting) and one drug hypersensitivity (related to treatment with doxycycline) was reported in the BNT162b2 group. In addition, one SAE of anaphylactic shock (related to an ant bite) was reported in the placebo group.

In the subset of individuals aged 16-17 years old, one SAE (facial bone fracture) was reported.

After the cut-off date and up to 5-Dec-20, additional 22 SAEs have been reported (blinded data).

SAEs related to study intervention

Up to the cut-off date, four of the SAEs in the BNT162b2 group and none in the placebo group were assessed by the investigator as related to study intervention. One event of lymphadenopathy and one event of shoulder injury due to incorrected administration were considered related to BNT162b2.

It is not agreed that the event of ventricular arrythmia and the event of pain in the lower back/extremities/and radicular paraesthesia have been convincingly demonstrated to be related to study intervention, since the subjects had underlying conditions that could have caused the two SAEs, there is little biological plausibility, and the overall numbers of reported events do not allow for a causal inference.

Death

Six events of death (2 in the BNT162b2 group and 4 in the placebo group) were reported in the Phase 2/3 study up to the cut-off date of 14-Nov-20. None of the deaths were considered related to study intervention, which is agreed since other pre-existing diseases were more likely to have caused death than the vaccine. After the cut-off date and up to 5-Dec-20, one additional event of death due to aortic rupture were reported (data blinded).

2.6.5. Laboratory findings

Laboratory results are available for the two Phase 1 studies, but not for the Phase 2/3 trials. This is considered acceptable. Except for minor transient decrease in lymphocyte count observed for some of the subjects, no abnormal lab results were reported from the Phase 1 studies.

2.6.6. Safety in special populations

No clinically meaningful differences in AEs were observed by age, country (mostly Argentina, Brazil, USA), ethnicity (Hispanic/Latino, Non-Hispanic/Non-Latino), gender and race (With, Black or African American, all other races) subgroups.

Pregnancy

At the time of the data cut-off in the Phase 2/3 study (14 Nov 2020), a total of 23 participants had reported pregnancies in the safety database, including 9 participants who withdrew from the vaccination period of the study due to pregnancy. These participants are being followed for pregnancy outcomes. Thus, data on pregnancy are very limited at this stage.

Elderly

The Phase 2/3 study included >40% of subjects >55 years of age. In general, reactogenicity and AE rate were slightly lower in older compared to younger individuals (stratified according to median age 55 years). No differences in AE frequency were detected among subjects >70 years of age compared to the older age group >55 year. Thus, no specific safety concern is anticipated for the elderly.

Immunocompromised individuals

Per protocol, participants with chronic stable HIV infection were defined as HIV disease with a documented viral load <50 copies/mL and CD4 count >200 cells/mm3 within 6 months before enrolment, and on stable antiretroviral therapy for at least 6 months. Stratification by CD4 count, efficacy and immunogenicity data are not available at this time but will be provided post-authorisation.

Safety data are available for 196 participants with stable HIV infection. The most frequent AEs in the BNT162b2 group were reported in the General Disorders and Administrative Site Conditions SOC including injection site pain, pyrexia, chills, fatigue, injection site erythema, and injection site swelling.

Assessment of paediatric data on clinical safety

Paediatric individuals age 16 to 17 years of age are included in the Phase 2/3 study that constitutes the safety database in this assessment. The population of subjects aged 16-17 years are limited (n=283). No additional or new AEs were observed compared to adults).

There were no participants in the 16 to 17 years of age group with ≥2 months of safety follow-up at the time of the data cut-off (14 November 2020). The longest duration of follow-up in this age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study.

The reactogenicity subset of ~8000 participants (n=4093 BNT162b2; n=4090 placebo) contributing e-diary data included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) include reactogenicity data (local reactions and systemic events) collected via e-diary up to the safety cut-off date of 14 November 2020. The reported adverse events were primarily reactogenicity events with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

In the reactogenicity subset including individuals aged 12-15 years and the 8 individuals aged 16-17 years, the most frequently reported systemic reaction in both treatment groups were fatigue (59.2% in the BNT162b2 group and 25.5% in the placebo group), followed by headache (57.1% BNT162b2, 43.1% placebo). Fever ≥38°C was reported for 26.5% more participants who received BNT162b2 over placebo; two (4.1%) of these participants reported severe fever (>38.9°C to 40.0°C).

2.6.7. Safety related to drug-drug interactions and other interactions

Interaction studies with other vaccines have not been performed, which is acceptable given the need to use the vaccine in an emergency situation. The Applicant will conduct a study post-authorisation as indicated in the RMP (see section 2.7).

2.6.8. Discontinuation due to adverse events

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn from the study because of AEs. The results were similar to the AEs leading to withdrawal in the group randomised before 9 October 2020 with median follow up of 2 months. Among 19,067 participants with at least 2 months of follow-up time post Dose 2, 1 participant in the BNT162b2 group and no participants in the placebo group had an AE leading to withdrawal from the study.

No participants in the 16 to 17 years of age group experienced an AE leading to withdrawal. Among all 43,448 participants, no clinically meaningful differences in AEs leading to withdrawal were observed by age or other subgroups.

2.6.9. Post marketing experience

Post-marketing data are not yet available as the vaccine has not been approved in any country at the time of the data cut-off (14-Nov-20). After the cut-off date, it is noted that several countries have recently authorised the vaccine for emergency use (e.g. UK, Canada, US). Two cases of anaphylactoid reaction out of 138,000 persons vaccinated have been reported in individuals carrying Epipen after initiation of vaccination in one country, which resolved with standard therapy. One case of anaphylaxis was reported in another country (unknown denominator) in a subject without known history of

allergies, which required ICU and was then resolved. Post-marketing safety data are expected with the next monthly summary safety report.

2.6.10. Discussion on clinical safety

The safety database for BNT162b2 constitutes of two Phase 1 studies (BNT162-01[3] and C4591001[4]) and one Phase 2/3 study (C4591001) which is still ongoing. The cut-off date for safety data included in this assessment is 14 November 2020.

Up to the cut-off date ~44,000 subjects had been recruited and received at least one dose of either BNT162b2 (n=21,720) or placebo (n=21,728). The core safety database of this assessment constitutes of ~19,000 participants who have been followed ≥2 months after the 2nd dose of BNT162b2 (n=9531) or placebo (n=9536). The Applicant has also presented data from a subset of ~38,000 subjects randomised before 9 October 2020 with a median follow-up period of 2 months after Dose 2 of BNT162b2 (n=18,860) or placebo (n=18,846).

Demographic characteristics are considered well balanced between vaccine and placebo arm (median follow up 2 months). Subjects were mostly white (83%) and had a median age of 52 years. The younger and older age groups included 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Gender was balanced (51% male). Of note, 35% of individuals were obese in study arms. The demographic distribution was different between seropositive and seronegative individuals, with a median age of 43 years in seropositive and of 52 years in seronegative subjects. Furthermore, the seropositive group covered a higher rate of obese individuals (42.2% versus 34.7%). Demographic characteristics in all participants were roughly comparable to those with median follow up of 2 months.

Charlson co-morbidity diagnoses were balanced in both study arms (20%). Most prevalent co-morbidities were diabetes (7.8%), COPD (7.8%) and malignant disease (3.9% in the vaccine arm and 3.5% in the placebo arm). Other diagnoses accounted for ≤ 1% of subjects in both study arms (median follow up of 2 months).

In the Phase 2/3 study reactogenicity was evaluated in a subset of 8,183 subjects who received BNT162b2 (n=4093) or placebo (n=4090) according to the proposed dosing regimen. The number of subjects aged 16-17 years included in the reactogenicity subset was small (n=8; BNT162b2 n=5; placebo n=3). After each dose, all subjects were asked to report any local reactions, systemic events, and antipyretic/pain medication usage for 7 days, by using an e-diary.

Pain at the injection site was the most common local reaction reported in the vaccine group, slightly more frequently reported among subjects 16-55 years (~80%) compared to >55 years (~70%). In the placebo group 8-14% reported pain at injection site. In the vaccine group redness and swelling were overall reported at a frequency of 5-7% in both age groups (vs. placebo 0-1%). Use of antipyretic/pain medication was more common after Dose 2 than after Dose 1 in both age groups, and overall slightly lower among subjects >55 years regardless of the dose (younger group: 28% after dose 1 vs 45% after dose 2; older group: 20% vs 38%). The use of antipyretic/pain medication was less common in the placebo group (younger group: 34% after dose 1 vs 23% after dose 2; older group: 23% vs 18%).

Among the systemic reactions, headache and fatigue were the most common events, and the frequency was higher after Dose 2 compared to Dose 1 (16-55 YOA [47% vs 59%]; >55 YOA [34% vs 51%]). Fever also occurred more frequently after Dose 2 (16-55 YOA [4% vs 16%]; >55 YOA [1% vs

[3] Phase I: End of study 28 days after Dose 2.
[4] Phase I: participants enrolled in Phase1 in groups that do not proceed to Phase 2/3 (i.e. other doses than 30 µg) may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

11%]). None of the subjects >55 YOA in the placebo group reported events of fever and 1% of the subjects aged 16-55 years reported fever after the first dose.

Overall, the local and systemic reactions were transient and of short duration (resolved within few days after vaccination), the majority were of mild to moderate intensity, and milder and of slightly lower frequency among older subjects (>55 years of age).

In the group of 19,067 participants with 2 months follow up after dose 2, 21.4% and 12.6% (vaccine vs placebo) of the subjects reported at least one AE. 13.6%/3.6% reported at least 1 related AE. Rates were lower compared to the whole enrolled trial population (26.7% (vaccine) and 12.2% (placebo)).

AEs in subjects with a follow up of at least 2 months belonged most often to the SOCs "General disorders and administration site conditions" (11.9% vs 2.9%), "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%), occurring more often in the vaccine than in the placebo arm. PTs comprised most often vaccine typical reactions, i.e. injection site pain, redness and swelling, fever, chills, fatigue, headache as well as myalgia and arthralgia and malaise. Nausea also occurred more often in the vaccine arm (79 cases, i.e. 0.8%, in vaccine vs. 21 cases, i.e. 0.2%, in placebo). Lymphadenopathy was seen in 0.4% subjects in the vaccine arm (38 cases) vs. 0% in the placebo arm (3 cases).

Severe AEs were reported by a small number of subjects (≤1.1%) and equally distributed between the study arms. No differences were seen between age groups. Frequencies are comparable in the whole enrolled trial population and when stratifying according to serostatus.

Numerical imbalances are observed for several hypersensitivity/immunisation reaction preferred terms (5/3 cases in the ≥ 2 months follow up subset, 13/6 cases in the whole enrolled trial population subset, 4 cases deemed severe (whole enrolled trial population), in the SOC immune system disorders).

Lymphadenopathy, nausea, and hypersensitivity are reported more often with the vaccine arm. For these items there is a reasonable possibility of a causal relation to vaccination and they are as such included in the SmPC section 4.8.

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and among those two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. There are incoming reports of anaphylactoid reactions from ongoing vaccination campaigns. A warning is included in the SmPC addressing the need of adequate emergency material in place at the vaccination site, which is common practice with any vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

Four cases of peripheral facial paralysis were observed in vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole enrolled trial population, however the case of paresis was not considered for this calculation). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days

had no previous history of Bell´s palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician. Taken together, this was considered to indicate there is a reasonable possibility of a causal relation to the vaccine, and to justify inclusion of peripheral facial paralysis (Bell´s palsy) in the SmPC 4.8 with a frequency as 'rare'.

An imbalance in PT connected to sleep disturbances was noted in the whole enrolled trial population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus in the placebo arm). The occurrence of insomnia may plausibly be due to e.g. local/systemic reactogenicity that may occur after vaccination. The CHMP agreed to include insomnia in section 4.8. of the SmPC.

A slight imbalance of hyperhidrosis/night sweats was noted in the whole enrolled trial population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole enrolled trial population). These events may be plausibly associated to the injection of BNT162b2 and should therefore be included in the SmPC section 4.8.

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole enrolled trial population). In addition to pain at injection site, which was commonly reported, pain in the extremity is also considered plausibly related to the vaccination and should therefore be included in the SmPC section 4.8.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole enrolled trial population)), however these are considered not related to study treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm. These were numerically balanced in frequency between vaccine and placebo arm. Autoimmune events will be monitored post-authorisation as described in the RMP.

SAEs occurred at a low frequency in both BNT162b2 and the placebo group (0.6%, 56 cases in vaccine vs. 53 cases in placebo) in subjects with ≥2 months of follow-up post Dose 2, and a similar frequency was observed in the total study population. One SAE of lymphadenopathy and one SAE of shoulder injury were considered related to study intervention. No cases of related SAEs were reported in the adolescent group (only one case of facial bone fracture). Six events of death (2 in the BNT162b2 group and 4 in the placebo group) have been reported in the entire study population, all deemed unrelated to the vaccine.

The rate of subjects discontinuing participation in the study due to AEs was low in both study arms (0.2%/0.1%).

The subgroup of seropositive subjects is limited in size (n=545 BNT162b2; n=580 Placebo). A stratification according to serostatus for AE investigation was specifically performed in individuals with a follow up of at least one month (median Follow up 2 months) and ≥2 months. Most reported SOCs are similar to those identified in the ≥ 2 months population. AE rate in seropositive individuals was lower (22%) compared to seronegative individuals (27%) and no specific safety concern is detected in this subpopulation.

23 participants reported pregnancies in the safety database, nine of them were withdrawn from the study due to the pregnancy status. These participants will be followed up for pregnancy outcomes.

The Applicant has not provided a specific analysis of elderly individuals > 70 years included in the development program. In general, reactogenicity and AE rate were slightly lower in older compared to

younger individuals (stratified according to median age 55 years). Thus, no specific safety concern is anticipated for the elderly.

Data on immunocompromised individuals are limited, which was raised as missing information in the RMP and will be further followed up. 196 participants with stable HIV infection were included in the trial and reported AEs that were mostly reactogenicity-related with no SAEs. No specific safety concern is detected in this subpopulation.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics as applicable.

Assessment of paediatric data on clinical safety

The longest duration of follow-up in the 16-17 years of age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study, albeit is numerically lower (11.6%/4.8%, vaccine/placebo).

The reactogenicity subset included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) show reactogenicity events (local reactions and systemic events) with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

Overall, the safety of BNT162b2 in individuals 16-17 years of age is extrapolated from young adults in general.

Additional safety data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.6.11. Conclusions on the clinical safety

The safety evaluation is based on one ongoing Phase 2/3 study that at the time of data cut-off (14-Nov-20) included 43,448 subjects who received either two doses of BNT162b2 30µg (n=21 720) or placebo (n=21 728). Overall, the reported reactogenicity profile are in line with any authorised vaccine. In addition, the frequency of reported AEs and SAEs were low. The emerging safety profile is presently considered favourable. Long term safety data, interaction with other vaccines, data on use in pregnancy and other subgroups (e.g. frail subjects, or subjects with pre-existing autoimmune diseases) are missing at this stage.

The lack of long-term follow up renders the data provided non-comprehensive. Therefore, the delivery of the final C4951001 study report, including a 2-year follow up of the studied population, is classified as a specific obligation in the context of a conditional marketing authorisation.

The plan for the generation of further safety data post authorisation is described in the section below.

2.7. Risk Management Plan

Safety Specification

Summary of safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use during pregnancy and while breast feeding Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long term safety data

Risks considered important for inclusion of the summary of safety concerns

The review of available safety data, including post-marketing data emerging from use in the UK and US, the experience with biological products and other vaccines leads to the conclusion that anaphylaxis is an important identified risk for Comirnaty. This safety concern will be followed up via routine pharmacovigilance activities and in the planned and ongoing safety studies and reported in the monthly summary safety reports and PSURs.

Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease) should be taken into account. The Applicant has included VAED/VAERD as an important potential risk and will further investigate it in the ongoing pivotal study and a post-authorisation safety study.

Missing information

Since pregnant and breast-feeding women were excluded from the study, no information is available for those populations. It is agreed to include use during pregnancy and while breastfeeding as missing information in the RMP.

At the data cut-off of 14 Nov-20, 10-14 weeks safety data are available. Thus, long-term safety is included as missing information and will be characterised as part of the continuation of the pivotal clinical trial and the PASS.

Interaction with other vaccines, has not been evaluated in clinical trials and may be of interest to prescribers. As elderly individuals will be one target group for vaccination, and they often may need vaccination with other vaccines such as influenza and pneumococcus vaccines, further data is

requested. The Applicant commits to conduct a study of the co-administration of Comirnaty with inactivated quadrivalent influenza vaccine.

Data from use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders), is limited, and it is desirable to gather further data in these groups. Therefore, use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) has been included as missing information in the RMP. Furthermore, information is limited on the use in patients with autoimmune or inflammatory disorders, as well as in immunocompromised patients. Thus, these groups are also included as missing information. Such missing information will be collected in the post-authorisation safety studies.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine, and it is considered acceptable to not include those events in the list of safety specifications.

Pharmacovigilance Plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond the receipt and review and submission of ADRs include:

- A **web-based AE reporting portal** will be available for vaccine providers (*e.g.* pharmacists, nurses, physicians and others who administer vaccines) and recipients, to assist with anticipated high volume of reports (based on expectations of a large target population for vaccination). The portal will capture key adverse event data in the initial interaction and will provide automated intake into the Pfizer safety database via E2B for safety review.
- **Signal detection activities** for the lifecycle of vaccines consist of individual AE assessment at case receipt, regular aggregate review of cases for trends and statistically disproportionately reported product-adverse event pairs. Aggregated and statistical reviews of data are conducted utilizing Pfizer's software interactive tools. Safety signal evaluation requires the collection, analysis and assessment of information to evaluate potential causal associations between an event and the product and includes subsequent qualitative or quantitative characterization of the relevant safety risk to determine appropriate continued pharmacovigilance and risk mitigation actions. Signal detection activities for the COVID-19 mRNA vaccine, will occur on a weekly basis. In addition, observed versus expected analyses will be conducted as appropriate as part of routine signal management activity.
- Routine signal detection activities for the COVID-19 mRNA Vaccine will include routine and specific review of AEs consistent with the AESI list provided in the RMP.
- In addition, published **literature** will be reviewed weekly for individual case reports and broader signal detection purposes.
- Regulatory authority **safety alerts monitoring**, to detect and further investigate potential signals being raised on other areas outside of EU.
- A specific adverse reaction **follow-up questionnaire** intended to capture clinical details about the nature and severity of COVID-19 illness particularly in relation to potential cases of vaccine lack of effect or VAED.

- In addition to routine 6-monthly PSUR production, monthly summary safety reports will be compiled and submitted to EMA, to support timely and continuous benefit risk evaluations during the pandemic. Minimum data to be submitted include:
  - Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately);
  - Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women);
  - Interval and cumulative number of reports per HLT and SOC;
  - Summary of the designated medical events;
  - Reports per EU country;
  - Exposure data (including age-stratified);
  - Changes to reference safety information in the interval, and current CCDS;
  - Ongoing and closed signals in the interval;
  - AESI reports – numbers and relevant cases;
  - Fatal reports – numbers and relevant cases;
  - Risk/benefit considerations.
- The submission of monthly reports complements the submission of PSURs (requested initially every six months). The need and frequency of submission of the summary safety reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 submissions).
- Joint adverse event and product complaint (including available batch/lot information) trending reviews will be conducted routinely by the Applicant.

The proposed routine pharmacovigilance activities are considered appropriate for the safety profile of the product and the pandemic circumstances.

Traceability

Full traceability from manufacturing to vaccination administration site is crucial to ensure maintenance of the cold-chain as well as for pharmacovigilance purposes should assessment of a safety signal need to be performed by batch/lot.

The Applicant's proposal to ensure traceability include:

- SmPC 4.4 labelling to raise HCP awareness regarding the need to clearly record the name and batch of the vaccine to improve traceability;
- a tracking device on every vaccine shipping container that provides real-time monitoring of GPS location and temperature 24 hours per day, 7 days per week;
- vaccine carton labelling also containing a 2-D barcode which has the batch/lot and expiry embedded within
- additional tools for vaccinators to record manufacturer and lot/batch information at the time of vaccination including a Traceability and Vaccination Reminder Card and peel-off labels (stickers with brand name and lot/batch numbers), acknowledging that each Member State will decided if and how the tools will be used, in accordance with the national provisions for pharmacovigilance.

Each shipment to a vaccination site should be accompanied with a sufficient number of corresponding vaccinee traceability and vaccination reminder cards; the lot/batch numbers will be for the first batches distributed copied manually by the vaccinators, with the Applicant's commitment that by 31 January 2021 all batches shipped will be accompanied at the receipt point in the Member States by sufficient peel-off labels to facilitate the recording of brand name and lot/batch number both in the vaccinators' records and the vaccinee traceability and vaccination reminder cards, where the Member States will require it.

The Traceability and Vaccination Reminder will include:

- Space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine, and keep it thereafter;
- QR code that links to additional information;
- Adverse event reporting information.

Additional pharmacovigilance activities

The Applicant proposes the following 11 studies, of which 1 global, 3 in Europe only, 2 in Europe and US, and 3 in US only; the countries where 2 studies will be conducted are not available at this time. There are 6 interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, 1 study in high risk adults and 1 study addressing co-administration with another vaccine) and 5 non-Interventional studies (4 safety and 1 effectiveness):

Study (*study short name, and title*) **Status *(planned/on-going)***	**Summary of Objectives**	**Safety concerns addressed**	**Milestone**	**Due dates**
Category 2				
C4591001 *Ongoing*	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
			CSR submission 6 months post Dose 2:	31-Dec-2021
			Final CSR submission with supplemental follow-up:	31-Aug-2023
Category 3				
C4591011	Assessment of occurrence of safety events of interest, including severe or	Anaphylaxis	Interim reports submission:	30-Jun-2021

Planned	atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.	AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.		31-Dec-2021 30-Jun-2022 31-Dec-2022
			Final CSR submission:	31-Dec-2023
C4591012 *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Long-term safety data.	Interim reports submission:	30-Jun-2021 31-Dec-2021 30-Jun-2022 31-Dec-2022
			Final CSR submission:	31-Dec-2023
C4591010 *Planned*	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest Use in pregnancy Long-term safety data.	Final draft protocol submission for EMA review:	31-Jan-2021
			Final CSR submission:	31-Mar-2024

C4591015 *Planned*	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Use in pregnancy and while breast feeding.	Protocol draft submission:	28-Feb-2021
			Final CSR submission:	30-Apr-2023
C4591014 *Planned*	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified	-	Protocol draft submission:	31-Mar-2021
			Final CSR submission:	30-Jun-2023
BNT162-01 Cohort 13 *Ongoing*	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022
C4591018 *Planned*	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Use in immunocompromised patients Use in patient with autoimmune or inflammatory disorders.	Protocol submission:	28-Feb-2021
			IA submission:	31-Dec-2021
Safety and immunogenicity in high risk adults *Planned*	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders).	Protocol submission:	30-Jun-2021
			Final CSR submission:	31-Dec-2022
ACCESS/VAC4EU *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders	Protocol submission:	28-Feb-2021
			Final CSR submission:	31-Jan-2024

		Long term safety data.		
Co-administration study with seasonal influenza vaccine *Planned*	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022

Non-Interventional Post Approval Safety Studies (4)

The Applicant proposes 4 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs.

Study C4591010 will be conducted in the EU using primary data collection to monitor a cohort of vaccinees and evaluate risk of safety events of interest reflecting the AESI list. A draft protocol C4591010 has been provided.

Additionally, Pfizer, on behalf of the Applicant, will sponsor one or more PASS using secondary electronic health records data sources in Europe based on a master surveillance protocol developed through the ACCESS project.

Two additional studies will be conducted using US data:

- 1 study using secondary data from EHR of active military and their families (C4591011),
- 1 study using secondary data from EHR of patients included in the Veterans Healthcare Administration system (C4591012).

The draft protocols for the proposed safety studies in the US (C4591011 and C4591012) have been provided.

Interventional studies (6)

The Applicant proposes 6 interventional studies, of which 2 are ongoing and 4 are planned.

- **Study C4591001** is an ongoing Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. At the time of the data cut-off date in Study C4591001 (14 November 2020), a total of 21,720 participants received at least one dose of the candidate vaccine.
- **Study BNT162-01 Cohort 13** is an ongoing multi-site (Germany), Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in 30 immunocompromised adults.
- **Study C4591015** is a planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID 19 mRNA vaccine.
- **Study C4591018** is a planned study of BNT162b2 in 100 adults receiving a stable dose of immunomodulators for the treatment of stable rheumatoid arthritis (RA), in two cohorts (50 tofacitinib, 50 TNF inhibitors). Subjects will be studied for safety, immunogenicity by neutralizing antibody titer, and evidence of asymptomatic infection by N-antigen antibodies.

- A planned **Phase II safety and immunogenicity study** (Safety and immunogenicity in high risk adults) in up to 150 immunocompromised adults (with a range of primary immunocompromising conditions and/or receiving immunocompromising treatments.
- **Co-administration study with seasonal influenza vaccine** study investigating the safety and immunogenicity of Comirnaty and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

Non-Interventional PASS in Pregnancy

The Applicant's proposed strategy to assess vaccination during pregnancy will be implemented in 2 stages. It is anticipated that initial use in pregnancy will be very limited; therefore, initially this information will derive from the 4 of the real-world safety studies (C4591010, C4591011, and ACCESS/VAC4EU), described in the preceding section. Study C4591012 is focused on patients in the Veterans Health Administration system and is not expected to capture many pregnancies given the demographics of the source population.

The findings from studies' interim analysis (where planned) will inform a strategy to assess pregnancy outcomes as vaccination in pregnancy expands. The Applicant will consider established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. The applicant's commitment and considerations are noted to evaluate pregnancy outcomes in a PASS using established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. Further feasibility analyses are awaited with RMP updates post-approval.

Non-Interventional Post-Approval Effectiveness study (1)

The Applicant will conduct at least one non-interventional study (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 illness in a real-world setting (C4591014). The effectiveness of COVID-19 mRNA vaccine will be estimated against laboratory confirmed COVID 19 illness requiring admission to the Emergency Department (ED) or hospital where SARS-CoV-2 is identified. These studies will allow to determine the effectiveness of Pfizer's vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups. The studies proposed below are under evaluation as potential commitments; studies are presented by geographical area (US and EU).

Overall conclusions on the Pharmacovigilance Plan

The proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

None proposed.

Risk minimisation measures

Routine Risk Minimisation Measures

Potential Medication Errors

The Applicant included a discussion on potential medication errors which is endorsed:

Large scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to: reconstitution and administration, vaccination scheme, storage conditions, errors associated with a multi-dose vial, and once other COVID-19 vaccines are available, confusion with other COVID-19 vaccines. These potential medication errors are mitigated through the information in the SmPC and further materials for healthcare providers which will be made available to the Member States to be integrated in the national campaign for communication, as needed.

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the COVID-19 mRNA vaccine.
- A poster with step-by-step instruction for vaccine storage, dose planning and preparation, and administration is available, which can be conspicuously displayed in settings where vaccine is to be administered for ongoing reference.
- Brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.
- Medical information call centres will be available for healthcare providers to obtain information on use of the vaccine.
- Traceability and Vaccination Reminder card will be provided with the pre-printed manufacturer name, dates of vaccination, batch/lot as a mitigation effort for potential confusion between vaccines.
- Peel-off labels with lot/batch number

These available resources will inform healthcare providers on the proper preparation and administration of the vaccine and reduce the potential for medication errors in the context of a mass vaccination campaign. Additionally, the patient information leaflet and, in those MSs where applicable, a Traceability and Vaccination Reminder card informs patients of the vaccine received so that a series is completed with the same product.

Summary of additional risk minimisation measures

None proposed.

The Applicant stated that Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. This is acceptable.

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks		
Anaphylaxis	Routine risk minimisation measures: SmPC sections 4.4. and 4.8. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine Additional pharmacovigilance activities: Studies (Final CSR Due Date): • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Important Potential Risks		
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: DCA is intended to facilitate the capture of clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591001 (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Missing information		
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC section 4.6; PL section 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	Additional risk minimisation measures: No risk minimisation measures.	Additional pharmacovigilance activities: Studies (Final CSR Due Date) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591015 (30-Apr-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in immunocompromised patients	Routine risk minimisation measures: SmPC sections 4.4 and 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR or IA Due Date) • BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Dec-2022) • C4591018 (IA: 31-Dec-2021) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date submission) • C4591001 subset (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024) • Safety and immunogenicity in high risk adults (31-Dec-2022).

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591018 (31-Dec-2021) • ACCESS/VAC4EU (31-Jan-2024).
Interaction with other vaccines	Routine risk minimisation measures: SmPC section 4.5. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: • Co-administration study with seasonal influenza vaccine (31-Dec-2022).
Long term safety data	Routine risk minimisation measures: None. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Studies (Final CSR Due Date or IA CSR submission) • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Summary of the risk management plan

The public summary of the RMP is acceptable.

Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan **version 1.0** is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. Furthermore, During the duration of the COVID-19 pandemic situation, the MAH shall submit summary safety reports submitted to EMA, including spontaneously reported data and data from compassionate use and expanded access programs. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

The following exemptions from labelling and serialization requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the *Questions and Answers on labelling flexibilities for COVID-19 vaccines* (EMA/689080/2020 rev.1, from 16 December 2020)[5] document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

Labelling exemptions

US packaging specific derogations (valid for December '20 and January '21)

All EU Members States (MSs), as well as Norway and Iceland, have agreed to grant a temporary

[5] Available at https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid19-vaccines_en.pdf, last consulted on 21 December 2021.

exemption to allow the placing in the EU market of the US packaging, under the following conditions:

a. The validity is only temporary and the MAH shall switch to the EU labelling requirements by February '21;

b. The US pack will have included a Quick Response (QR) code which the vaccine recipient could scan and gain access to the package leaflet (PL) in his/her national language;

c. The MAH shall supply a separate printed PL in the national language(s) of those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine.

EU packaging specific derogations (from February '21 onwards)

a. Outer and immediate labelling will be provided in English only.

The MAH shall provide outer and immediate labelling in all EU languages by 2nd Q 2022. This exemption is justified on the deep-frozen storage/shipping requirements and the necessity to label batches ahead of time. Production of different vaccine packs in different languages will significantly reduce the supply chain efficiency. The multiple changes on packaging lines will result in significant time and capacity losses and would slow down the rapid deployment of COVID-19 vaccines. Moreover, English only labelling will better help to manage a shortage situation in one country by using immediately the supply from another country.

b. A printed package leaflet will be provided in the national language(s) for those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine. In addition, a QR code printed on the outer label and the PL will provide access to the package leaflet in the national language(s).

The MAH shall provide a printed package leaflet in all EU languages by 2nd Q 2022.

The MAH shall engage with the National Competent Authorities (other than the 6 mentioned above) to discuss and speed up the provision of PLs in the respective national language(s) of the MSs concerned. The MAH shall also contact MSs directly to agree on the exact numbers of PLs to be distributed, again in line with the published Q&A on labelling flexibilities.

c. The Blue Box will be omitted for the initial batches. The MAH shall provide the Blue Box via a QR code at a later stage following agreement on exact timing of implementation with the National Competent Authorities in each MS.

d. The inclusion of the EU Marketing Authorisation number in the labelling will be implemented with the switch from US packaging to EU compliant packs in February 2021.

Exemption from the obligation of serialisation

US packaging specific derogations (valid for December '20 and January '21)

a. It is acceptable that the US pack will be placed in the EU market without serialisation according to the EU FMD requirements. Only the Global Trade Item Number (GTIN) will be common for US & EU and this will be printed on the US pack.

EU packaging specific derogations (from February until March '21)

- All EU Member States have accepted a temporary derogation from serialisation for the EU pack from February until the end of March 2021.

- The MAH shall provide two progress reports on the serialisation: a first by 1st of February '21 and a second by 1st of March '21 referring to details on the progress achieved in terms of ensuring compliance, e.g. proof of acquiring the relevant equipment, the date for the validation, the proof of contract to connect to the European Medicines Verification Organisation.

- The MAH shall provide additional mitigating measures, e.g. immediate reporting of any stolen product during the period of exemption, reporting of any counterfeit or falsified vaccine in the EU or third countries in the legal supply or internet, reconciliation of product distributed and used in the respective territory.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- The Summary of Product Characteristics
- The Package Leaflet
- Safe Handling Guidelines for Dry Ice
- Shipping and Handling Guidelines Brochure
- Preparation and Administration Video
- Storage and Handling Video
- Returning the Thermal Shipping Container video
- How to prepare and Administer Poster
- Traceability and vaccination reminder card
- Returning the thermal Shipping Container brochure
- Dry Ice Replenishment Brochure
- Link to Adverse Event Reaction Reporting

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation (EC) No 726/2004, Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS). The pandemic is ongoing despite unprecedented efforts to control the outbreak. According to ECDC histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

As of 1 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

Comirnaty is intended for active immunisation against SARS-CoV-2, thereby preventing COVID-19.

3.1.2. Available therapies and unmet medical need

There is currently no approved vaccine in the EU available to prevent COVID-19. Several development programs are ongoing globally and currently other applications are under evaluation by regulatory authorities worldwide. There is a very high global demand for vaccines to help contain the pandemic and decrease morbidity and mortality in at risk groups.

3.1.3. Main clinical studies

The clinical development consists of one FIH phase 1 study (BNT162-01) in younger and older adults (18-55 years and 56-85 years) comparing 4 vaccine candidates, and one pivotal clinical study, C4591001 (or BNT162-02).

The pivotal study is a phase 1/2/3 placebo-controlled, randomised, observer-blind, dose finding, multicentre study performed in the US (start date 4 May 2020), Argentina, Brazil, Turkey, Germany, and South Africa, to evaluate the safety, immunogenicity and efficacy of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 in healthy adults. The phase 1 part of the study was designed for dose evaluation of 2 vaccines: BNT162b1 and BNT162b2 in younger (18-55 years) and older (65-85 years) adults. The Phase 2 part was designed to confirm safety and immunogenicity of the selected vaccine, BNT162b2, in the first 360 subjects enrolled in the Phase 2/3 part of the study.

The Phase 2/3 part of the study was designed to enrol up to 43,998 subjects (randomised 1:1 to BNT162b2 or placebo) to receive BNT162b2 at the dose of 30 µg, given as 2 IM injections 21 day apart (within 19 to 42 days), for an efficacy assessment in addition to safety and exploratory immunogenicity assessments.

The primary endpoint was symptomatic COVID-19 incidence per 1000 person-years of follow-up based on centrally or locally confirmed nucleic acid amplification test (NAAT) in subjects without serological or virological evidence of SARS-CoV-2 infection before and during vaccination regimen (cases confirmed ≥7 days after Dose 2), and in subjects with and without evidence of SARS-CoV-2 infection before and during vaccination regimen. The study was event-driven, i.e. the final efficacy analysis was to be triggered by 162 cases; in practice 170 cases were reached.

3.2. Favourable effects

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9) in subjects ≥16 years of age without prior evidence of SARS-CoV2 infection and 94.6% (95% CI 89.6, 97.6) in all subjects regardless of prior evidence of SARS-CoV-2 infection (primary endpoint). This outcome met the pre-specified success criteria.

Vaccine efficacy after dose 1 to before dose 2 was 52.4% (95% CI 29.5, 68.4). Vaccine efficacy from 10 days after dose 1 to before dose 2 was estimated to be 86.7% (95% CI 68.6, 95).

The efficacy analyses in the all-available efficacy population (including participants who had protocol violations), showed consistent results with those in the primary analysis population. The efficacy analyses using CDC defined symptoms to identify a COVID-19 case gave similar efficacy results as the primary endpoints.

The VE in each demographic subgroup analysed, as defined by age (including subjects >65 years), sex, race, ethnicity, and country and in individuals with comorbidities including obesity, diabetes, hypertension and cardiopulmonary diseases was >90%. In the obese population, VE was 95.4% (CI 95% 86.0%, 99.1%).

VE among 65-74-year-olds was 92.9% (CI95% 53.1%, 99.8%). VE among >75-year-olds was 100% (CI95% -13.1%, 100.0) with 0 cases in the vaccine group and 5 cases in the placebo group. VE among >65 years and at risk of severe COVID-19 was 91.7% (95% 44.2%, 99.8%).

Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, but the number of cases after second dose was very low, 1 case in the vaccine group and 4 cases in placebo group. Counting cases from after dose 1, there were 1 case in the vaccine group and 9 cases in the placebo group.

Phase 1 and phase 2 immunogenicity data from both the pivotal study C4591001 and supportive study BNT162-01 have shown robust humoral responses after vaccination with 2 doses of BNT162b2 at 30 µg in both younger (18-55 years) and older adults (age groups 56-85 years and 65-85 years), and both in terms of neutralising antibodies and IgG-antigen binding antibodies. The second dose given 21 days post-dose 1 induced a marked boosting effect in both younger and older adults. Responses were generally faster and higher in younger adults than in older adults. The levels of neutralizing antibodies titres were moderate 21 days after dose 1. The peak of neutralizing antibodies titres was reached 14 days post-dose 2 in older adults versus 7 days post-dose 2 in younger adults. Immune responses were maintained up to 1-month post-dose 2 in both age groups based on available data.

Study BNT162-01 provides evidence for T cell-mediated immune response, with antigen-induced IFNγ expression demonstrating a Th1 CD4+ and CD8+ phenotype following the second dose of vaccine. For the 30 µg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults.

The immunogenicity results are only considered supportive at this stage, as no correlate of protection has been established. The immune responses support the need for two doses, as neutralising antibody

levels increased substantially following the second dose compared to the first dose. Cell mediated immune responses were demonstrated in very few subjects in phase 1 but confirm a Th1 dominated cytokine pattern.

3.3. Uncertainties and limitations about favourable effects

Based on the available limited data, no reliable conclusion on the efficacy of the vaccine against severe COVID-19 can be drawn from 7 days after the second dose (secondary endpoint). The estimated efficacy against severe COVID-19 occurring at least 7 days after dose 2 was 66.4%, with a large and negative lower bound CI (95% CI: -124.8%; 96.3%). Only a limited number of events occurred at the cut-off date of analysis (1 and 4 cases in the vaccine and placebo groups respectively). The posterior probability for the true vaccine efficacy ≥ 30% (74.29%) did not meet the pre-specified success criterion. Consequently, the efficacy against the severe disease across subgroups, notably certain populations at high-risk of severe COVID-19 cannot be estimated (elderly and subjects with comorbidities).

Efficacy against asymptomatic infection is not available but, notwithstanding all the limitations, will be assessed through seroconversion of N-binding antibodies in BNT162b2 and placebo recipients who did not experience COVID-19.

The pivotal study was not designed to assess the effect of the vaccine against transmission of SARS-CoV-2 from subjects who would be infected after vaccination. The efficacy of the vaccine in preventing SARS-CoV-2 shedding and transmission, in particular from individuals with asymptomatic infection, can only be evaluated post-authorisation in epidemiological or specific clinical studies.

Duration of protection has currently been followed up for approximately 100 days after dose 1. Data on longer term protection are anticipated to the extent that the ongoing phase 3 study can continue as planned with a placebo group. The assessment of efficacy over a period of at least 6 months is expected to determine the need and the appropriate time of a booster dose.

There seems to be at least a partial onset of protection after the first dose, but this remains unconfirmed at this stage.

There are very limited or no data in immunocompromised subjects and in pregnant women. Efficacy in subjects aged 16-17 years is extrapolated from young adults as no cases of disease were reported in this small group at this stage.

Available data do not suffice to establish efficacy in subjects seropositive for SARS-CoV-2 at baseline, and subjects with a known history of COVID-19. However, efficacy is anticipated in this group; to the extent that they are not naturally protected against re-infection, which is presently incompletely characterised.

3.4. Unfavourable effects

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies (BNT162-01 and C4591001) that included 21,744 participants that have received at least one dose of Comirnaty.

In Study C4591001, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study C4591001, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older. Reactogenicity was evaluated in a subset of 8183 subjects (n=4093 vaccinated; n=4090 placebo) up to 7 days after each dose.

Regarding reactogenicity, the most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%). All reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. The frequency of headache, fatigue and fever was higher after Dose 2 in both age groups.

Regarding AEs, at least one AE was reported in 21% of the vaccinated subjects and in 13% of the placebo arm. The frequency of severe AEs was low (<1%) in both study arms. The most frequently reported SOC were "General disorders and administration site conditions (11.9% vs 2.9%)", "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%). PTs comprised mainly of vaccine typical reactions such as injection site pain, headache, fever, fatigue, malaise as well as myalgia and arthralgia.

For subjects with a follow-up of ≥2 months, SAE were reported at a low frequency (0.5-0.6%) in both the vaccine and the placebo group, with no clinically meaningful differences by age, baseline serostatus, ethnicity, race or sex. Lymphadenopathy and nausea were reported to occur more often in the vaccine group compared to the placebo group in the whole enrolled trial population (respectively 0.4% and 0.6% higher rate than placebo). Numerical imbalances in reporting were observed for insomnia, injection site pruritus and pain in extremity. Since these are supported by a biologically plausible relation to vaccination, these AEs are reflected in the SmPC.

Acute peripheral paralysis was reported in 4 vs. 0 cases (vaccine vs placebo) in the whole study population, of which 2 cases were deemed related to study treatment (see section 2.6.10). For acute peripheral paralysis, there is a reasonable possibility of a causal relation to vaccination and should therefore be included in the SmPC.

In the ~38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. Three reports of anaphylaxis were identified during vaccination campaigns by the time this report was written.

Few cases of hypersensitivity/immunisation reaction events have been observed with the vaccine (13 vs 6 cases) in the whole study population. Hypersensitivity should be annotated in the SmPC, section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

Long term safety data is not available at this stage, however the Phase 2/3 study will follow the included subjects up to 2 years post vaccination, so these data are expected post-authorisation.

AEs were slightly lower in subjects seropositive to SARS-CoV-2 at baseline (22% vs. 27% in seronegatives), however the number of such subjects was limited (vaccinated n=558; placebo n=590).

Data on immunocompromised individuals is limited, as only 196 participants with stable HIV infection were included in the study. No specific safety concern was detected.

Data from exposure during pregnancy is very limited. Up to the cut-off date 23 pregnancies have been reported in the Phase 2/3 trial and will be followed up for outcome.

Multiple long-term pharmacoepidemiology safety studies are planned to be conducted in order to confirm the safety profile in the already studied population as well as in a broader population including pregnant, immunocompromised and very elderly subjects.

There is no data available on interaction with other vaccines given in co-administration.

In the Phase 2/3 study, the total number of included subjects aged 16-17 years was smaller compared to other age groups (n=138 BNT162b; n=145 placebo), however no safety concerns were identified.

Uncertainties remain regarding causality association of acute peripheral paralysis to vaccination due to the limited number of cases, which are consistent with background rates. Nevertheless, facial paralysis will be included as an adverse event of special interest (AESI) for pharmacovigilance monitoring and in the active surveillance study protocols.

While apart from facial paralysis, whose aetiology is currently unknown, no possible autoimmune adverse events where identified as causally related to vaccination, rare events of this nature cannot be excluded based on the size of the available data set.

There is a theoretical risk, based on non-clinical data with MERS and SARS vaccines, of vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), however no cases were identified in clinical studies with COVID-19 vaccines, including Comirnaty, and the characterisation of the immune response does not indicate a risk profile in this regard (Th1 skewed).

This vaccine contains two new components (cationic lipid ALC-0315 and PEGylated liquid ALC-0159) in the LNP, for which there is limited experience. Some uncertainties remain regarding the ALC-0315 long half-life. Regarding PEG related toxicity which is known to depend on the dose, dose frequency, duration of treatment and molecular weight of the PEG protein, immunogenicity is not expected to be an issue due to the low molecular weight of this PEG (<2KDa). The scientific data available at this stage do not raise noticeable concerns regarding immunogenicity or immunotoxicity of the PEG, but current evidence is not definitive.

3.6. Effects Table

Table 20 Effects Table for Comirnaty intended for active immunisation to prevent COVID-19 caused by against SARS-CoV-2 in individuals 16 years of age and older (data cut-off: 14 Nov 2020)

Effect	Short Description	Unit	BNT162b2 (30 µg)	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Vaccine efficacy	First COVID-19 occurrence from 7	**% (95% CI)**	**95.0** (90.0, 97.9)			

Effect	Short Description	Unit	BNT162b2 (30 µg)	Placebo	Uncertainties / Strength of evidence	References
	days after Dose 2, without prior SARS-COV-2, **overall**	**Cases/** Number of subjects at risk for the endpoint	**8/** 17411	**162/** 17511	Robust data with similar efficacy confirmed in all age sub-groups (16-64YOA, >65YOA, 65-74YOA, >75YOA)	Evaluable efficacy population (7 days post dose 2) - Study C495100
		% **(95% CI)**	**94.7** (66.7, 99.9)			
	Patients aged ≥65	**Cases/** Number of subjects at risk for the endpoint	**1**/3848	**19**/3880		
Unfavourable Effects						
Lymphadenopathy		% (denominator)	0.3% (n=21720)	0% (N=21728)	Small number of cases, short duration of follow-up	All enrolled Phase 2/3 participants
Facial paralysis		Number of cases	4	1		
Hypersensitivity/immunisation reaction		Number of cases	13	6		
			Post dose 1 / **Post dose 2**	**Post dose 1** / **Post dose 2**		
Pain at injection site	16-55 years	%	83% / 79%	14% / 12%	Transient events, majority mild to moderate intensity	Reactogenicity subset of study C495100
	>55 years		71% / 66%	9% / 8%		
Headache	16-55 years		42% / 52%	34% / 24%		
	>55 years		25% / 39%	18% / 14%		
Fatigue	16-55 years		25% / 39%	25% / 39%		
	>55 years		34% / 51%	23% / 17%		

Abbreviations:
COVID-19: Coronavirus disease, SARS-CoV-2: Severe Acute Respiratory Syndrome, CI: Confidence Interval

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, substantial efficacy in preventing symptomatic COVID-19 infection has been demonstrated, as well as an acceptable safety profile in a large phase 3 study. Uncertainties relate to the

characterization of active substance and finished product. Given the comparable immunogenicity from 10 to 30µg doses, an impact on efficacy of the acceptance of somewhat lower levels of intact mRNA in the commercial product is not considered likely. Furthermore, based on low levels and biological plausibility, an impact of mRNA impurities on safety is deemed unlikely (see section 3.7.3).

Due to the limited extent of safety follow-up, the delivery of final data from the full 2-year follow up in the pivotal clinical trial are considered important to confirm the current knowledge.

With regards to the balance of efficacy and safety benefits and risks, it is overwhelmingly positive for subjects at risk of severe COVID-19, including the elderly and those with comorbid conditions, which are known to increase the risk of complication and death due to infection.

Uncertainties concerning the pharmaceutical characterization of the commercial product are compatible with a positive benefit/risk balance. This pertains not only to adults but, by extrapolation, to individuals 16-17 years of age.

Data are limited in individuals seropositive against SARS-CoV-2 at baseline. Available data however do not indicate any specific safety concerns, and efficacy is anticipated also in this subset.

There are no data on use in pregnant women, but a protective effect is anticipated. In the light of the reassuring data from the DART study, noting that pregnancy as such is a risk factor for severe COVID-19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis.

Based on biological plausibility no risk in breastfeeding is anticipated.

While there was no indication of an excess risk of severe allergic reactions such as anaphylaxis in the clinical study program, three post marketing cases, of which 2 in patients carrying adrenaline pens and one in a person with no known history of allergies, have been reported during vaccination campaigns, and all resolved with standard treatment. Hypersensitivity to the active substance or to any of the excipients is a contraindication. However, there is presently no substantial evidence of a negative benefit/risk balance in a subject with severe allergy to substances absent in the vaccine. For all subjects, the vaccine should be administered in settings where resuscitation facilities are available, as specified in the SmPC and in line with other vaccines. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

There are no efficacy data in immunocompromised individuals. Such patients may not be protected as well as immunocompetent individuals by vaccination. While there are limited safety data too in the immunocompromised subjects (a broad and disparate category), no particular safety issues are anticipated, and the benefit/risk balance of vaccination of such subjects is deemed positive, also in light of the underlying excess risk of COVID-19.

Studies to monitor potential safety concerns (autoimmune disorders, VAED) are planned.

3.7.2. Balance of benefits and risks

Overall, the available data are supportive of a positive B/R in the proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

Given the emergency situation, it is considered that the identified uncertainties can be addressed post-authorisation in the context of a conditional MA, including further characterisation of the active substance and finished product, the continuation of the pivotal study as long as possible, and post-approval effectiveness studies and routine disease surveillance.

Conditional marketing authorisation

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine (Process 1). The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities.

Data demonstrates the presence of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are not sufficiently characterised, and although the limited data provided for protein expression does not fully address uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein, the amount of any such proteins, is expected to be too low to elicit an immune response of biological relevance.

Indeed, considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell it cannot be excluded that different proteins than the intact full-length spike will be expressed. The risk of unwanted immunological events is considered low based on the following observations and considerations:

- Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
- The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA able to be translated into a specific protein or peptide.
- The level of any individual fragment of mRNA species would anyway be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the truncated proteins would be non-significant.

Also, lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

Regarding the proposed control strategy for active substance and finished product, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Considering the above and the current public health emergency, the characterisation of the active substance and finished product are considered acceptable, and the proposed specifications for RNA integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product, and considering clinical experience, are considered important to confirm the adequacy of these specifications, and these data should be provided post-approval as specific obligations to the MA.

Therefore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

Studies are underway to complete the characterisation of the active substance and finished product, and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment by the CHMP in order to complete all proposed specific obligations. Based on the Applicant's plans and documentation, it is expected that data to fulfil all quality SOs will be submitted gradually between March and July 2021.
Furthermore, the applicant will continue the ongoing pivotal Phase 3 randomized, placebo-controlled, observer-blind study C4591001 to obtain 2-year long-term data and to ensure sufficient follow-up in order to confirm the efficacy and safety of Comirnaty.

- Unmet medical needs will be addressed

There is no approved or widely available COVID-19 vaccine, and COVID-19 remains associated with substantial morbidity and mortality. While care for patients who have COVID-19 has improved over time and with clinical experience, no medications to cure COVID-19 are available and there remains an urgent need for a prophylactic vaccine during the ongoing pandemic.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Convincing efficacy evidence including the elderly and those with comorbid conditions has been provided and long-term effectiveness and safety data will be provided post-authorisation. Taking all this into account, it would not be considered appropriate to withhold a highly beneficial vaccine considering the severity of COVID-19 disease and the current global pandemic situation, since the demonstrated benefits in the current emergency setting clearly outweigh the uncertainties of the available data as outlined above.

3.8. Conclusions

The overall benefit/risk balance of Comirnaty is positive.

As available data are non-comprehensive, granting of a conditional marketing authorisation is relevant, and in line with provisions of Article 14-a of Regulation (EC) No 726/2004 it is supported.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Comirnaty is favourable in the following indication:

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions and specific obligations:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Vaccines and Related Biological Products Advisory Committee Meeting
December 10, 2020

FDA Briefing Document

Pfizer-BioNTech COVID-19 Vaccine

Sponsor:
Pfizer and BioNTech

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Glossary

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	Che
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
modRNA	nucleoside-modified messenger RNA
NAAT	nucleic acid amplification-based test
PVP	Pharmacovigilance Plan
RBD	receptor binding domain
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On November 20, 2020, Pfizer and BioNTech (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older." The proposed dosing regimen is 2 doses, 30 µg each, administered 21 days apart.

The EUA request includes safety and efficacy data from an ongoing phase 3 randomized, double-blinded and placebo-controlled trial of BNT162b2 in approximately 44,000 participants. The primary efficacy endpoint is incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen. In a mid-November analysis of 36,621 participants randomized 1:1 to vaccine or placebo who were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to 7 days after completion of the vaccination regimen, efficacy in preventing confirmed COVID-19 occurring at least 7 days after the second dose of vaccine was 95.0%, with 8 COVID-19 cases in the vaccine group and 162 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for these outcomes did not allow for firm conclusions.

Safety data from approximately 38,000 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. Available safety data from all participants enrolled through the November 14, 2020 data cut-off (N=43,252, which includes late enrollment of additional adolescent and adult participants), was consistent with the safety profile for the approximately 38,000 participants with median follow-up of 2 months and also did not raise specific safety concerns. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in participants ≥55 years of age (≤ 2.8%) as compared to younger participants (≤4.6%). The frequency of serious adverse events was low (<0.5%), without meaningful imbalances between study arms. Among non-serious unsolicited adverse events, there was a numerical imbalance of four cases of Bell's palsy in the vaccine group compared with no cases in the placebo group, though the four cases in the vaccine group do not represent a frequency above that expected in the general population. Otherwise, there were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine. With the exception of more frequent, generally mild to moderate reactogenicity in participants <55 years of age, the safety profile of BNT162b2 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations on whether:

- based on the totality of scientific evidence available, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 in individuals 16 years of age and older, and
- the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks for use in individuals 16 years of age and older.

The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

2. Background

2.1. SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of November 30, 2020, has caused more than 60 million cases of COVID-19 and claimed the lives of 1.5 million people worldwide. In the United States, over 13 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 260,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is a main target for neutralizing antibody, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain (RBD), as the immunogenic determinant.

2.2. EUA Request for the Pfizer and BioNTech COVID-19 Vaccine BNT162b2

Pfizer, in partnership with BioNTech Manufacturing GmbH, is developing a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNP). The Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2) is administered intramuscularly as a 2-dose series spaced 21 days apart at a dose of 30 µg each. The vaccine is supplied as a multi-dose vial (5 doses) containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for five 0.3 mL doses. The vaccine is preservative free.

A phase 3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. Vaccine efficacy for the primary endpoint against confirmed COVID-19 occurring at least 7 days after the second dose was 95.0% with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group. Data from about 38,000 participants randomized 1:1 with a median of 2 months of follow-up after the second dose of vaccine showed a favorable safety profile at a dose of 30 µg in participants 16 years of age and older. On November 20, 2020, Pfizer and BioNTech submitted an EUA request to FDA for its investigational COVID-19 vaccine (BNT162b2) intended to prevent COVID-19 caused by SARS-CoV-2.

2.3. U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and it would be under further investigation (under an Investigational New Drug Application) until it is licensed under a Biologics License Application (BLA). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4. Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" (Appendix C, page 53) describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.

2.5. Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[6]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing phase 3 studies.

Phase 3 Follow-up

Data from phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[7] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.6. Continuation of clinical trials following issuance of an EUA for a COVID-19 vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Some developers have proposed maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[8-10]

2.7. Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session, to discuss, in general, the development, authorization and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents

- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine
- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
  - Further evaluate safety, effectiveness and immune markers of protection
  - Evaluate the safety and effectiveness in specific populations.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on December 10, 2020, to discuss and provide recommendations on whether:

- based on the totality of scientific evidence available, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 in individuals 16 years of age and older, and
- the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks for use in individuals 16 years of age and older.

The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

4. Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

4.1. Vaccine Composition, Dosing Regimen

The Pfizer-BioNTech COVID-19 Vaccine is a white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection. The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen [between -80°C to -60°C (-112°F to -76°F)] multi-dose (5-dose) vial. The vaccine must be thawed and diluted in its original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to administration. After dilution, the vial contains 5 doses of 0.3 mL per dose. After dilution, the multiple-dose vials must be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution.

The Pfizer-BioNTech COVID-19 Vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 21 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. As such, FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2. Proposed Use Under EUA

The proposed indication and use of the vaccine under an EUA is "for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older."

5. FDA Review of Clinical Safety and Effectiveness Data

5.1. Overview of Clinical Studies

Data from two ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study C4591001 is a multi-center, multi-national Phase 1,2,3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study BNT162-01 is a Phase 1 study that explored various vaccine candidates and dose levels and will not be discussed in detail. A brief summary of the BNT162-01 study design and results to date is found in Appendix A, page 51.

Table 1: Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Pfizer-BioNTech COVID-19 Vaccine

Study Number/ Country	Description	BNT162b2 (30 µg)* participants (N)	Placebo participants (N)	Study Status
C4591001 USA, Argentina, Brazil, Germany, S. Africa, Turkey	Phase 1,2,3 randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 24 Phase 2/3: 21823	Phase 1: 6 Phase 2/3: 21828	Ongoing
BNT162-01 Germany	Phase 1/2 randomized, open-label; to evaluate safety and immunogenicity, dose escalation	12	0	Ongoing

N= total number of randomized participants as of November 14, 2020. Placebo: saline.
*Phase 1 studies included additional participants vaccinated with other dose levels and other mRNA vaccine candidates.
Studies C4591001 and BNT162-01 started in April 2020 (first participant, first visit).

5.2. Study C4591001

5.2.1. Design

Study C4591001 is an ongoing, randomized, placebo-controlled, phase 1/2/3 study being conducted in the US, Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a phase 1/2 study in healthy adults in the US for vaccine candidate and dosage selection, immunogenicity and preliminary efficacy, but the protocol was revised to expand the study design for inclusion of a phase 2/3 portion to evaluate clinical disease endpoint efficacy in individuals 12 years of age and older in the US and additional sites outside of the US.

In phase 1, two age groups were evaluated in separate cohorts, younger participants 18 through 55 years of age (N=45) and older participants 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received escalating dose levels with progression to subsequent dose levels and evaluation of escalating dose levels in the older age group (65 through 85 years), based on recommendations from an internal review committee that reviewed safety and immunogenicity data. For each vaccine candidate and dose

level, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from phase 1, in combination with data from Study BNT162-01 (See Section 10), supported the final vaccine candidate and dose level (BNT162b2 at 30 µg, given 21 days apart) to proceed into phase 2/3.

In phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) and a goal of 40% enrollment in the older adult age group. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study, so the age strata were revised as follows: 12 through 15 years of age, 16 through 54 years of age, and 55 years of age and older. The study population for phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19 disease, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. The phase 2 portion of the study evaluated reactogenicity and immunogenicity for 360 participants enrolled early-on, and these participants also contribute to the overall efficacy and safety data in the phase 3 portion. The ongoing phase 3 portion of the study is evaluating the safety and efficacy of BNT162b2 for the prevention of COVID-19 disease occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (midturbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (e.g., Cepheid; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001) Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design includes planned interim analyses of the first primary efficacy endpoint at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases), and all primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued (see Statistical Analysis section, below). Participants are expected to participate for a maximum of approximately 26 months.

Primary Efficacy Endpoints

Study C4591001 has two primary endpoints

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥7 days after Dose 2

Secondary Efficacy Endpoints

Study C4591001 has secondary endpoints based on different approaches to COVID-19 case evaluation criteria as follows:

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥14 days after Dose 2

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2

CDC-defined COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥7 days after Dose 2 or (2) ≥14 days after Dose 2.

For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was the presence of at least one of the following symptoms and a positive SARS-CoV-2 NAAT within 4 days of the symptomatic period:

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhea;
- Vomiting.

For a secondary efficacy endpoint, a second definition, which may be updated as more is learned about COVID-19, included the following additional symptoms defined by CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

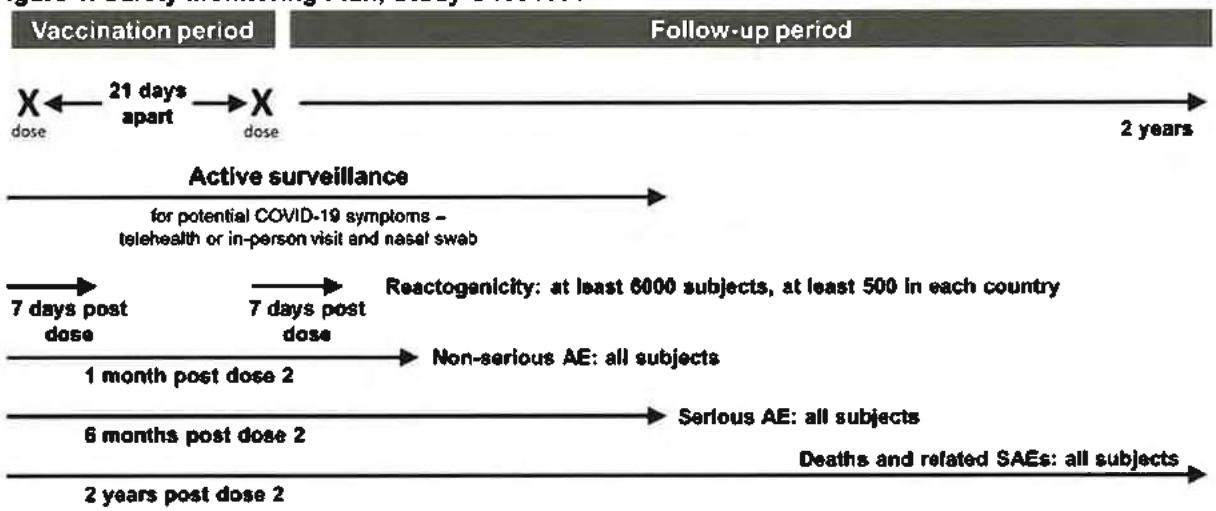
For another secondary endpoint, the case definition for a severe COVID-19 case was a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of BNT162 vaccine(s) in healthy adults after 1 or 2 doses. All phase 1 participants (n=30), and then 6653 U.S. participants (360 phase 2, 6293 phase 3) and the first ~500 phase 3 participants/per country with enrollment through October 9, 2020 (Argentina, Brazil and South Africa) recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from Dose 1 to 1 month after the last dose and serious AEs (SAEs) from Dose 1 to 6 months after the last dose. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study C4591001



Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), and antipyretic/pain medication use were recorded in an e-diary. At the data cutoff date for the EUA, reactogenicity events were not collected from adolescents 16 to 17 years of age (enrolled prior to the implementation of Protocol Amendment 9, finalized on 29 October 2020) using an e-diary but were detected and reported as unsolicited AEs. For any phase 3 participants who were not in the reactogenicity subset, local reactions and systemic events consistent with reactogenicity were detected and reported as unsolicited AEs. HIV-positive participants and adolescents 12 through 15 years of age were included in the reactogenicity subset with implementation of protocol amendment 6 (finalized on September 8, 2020) and amendment 7 (finalized on October 6, 2020), respectively. Solicited reactogenicity data in adolescents 16-17 years of age are not available for the reporting period. Reactogenicity data from a total of 100 adolescents 12 through 15 years of age enrolled in C4591001 phase 2/3 were provided in the EUA submission. However, the Sponsor did not request inclusion of this age group in the EUA because the available data, including number of participants and follow-up duration, were insufficient to support favorable a benefit-risk determination at this time. Therefore, the reactogenicity data for participants 12 through 15 years of age are not presented in this document.

Clinical laboratory tests were assessed in phase 1 at 1-week postvaccination. The planned safety follow-up for currently enrolled adolescents and adults is through 24 months after vaccination #2.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

In phase 2/3, monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants, and alert criteria were triggered when this probability was less than 11%.

Analysis Populations

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed informed consent document.
Randomized	All participants who are assigned a randomization number.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.

Phase 2/3 safety analysis populations were as follows:

- Phase 2/3 all-enrolled population: composed of a total of 43,448 (21720 vaccine, 21728 placebo) participants ≥16 years of age, regardless of duration of follow-up, for whom written informed consent was obtained. Initial enrollment included individuals 18 years and older, then included individuals as young as 16 years of age and individuals with known HIV (protocol amendment 6; finalized on September 8, 2020). As of November 14, 2020, 43.9% and 79.5% of vaccine recipients completed at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (≥8 weeks) and at least 1 month (≥4 weeks) were similar to the vaccine group.

- Phase 2/3 safety population (median follow-up time of 2 months after vaccination #2): comprised of a total of 37586 (18801 vaccine,18785 placebo) participants >16 years of age enrolled by October 9, 2020 and received at least 1 dose of study vaccine or placebo; overall, 98.1% of participants completed the 2-dose series. As of November 14, 2020, 50.6% and 91.6% of vaccine recipients completed at least 2 months (>8 weeks) and at least 1 month (>4 weeks), respectively, of safety follow-up after Dose 2. The percentages of placebo recipients completing at least 2 months (>8 weeks) and at least 1 month (>4 weeks) were similar to the vaccine group. A total of 283 (138 vaccine,145 placebo) individuals were 16 to <18 years of age. HIV-positive individuals were included in the all-enrolled population, but not the phase 2/3 safety population because the number of participants enrolled by October 9, 2020 was small (n=120) and the median duration of safety follow-up was short.

5.2.2. FDA Assessment of Phase 2/3 Follow-Up Duration

Study C4591001 initially enrolled approximately 30,000 participants and then several months later began enrollment of approximately 14,000 additional participants, including adolescents and participants with chronic, stable HIV, hepatitis B, or hepatitis C infections. Because of the gap in enrollment, the entire enrolled study population had a median follow-up of less than 2 months as of the EUA submission data cut-off date of November 14, 2020. However, the analyses submitted to support this EUA request meet the expectation for median duration of follow-up time, as follows:

- Submitted safety analyses for participants enrolled through October 9, 2020, and followed through November 14, 2020 (referred to by Pfizer and in this document as the phase 2/3 safety population and including a total of 37,586 participants), represent a median follow-up of 2 months. Additionally, this safety database is larger than for the initial planned enrollment of approximately 30,000 participants.

- The date for data cut-off for the first interim analysis for efficacy was November 4, 2020, when a total of 94 confirmed COVID-19 cases were accrued. All of the participants included in the first interim efficacy analysis had at least 7 days of follow-up after Dose 2, and thus were enrolled no later than October 7, 2020. All participants in the first interim efficacy analysis were therefore included in the phase 2/3 safety population defined above. Although the median follow-up duration for participants included in the first interim efficacy analysis was slightly less than 2 months as of November 4, 2020, these participants were also included in the final efficacy analyses with data cut-off of November 14, 2020, which extended the median follow-up for these participants to greater than 2 months. The results of the final efficacy analysis on data to November 14, 2020, indicate that the conclusions from the first interim efficacy analysis would not change when including additional follow-up to November 14, 2020.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued. As noted above, the median follow-up duration after completion of the full vaccination regimen for all participants enrolled at that time was less than 2 months for both safety and efficacy populations, due to a gap in enrollment. Because the data for the final efficacy analysis could be submitted in support of the EUA request and could provide data from a greater number of participants than from the interim analysis, FDA has focused its review on the efficacy data from the final efficacy analyses. Additional safety analyses from this larger database of all enrolled participants were also reviewed to evaluate for differences compared with the smaller phase 2/3 safety population.

5.2.3. Subject Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 2 (efficacy analysis populations) and Table 3 (phase 2/3 safety population). Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. Of 43,448 participants in the phase 2/3 all-enrolled population, 94.2% of vaccine recipients and 94.1% of placebo recipients completed 2 doses (data not shown).

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Table 2. Efficacy Populations, Treatment Groups as Randomized

	BNT162b2 (30 µg) n[a] (%)	Placebo n[a] (%)	Total n[a] (%)
Randomized[b]	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Participants without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Participants excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion[c]			
Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Participants without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Participants without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Participants excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion[c]			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Participants excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Participants excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion[c]			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-42 days after Dose 1)	1550 (7.1)	1561 (7.2)	3111 (7.1)
Had other important protocol deviations on or prior to 7 days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)

[a]n = Number of participants with the specified characteristic.
[b]These values are the denominators for the percentage calculations.
[c]Participants may have been excluded for more than 1 reason.
Note: 100 participants 12 through 15 years of age with limited follow-up are included in the randomized population (49 in the vaccine group and 51 in the placebo group). Some of these subjects were included in the denominators of efficacy analyses, depending on the population analyzed, but did not contribute primary endpoint cases and do not affect efficacy conclusions for ages 16 years and above.

Table 3. Disposition of All Randomized Participants, Phase 2/3 Safety Population

Treatment Group	BNT162b2 N=18904 n (%)	Placebo N=18892) n (%)	Total N=37796 n (%)
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Vaccinated			
Completed 1 dose	18858 (99.8)	18849 (99.8)	37707 (99.8)
Completed 2 doses	18555 (98.2)	18533 (98.1)	37088 (98.1)
Withdrawn from Study	180 (1.0)	259 (1.4)	439 (1.2)
Reason for Withdrawal			
Adverse Event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	4 (0.0)	6 (0.0)
Withdrawal by Subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to Follow-up	80 (0.4)	86 (0.5)	166 (0.4)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)

Source: EUA 27036, amendment 3, Table 2; c4591001-safety-tables-cos-reacto.pdf, page 43.
Note: One participant was randomized but did not sign informed consent and therefore not included in any analysis population.
Note: 120 HIV-positive participants included in this table. HIV population analyses were summarized separately from analyses based on the phase 2/3 safety population, but included in the all-enrolled poplation analyses presented in this briefing document.
%:n/N. n = number of subjects with the specified characteristic. N = number of participants ≥16 years of age enrolled by October 9, 2020, including 120 HIV-positive participants, and received at least 1 dose of study vaccine or placebo. N is the denominator used for the percentage calculations.
Data analysis cutoff date: November 14, 2020

The numbers of randomized participants contributing to efficacy analyses presented in this document include 100 participants 12 through 15 years of age (49 in the vaccine group and 51 in the placebo group) who had limited follow-up at the time of the November 14, 2020 data cut-off. However, the sponsor did not include this age group in the EUA request. The numbers of participants presented and used as denominators for efficacy calculations were not adjusted to remove participants 12 through 15 years of age. Because the number of participants 12 through 15 years of age is very small relative to the overall efficacy analysis populations, and no primary endpoint COVID-19 cases occurred in this age group, the vaccine efficacy conclusions are not impacted. No participants 12 through 15 years of age are included in the safety analyses. However, the safety disposition table includes 120 HIV-positive participants who were not included in the phase 2/3 safety population analyses.

5.2.4. Demographics and Other Baseline Characteristics

Overall, the phase 2/3 evaluable efficacy population included 49.4% females, 81.9% White, 9.8% African American, 4.4% Asian participants, and <3% from other racial groups; 26.2% of participants were Hispanic/Latino; 21.4% of participants were ≥65 years of age. The median age was 51 years. The most frequently reported comorbidities were obesity (35.1%), diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-available efficacy population were similar to the evaluable efficacy population. Please refer to the table below.

Table 4. Demographic Characteristics, Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Characteristic	BNT162b2 (N[a]=20033) N[b] (%)	Placebo (N[a]=20244) N[b] (%)	Total (N[a]=40277) N[b] (%)
Sex: Female	9794 (48.9)	10107 (49.9)	19901 (49.4)
Sex: Male	10239 (51.1)	10137 (50.1)	20376 (50.6)
Age at Vaccination: Mean years (SD)	50.3 (15.73)	50.1 (15.78)	50.2 (15.76)
Age at Vaccination: Median (years)	51.0	51.0	51.0
Age at Vaccination: Min, max (years)	(12, 89)	(12, 91)	(12, 91)
Age Group: 16 to <18 years	77 (0.4)	76 (0.4)	153 (0.4)
Age Group: 16 to 55 years	11589 (57.8)	11743 (58.0)	23332 (57.9)
Age Group: >55 years	8396 (41.9)	8454 (41.8)	16850 (41.8)
Age Group: ≥65 years	4294 (21.4)	4319 (21.3)	8613 (21.38)
Age Group: ≥75 years	860 (4.3)	852 (4.2)	1712 (4.3)
Race: American Indian or Alaska Native	131 (0.7)	122 (0.6)	253 (0.6)
Race: Asian	880 (4.4)	883 (4.4)	1763 (4.4)
Race: Black or African American	1957 (9.8)	1972 (9.7)	3929 (9.8)
Race: Native Hawaiian or Other Pacific Islander	54 (0.3)	29 (0.1)	83 (0.2)
Race: White	16387 (81.8)	16619 (82.1)	33006 (81.9)
Race: Multiracial	523 (2.6)	493 (2.4)	1016 (2.5)
Race: Not reported	101 (0.5)	126 (0.6)	227 (0.6)
Ethnicity: Hispanic or Latino	5272 (26.3)	5281 (26.1)	10553 (26.2)
Ethnicity: Not Hispanic or Latino	14652 (73.1)	14847 (73.3)	29499 (73.2)
Ethnicity: Not reported	109 (0.5)	116 (0.6)	225 (0.6)
Comorbidities[c]: Yes	9278 (46.3)	9314 (46.0)	18592 (46.2)
Comorbidities: No	10755 (53.7)	10930 (54.0)	21685 (53.8)
Comorbidity: Obesity	6934 (34.6)	7093 (35.0)	14027 (34.8)

[a].N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b].n = number of participants with the specified characteristic.
[c]. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity only (BMI ≥30 kg/m^2).

Overall, the phase 2/3 safety population included 83.1% White, 9.1% African American, 4.3% Asian participants, and <3% from other racial groups; 28.0% of participants were Hispanic/Latino; 21.6% of participants were >65 years of age. The median age was 52 years, and safety data from a total of 103 participants 16 and 17 years of age were included in this submission. The most frequently reported comorbidities were obesity (35.1%), diabetes (without chronic complications, 7.8%) and chronic pulmonary disease (7.8%). Geographically, 76.7% of participants were from the US, 15.3% from Argentina, 6.1% from Brazil, and 2.0% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-enrolled population were similar and were also enrolled from sites in Germany (1%) and Turkey (1%). There were no significant imbalances in demographic and other baseline characteristics between the all-enrolled population and phase 2/3 safety population with median 2-month follow-up.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
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Court File No./N° du dossier du greffe : CV-22-00691880-0000

Table 5. Demographics and Other Baseline Characteristics, Phase 2/3 Safety Population

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Age (years)									
Mean [SD]	16.40 [0.49]	44.99 [12.66]	68.84 [2.80]	78.07 [2.78]	16.36 [0.48]	44.78 [12.72]	68.84 [2.78]	78.10 [2.81]	50.38 [15.70]
Median	16	46	68	77	16	46	69	77	52
Min, max	16-17	18-64	65-74	75-89	16-17	18-64	65-74	75-91	16-91
Sex									
Male	33 (0.2)	7385 (39.3)	1714 (9.1)	470 (2.5)	24 (0.1)	7153 (38.1)	1724 (9.2)	498 (2.7)	19001 (50.6)
Female	20 (0.1)	7305 (38.9)	1513 (8.0)	361 (1.9)	26 (0.1)	7539 (40.1)	1511 (8.0)	310 (1.7)	18585 (49.4)
Race									
White	37 (0.2)	11895 (63.3)	2908 (15.5)	775 (4.1)	38 (0.2)	11891 (63.3)	2930 (15.6)	756 (4.0)	31230 (83.1)
African American	11 (0.1)	1477 (7.9)	186 (1.0)	20 (0.1)	7 (0.0)	1505 (8.0)	189 (1.0)	21 (0.1)	3416 (9.1)
Asian	0 (0.0)	693 (3.7)	81 (0.4)	26 (0.1)	0 (0.0)	715 (3.8)	72 (0.4)	19 (0.1)	1606 (4.3)
Multiracial	3 (0.0)	417 (2.2)	21 (0.1)	7 (0.0)	3 (0.0)	379 (2.0)	18 (0.1)	5 (0.0)	853 (2.3)
Not reported	0 (0.0)	82 (0.4)	11 (0.1)	0 (0.0)	1 (0.0)	98 (0.5)	10 (0.1)	5 (0.0)	207 (0.6)
American Indian or Alaska native	0 (0.0)	84 (0.4)	15 (0.1)	2 (0.0)	1 (0.0)	83 (0.4)	11 (0.1)	2 (0.0)	198 (0.5)
Nat. HI or other Pac. Isl.	2 (0.0)	42 (0.2)	5 (0.0)	1 (0.0)	0 (0.0)	21 (0.1)	5 (0.0)	0 (0.0)	76 (0.2)
Ethnicity									
Hispanic or Latino	6 (0.0)	4595 (24.4)	549 (2.9)	103 (0.5)	5 (0.0)	4616 (24.6)	558 (3.0)	90 (0.5)	10522 (28.0)
Non-Hispanic/non-Latino	47 (0.2)	10009 (53.2)	2658 (14.1)	722 (3.8)	44 (0.2)	10004 (53.3)	2652 (14.1)	707 (3.8)	26843 (71.4)
Not reported	0 (0.0)	86 (0.5)	20 (0.1)	6 (0.0)	1 (0.0)	72 (0.4)	25 (0.1)	11 (0.1)	221 (0.6)
Baseline Body Mass Index (BMI)									
Obese	3 (0.0)	5200 (27.7)	1079 (5.7)	248 (1.3)	14 (0.1)	5242 (27.9)	1147 (6.1)	235 (1.3)	13168 (35.0)
Overweight	14 (0.1)	4901 (26.1)	1278 (6.8)	368 (2.0)	9 (0.0)	4857 (25.9)	1255 (6.7)	340 (1.8)	13022 (34.6)

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Baseline Evidence of Prior SARS-CoV-2 Infection									
Negative	48 (0.3)	13879 (73.8%)	3109 (16.5)	805 (4.3)	47 (0.3%)	13858 (73.8%)	3115 (16.6%)	788 (4.2%)	35649 (94.8%)
Positive	3 (0.0)	473 (2.5%)	53 (0.3)	16 (0.1)	3 (0.0%)	520 (2.8%)	52 (0.3%)	5 (0.0%)	1125 (3.0%)
Missing	2 (0.0)	338 (1.8%)	65 (0.3)	10 (0.1)	0 (0.0%)	314 (1.7%)	68 (0.4%)	15 (0.1%)	812 (2.2%)
Comorbidities									
No	48 (0.3)	12353 (65.7%)	2081 (11.1)	444 (2.4)	37 (0.2%)	12412 (66.1%)	2118 (11.3%)	470 (2.5%)	29963 (79.7%)
Yes	5 (0.0)	2337 (12.4%)	1146 (6.1)	387 (2.1)	13 (0.1%)	2280 (12.1%)	1117 (5.9%)	338 (1.8%)	7623 (20.3%)
Diabetes Without Chronic Complication	0 (0.0)	814 (4.3%)	497 (2.6)	156 (0.8)	1 (0.0%)	849 (4.5%)	491 (2.6%)	132 (0.7%)	2940 (7.8%)
Chronic Pulmonary Disease	5 (0.0)	1093 (5.8%)	286 (1.5)	89 (0.5)	12 (0.1%)	1060 (5.6%)	309 (1.6%)	66 (0.4%)	2920 (7.8%)
Myocardial Infarction	0 (0.0)	82 (0.4%)	71 (0.4)	41 (0.2)	0 (0.0%)	73 (0.4%)	83 (0.4%)	31 (0.2%)	381 (1.0%)
Peripheral Vascular Disease	0 (0.0)	26 (0.1%)	67 (0.4)	31 (0.2)	0 (0.0%)	29 (0.2%)	52 (0.3%)	33 (0.2%)	238 (0.6%)
Liver Disease (mild, moderate or severe)	0 (0.0)	83 (0.4%)	34 (0.2)	7 (0.0)	0 (0.0%)	67 (0.4%)	17 (0.1%)	6 (0.0%)	214 (0.6%)
Diabetes With Chronic Complication	0 (0.0)	47 (0.2%)	36 (0.2)	15 (0.1)	0 (0.0%)	47 (0.3%)	47 (0.3%)	18 (0.1%)	210 (0.6%)
Congestive Heart Failure	0 (0.0)	44 (0.2%)	26 (0.1)	17 (0.1)	0 (0.0%)	36 (0.2%)	30 (0.2%)	16 (0.1%)	169 (0.4%)
AIDS/HIV	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)

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Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

Characteristic	BNT162b2 N=18801 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	BNT162b2 n (%)	Placebo N=18785 n (%)	Placebo n (%)	Placebo n (%)	Placebo n (%)	Total N=37586 n (%)
Age (years)	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	**16 to <18**	**18 to <65**	**65 to <75**	**≥75**	
Hypertension only	0 (0.0)	2569 (13.7%)	1528 (8.1)	488 (2.6)	1 (0.0%)	2621 (14.0%)	1569 (8.4%)	432 (2.3%)	9208 (24.5%)

Source: FDA-generated table.
Abbreviations: n = number of participants with the specified characteristic; N = number of participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo, N is denominator for the percentage calculations; SD = standard deviation; min, max = minimum, maximum; Nat. HI = Native Hawaiian; Pac. Isl. = Pacific Islander
Data analysis cutoff date: November 14, 2020.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

5.2.5. Vaccine Efficacy

Primary Efficacy Analyses

Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 6). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

For participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively (Table 7). The posterior probability was >99.99% for the true VE being greater than 30%. The 95% credible interval for the vaccine efficacy was 89.9% to 97.3%, indicating that the true VE is at least 89.9% with a 97.5% probability given the available data.

Table 7. Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants With And Without Evidence of Prior SARS-CoV-2 Infection, Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.9, 97.3)[e]	Yes
16 to 55 years	6 1.309 (10653)	120 1.317 (10738)	95.0 (88.7, 98.2)[f]	NA
>55 years and older	3 1.022 (7892)	49 1.028 (7956)	93.8 (80.9, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy >30% conditioning on the available data is >99.5% at the final analysis
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Subgroup Analyses of Vaccine Efficacy

Subgroup analyses of the second primary efficacy endpoint provide additional information about the VE for participants with and without evidence of infection prior to vaccination in specific populations enrolled, which is the endpoint considered to represent the general population who may receive the vaccine, as baseline evidence of prior infection may not be known by all people who might receive the vaccine. The results are displayed below in Table 8. The VE point estimates for the subgroup analyses were comparable to results for the first primary efficacy endpoint.

VE point estimates were uniformly high across the subgroups examined with the exception of participants identifying as multiracial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 cases occurred to interpret efficacy data for these subgroups. Additionally, the numbers of participants and cases in some other specific subgroups, such as the adolescent age group and racial subgroups, limits the interpretability of the VE results because of the wide credible intervals, but are displayed for completeness.

Table 8: Subgroup Analyses of Second Primary Endpoint: First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup, Participants With and Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Overall	9 2.332 (18559)	169 2.345 (18708)	94.6 (89.6, 97.6)
Age group (years)			
16 to 17	0 0.003 (58)	1 0.003 (61)	100.0 (-3969.9, 100.0)
18 to 64	8 1.799 (14443)	149 1.811 (14566)	94.6 (89.1, 97.7)
65 to 74	1 0.424 (3239)	14 0.423 (3255)	92.9 (53.2, 99.8)
≥75	0 0.106 (805)	5 0.109 (812)	100.0 (-12.1, 100.0)
At risk[f]			
Yes	4 1.083 (8584)	87 1.084 (8609)	95.4 (87.8, 98.8)
No	5 1.250 (9975)	82 1.261 (10099)	93.8 (85.0, 98.1)
Age group (years) and at risk			
16-64 and not at risk	5 1.012 (8172)	75 1.019 (8239)	93.3 (83.6, 97.9)
16-64 and at risk	3 0.790 (6329)	75 0.794 (6388)	96.0 (87.8, 99.2)
≥65 and not at risk	0 0.238 (1794)	7 0.241 (1849)	100.0 (29.5, 100.0)
≥65 and at risk	1 0.293 (2250)	12 0.290 (2218)	91.7 (44.2, 99.8)
Obese[g]			
Yes	3 0.810 (6445)	68 0.832 (6582)	95.5 (86.2, 99.1)
No	6 1.522 (12108)	101 1.513 (12120)	94.1 (86.7, 97.9)
Age group (years) and obese			
16-64 and not obese	5 1.163 (9380)	89 1.162 (9422)	94.4 (86.4, 98.2)
16-64 and obese	3 0.637 (5116)	61 0.651 (5199)	95.0 (84.6, 99.0)
≥65 and not obese	1 0.358 (2715)	12 0.351 (2685)	91.8 (44.7, 99.8)
≥65 and obese	0 0.172 (1328)	7 0.180 (1382)	100.0 (27.4, 100.0)
Sex			
Female	5 1.149 (9102)	84 1.176 (9366)	93.9 (85.2, 98.1)
Male	4 1.183 (9457)	85 1.170 (9342)	95.3 (87.6, 98.8)
Ethnicity			
Hispanic or Latino	3 0.637 (5074)	55 0.638 (5090)	94.5 (83.2, 98.9)

Efficacy Endpoint Subgroup	BNT162b2 N[a]=19965 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20172 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
Not Hispanic or Latino	6 1.681 (13380)	114 1.693 (13509)	94.7 (88.1, 98.1)
Race			
American Indian or Alaska native	0 0.011 (104)	1 0.010 (104)	100.0 (-3511.0, 100.0)
Asian	1 0.095 (796)	4 0.097 (808)	74.4 (-158.7, 99.5)
Black or African American	0 0.187 (1758)	7 0.188 (1758)	100.0 (30.4, 100.0)
Native Hawaiian or other Pacific Islander	0 0.006 (50)	1 0.003 (29)	100.0 (-2112.1, 100.0)
White	7 1.975 (15294)	153 1.990 (15473)	95.4 (90.3, 98.2)
Multiracial	1 0.047 (467)	1 0.042 (424)	10.4 (-6934.9, 98.9)
Not reported	0 0.010 (90)	2 0.013 (112)	100.0 (-581.6, 100.0)
Baseline SARS-CoV-2 Status			
Positive[h]	1 0.056 (526)	1 0.060 (567)	-7.1 (-8309.9, 98.6)
Negative[i]	8 2.237 (17637)	164 2.242 (17720)	95.1 (90.1, 97.9)
Unknown	0 0.039 (396)	4 0.043 (421)	100.0 (-68.9, 100.0)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.
[f] At risk is defined as having at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity (BMI ≥30 kg/m^2).
[g] Obese is defined as BMI ≥30 kg/m^2.
[h] Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.
[i] Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 9.

Table 9. Demographic Characteristics, Participants With Protocol Defined Case (Without Evidence of Infection Prior to 7 Days After Dose 2)

Characteristic	BNT162b2 (N[a]=8) n[b] (%)	Placebo (N[a]=162) n[b] (%)	Total (N[a]=170) n[b] (%)
Sex: Female	5 (62.5)	81 (50.0)	86 (50.6)
Sex: Male	3 (37.5)	81 (50.0)	84 (49.4)
Age at Vaccination: Mean years (SD)	51.4 (12.47)	47.4 (15.21)	47.6 (15.09)
Age at Vaccination: Median (years)	51	48	48
Age at Vaccination: Min, max (years)	(30, 69)	(18, 79)	(18, 79)
Age Group: 16 to < 18 years	0	0	0
Age Group: 18 to < 65 years	7 (87.5)	143 (88.3)	150 (88.2)
Age Group: ≥ 65 to < 75 years	1 (12.5)	14 (8.6)	15 (8.8)
Age Group: ≥ 75 years	0	5 (3.1)	5 (2.9)
Race: American Indian or Alaska Native	0	1 (0.6)	1 (0.6)
Race: Asian	1 (12.5)	4 (2.5)	5 (2.9)
Race: Black or African American	0	7 (4.3)	7 (4.1)
Race: Native Hawaiian or Other Pacific Islander	0	1 (0.6)	1 (0.6)
Race: White	7 (87.5)	146 (90.1)	153 (90.0)
Race: Multiracial	0	1 (0.6)	1 (0.6)
Race: Not reported	0	2 (1.2)	2 (1.2)
Ethnicity: Hispanic or Latino	3 (37.5)	53 (32.7)	56 (32.9)
Ethnicity: Not Hispanic or Latino	5 (62.5)	109 (67.3)	114 (67.1)
Ethnicity: Not reported	0	0	0
Comorbidities[c]: Yes	4 (50.0)	86 (53.1)	90 (52.9)
Comorbidities: No	4 (50.0)	76 (46.9)	80 (47.1)
Comorbidity: Obesity	3 (37.5)	67 (41.4)	70 (41.2)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = Number of participants with the specified characteristic.
[c] Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as patients who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or obesity only (BMI ≥30 kg/m²).

Only 3% of participants had evidence of prior infection at study enrollment, and additional analyses showed that very few COVID-19 cases occurred in these participants over the course of the entire study (9 in the placebo group and 10 in the BNT162b2 group, only 1 of which occurred 7 days or more after completion of the vaccination regimen – data not shown). The placebo group attack rate from enrollment to the November 14, 2020, data cut-off date was 1.3% both for participants without evidence of prior infection at enrollment (259 cases in 19,818 participants) and for participants with evidence of prior infection at enrollment (9 cases in 670 participants). While limited, these data do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the vaccine efficacy, by comorbidity status. VE point estimates were uniformly high across the comorbidities examined, though for some interpretation of the results is limited by small numbers of participants and/or cases.

Table 10. Vaccine Efficacy: First COVID-19 Occurrence From 7 Days After Dose 2, by Comorbidity Status, Among Participants Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy (7 Days) Population

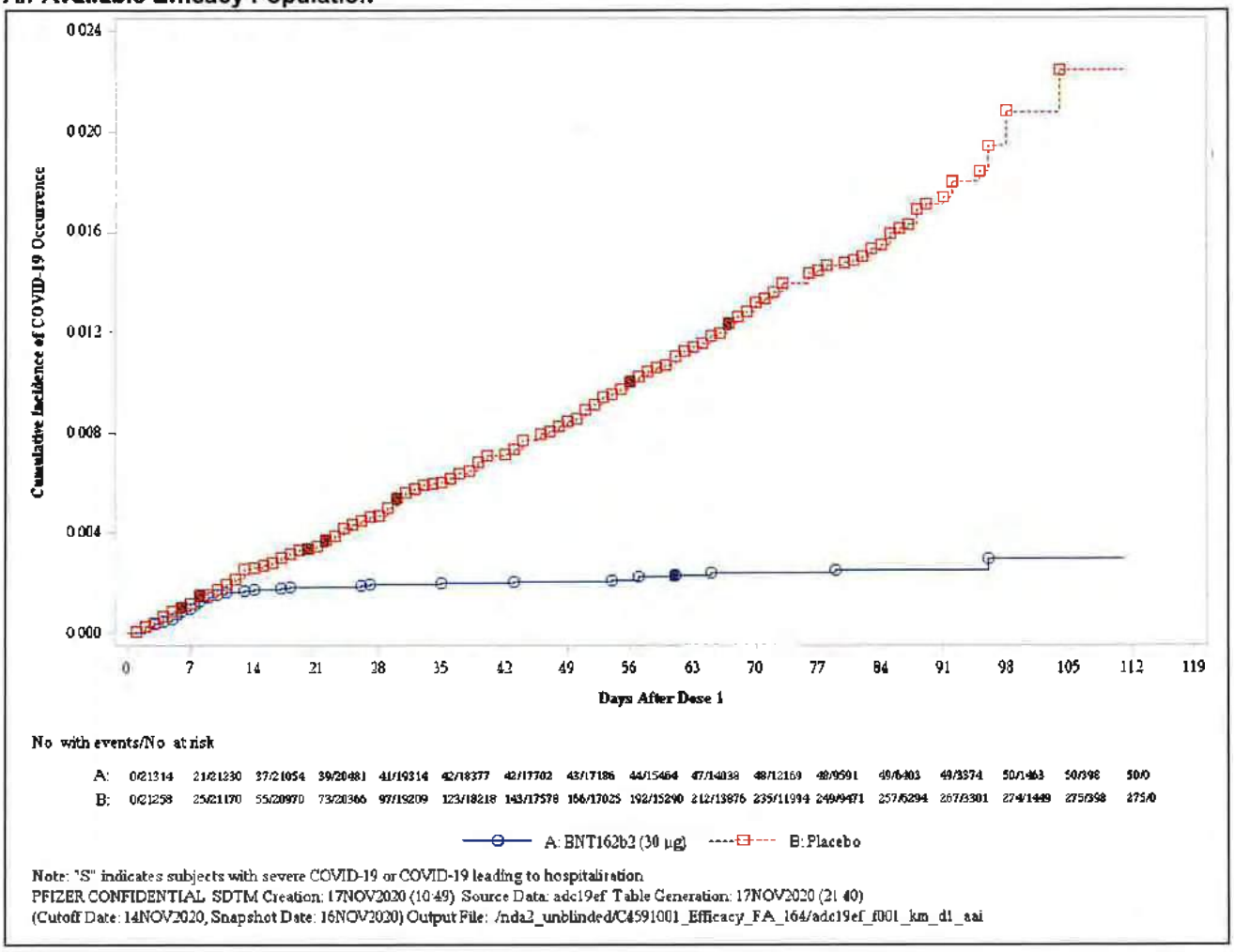
Efficacy Endpoint Subgroup	BNT162b2 (30 µg) N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
Overall	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.0, 97.9)
Comorbidity			
No comorbidity	4 1.189 (9381)	76 1.197 (9482)	94.7 (85.9, 98.6)
Any comorbidity[f]	4 1.025 (8030)	86 1.025 (8029)	95.3 (87.7, 98.8)
Any malignancy	1 0.092 (704)	4 0.090 (681)	75.7 (-145.8, 99.5)
Cardiovascular	0 0.067 (534)	5 0.062 (492)	100.0 (-0.8, 100.0)
Chronic pulmonary disease	1 0.175 (1374)	14 0.171 (1358)	93.0 (54.1, 99.8)
Diabetes	1 0.176 (1372)	19 0.176 (1374)	94.7 (66.8, 99.9)
Obese (BMI≥30.0 kg/m²)	3 0.763 (6000)	67 0.782 (6103)	95.4 (86.0, 99.1)
Hypertension	2 0.567 (4413)	44 0.567 (4437)	95.4 (82.6, 99.5)
Diabetes (including gestational diabetes)	1 0.177 (1381)	20 0.178 (1384)	95.0 (68.7, 99.9)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2 = Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
[f] Subject who had 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the Charlson comorbidity index (Appendix B, page 52) category or BMI ≥30 kg/m2.

Cumulative Incidence Curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1, (Figure 2), COVID-19 disease onset appears to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the BNT162b2 group, and there does not appear to be evidence of waning protection during the follow-up time of approximately 2 months following the second dose that is being evaluated at this point in time.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



Secondary Efficacy Analyses

The secondary efficacy endpoints evaluate the VE of BNT162b2 for the prevention of COVID-19 disease from 14 days after Dose 2 and based on the CDC's definition of COVID-19 disease from 7 and 14 days after Dose 2. The case splits and VE for each of these secondary efficacy endpoints were each similar to the primary efficacy endpoints described above.

Severe COVID-19 Cases

In the final analysis of the evaluable efficacy population (7 days), four participants had severe COVID-19 disease at least 7 days after Dose 2 (one subject who received BNT162b2 and three participants who received placebo). The vaccine recipient who had severe COVID-19 disease met the severe case definition because oxygen saturation at the COVID-19 illness visit was 93% on room air. The subject was not hospitalized, did not seek further medical care, and did not have risk factors for severe disease. The three placebo recipients who had severe COVID-19 disease met the severe case definition for the following reasons: one subject had an oxygen saturation of 92% on room air without other severe disease criteria, one subject was

hospitalized for noninvasive positive pressure ventilation with bilateral pneumonia, and one subject had an oxygen saturation of 92% and ICU admission for heart block. One of these placebo recipients with severe disease also had a body mass index > 30 kg/m^2 as a risk factor, while the other two participants did not have any risk factors for severe disease. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 11.

Table 11. First Severe COVID-19 Occurrence from 7 Days after Dose 2 - Evaluable Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
First severe COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection	1 2.215 (17411)	3 2.232 (17511)	66.4 (-124.8, 96.3)[e]	No

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >98.6% at the final analysis.
[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

In the all-available efficacy population, ten participants had severe COVID-19 disease after Dose 1 (one subject who received BNT162b2 and nine participants who received placebo). Five of the remaining six placebo recipients who had severe COVID-19 disease were hospitalized, two of whom were admitted to an intensive care unit. Five of these remaining six placebo recipients who had severe disease had at least one risk factor for severe disease. The total number of severe cases is small, which limits the overall conclusions that can be drawn; however, the case split does suggest protection from severe COVID-19 disease.

Table 12. First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

Secondary Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First severe case occurrence after Dose 1	1 4.021 (21314)	9 4.006 (21259)	88.9 (20.1, 99.7)[f]
After Dose 1 to before Dose 2	0	4	100.0 (-51.5, 100.0)
Dose 2 to 7 days after Dose 2	0	1	100.0 (-3800.0, 100.0)
≥7 Days after Dose 2	1	4	75.0 (-152.6, 99.5)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Additional Efficacy Analyses

Additional analyses of the first primary efficacy endpoint were conducted to evaluate the all-available efficacy population, for all participants regardless of evidence of prior infection through 7 days after Dose 2 (Table 13).

Table 13. Primary Efficacy Endpoint –All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=21669 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21686 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after	50	275	82.0
Dose 1 – Dose 1	4.015 (21314)	3.982 (21258)	(75.6, 86.9)[f]
After Dose 1 to before Dose 2	39	82	52.4 (29.5, 68.4)
Dose 2 to 7 days after Dose 2	2	21	90.5 (61, 98.9)
≥7 Days after Dose 2	9	172	94.8 (89.8, 97.6)

[a] N = number of participants in the specified group.
[b] n1 = Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 or 14 days after Dose 2 to the end of the surveillance period depending on specified endpoint.
[d] n2 = Number of participants at risk for the endpoint.
[e] Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.
[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 82%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, these data do not provide information about longer term protection beyond 21 days after a single dose.

Efficacy Summary

The data submitted in this EUA request were consistent with the recommendations set forth in the FDA Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19 and met the prespecified success criteria established in the protocol. In the planned interim and final analyses, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the group of participants with or without prior infection. Efficacy outcomes were consistently robust (≥93%) across demographic subgroups.

Efficacy against severe COVID-19 occurring after the first dose was 88.9% (95% CI 20.1, 99.7), with an estimated VE of 75.0% (95% CI -152.6, 99.5) (1 case in BNT162b2 group and 4 cases in placebo group) against severe COVID-19 occurring at least 7 days after Dose 2.

Among all participants (regardless of evidence of infection before or during the vaccination regimen), 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared with 275 cases in the placebo group, indicating an estimated VE of 82% (95% CI: 75.6%, 86.9%) against confirmed COVID-19 occurring after Dose 1, with VE of 52.4% (95% CI: 29.5%, 68.4%) between Dose 1 and Dose 2. The efficacy observed after Dose 1 and before Dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the time of observation is limited by the fact that most of the participants received a

second dose after three weeks. The trial did not have a single-dose arm to make an adequate comparison.

5.2.6. Safety

Overview of Adverse Events

Table 14 below presents an overview of all adverse events in the phase 2/3 safety population. A higher proportion of vaccine recipients reported adverse events compared with placebo recipients, and this imbalance was driven by reactogenicity (solicited adverse events) reported in the 7 days following vaccination and unsolicited adverse events corresponding to reactogenicity symptoms among participants not in the reactogenicity subset (see presentation of unsolicited adverse events in a later section). Proportions of participants with serious adverse events, deaths, and withdrawals due to adverse events were balanced between treatment groups.

Table 14. Study C4591001 Safety Overview- Ages 16 years and older

Participants Experiencing at Least One:	BNT162b2 n/N (%)	Placebo n/N (%)
Immediate unsolicited AE Within 30 minutes after vaccination[a]		
Dose #1	78/18801 (0.4)	66/18785 (0.4)
Dose #2	52/18494 (0.3)	39/18470 (0.2)
Solicited injection site reaction within 7 days[b]		
Dose #1	3216/4093 (78.6)	525/4090 (12.8)
Dose #2	2748/3758 (73.1)	396/3749 (10.6)
Solicited systemic AE within 7 days[b]		
Dose #1	2421/4093 (59.1)	1922/4090 (47.0)
Dose #2	2627/3758 (69.9)	1267/3749 (33.8)
From Dose 1 through 1 month after Dose 2[a]		
Unsolicited non-serious AE	5071/18801 (27.0)	2356/18785 (12.5)
SAE	103/18801 (0.5)	81/18785 (0.4)
From Dose 1 through cutoff date (safety population)		
SAE	124/18801 (0.7)	101/18785 (0.5)
From Dose 1 through cutoff date (all-enrolled)[c]		
Withdrawal due AEs	37/21621 (0.6)	30/21631 (0.5)
SAE	126/21621 (0.6)	111/21631 (0.5)
Deaths	2/21621 (0.0)	4/21631 (0.0)

Source: c4591001-safety-tables-ae3.pdf pages 216,446,459,463; c4591001-safety-tables-cos-reacto.pdf, pages 113-114.
n= number of participants with the specified reaction or AE.
[a] N: number of participants in the phase 2/3 safety population.
[b] N: number of participants in the reactogenicity subset of the phase 2/3 safety population.
[b] N: number of participants in the all-enrolled population.
Data analysis cutoff date: November 14, 2020.

Solicited Local Reactions and Systemic Adverse Events

As of the cutoff date, solicited reactogenicity data in participants 16 and 17 years of age were not collected by e-diary and are not available. Symptoms consistent with solicited reactogenicity that were reported by these participants were collected and analyzed as unsolicited adverse events and are discussed with review of those data.

Solicited Local Reactions

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of local reactions in the vaccine group was 0 (day of vaccination) to 2 days after either dose and lasted a median duration between 1 and 2 days.

For both age groups, injection site pain was the most frequent solicited local adverse reaction. After dose 2, the younger age group reported any pain more frequently than the older age group (77.8% vs 66.1%) and pain characterized as moderate (27.1% vs. 18.0%); a similar pattern was observed after Dose 1. Injection site redness and swelling after each dose were generally similar for both age groups.

Subgroup analyses by age

Table 15. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Local Reaction	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Pain[a]				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)
Redness[b]				
Any	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)
Swelling[b]				
Any	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)

Source: adapted from EUA 27034, amendment 3, Table 17.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, >55 Years of Age and Older

Local Reaction	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Pain[a]				
Any	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)
Redness[b]				
Any	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling[b]				
Any	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)

Source: EUA 27036, amendment 3, Table 21.
n = number of participants with the specified reaction.
N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[b] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Solicited Systemic AEs

For each age group in the reactogenicity subset (younger: 18 to 55 years, older: >55 years) and overall (18 years and older), the median onset of systemic AEs in the vaccine group in general was 1 to 2 days after either dose and lasted a median duration of 1 day.

The frequency and severity of systemic AEs were higher in the younger than the older age groups. Within each age group, the frequency and severity of systemic AEs was higher after Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar regardless of dose. For both age groups, fatigue, headache and new/worsened muscle pain were most common.

Subgroup analyses by age

Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Adverse Event	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
>38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)

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Adverse Event	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Fatigue[a]				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	46 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache[a]				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Chills[a]				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting[b]				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea[c]				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain[a]				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain[a]				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

Source: adapted from EUA 27036, amendment 3, Table 19.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 18. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Vaccination-Reactogenicity Subset of the Phase 2/3 Safety Population*, >55 Years of Age and Older

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
>38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue[a]				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)
Headache[a]				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills[a]				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting[b]				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea[c]				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain[a]				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain[a]				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)

Adverse Event	BNT162b2 Dose 1 N=1802 n (%)	Placebo Dose 1 N=1792 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

Source: EUA 27036, amendment 3, Table 23.
n = number of participants with the specified reaction.
N = number of participants in the reactogenicity subset reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[b] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[c] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
* Participants in the reactogenicity subset of the safety population ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Unsolicited (non-serious) AEs

A higher frequency of unsolicited, non-serious adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local reactions and systemic adverse events in subjects not in the reactogenicity subset and are consistent with solicited reactions/events reported by reactogenicity subset participants during the first 7 days following vaccination. Table 19 below presents unsolicited adverse events reported by at least 1% of participants in any treatment group for the phase 2/3 safety population.

Reports of lymphadenopathy were imbalanced with notably more cases in the vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Bell's palsy was reported by four vaccine participants and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days postvaccination) was reported as resolved with sequelae within three days after onset, and the other three were reported as continuing or resolving as of the November 14, 2020 data cut-off with ongoing durations of 10, 15, and 21 days, respectively. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and there is no clear basis upon which to conclude a causal relationship at this time, but FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories (system organ class or preferred term) of non-serious adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Table 19. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1-month After Dose 2, Phase 2/3 Safety Population*, 16 Years of Age and Older

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
General disorders and administration site conditions	3521 (18.7)	737 (3.9)	4258 (11.3)
Injection site pain	2125 (11.3)	286 (1.5)	2411 (6.4)
Fatigue	1029 (5.5)	260 (1.4)	1289 (3.4)
Pyrexia	1146 (6.1)	61 (0.3)	1207 (3.2)
Chills	999 (5.3)	87 (0.5)	1086 (2.9)
Pain	455 (2.4)	36 (0.2)	491 (1.3)
Musculoskeletal and connective tissue disorders	1387 (7.4)	401 (2.1)	1788 (4.8)
Myalgia	909 (4.8)	126 (0.7)	1035 (2.8)
Arthralgia	212 (1.1)	82 (0.4)	294 (0.8)
Nervous system disorders	1158 (6.2)	460 (2.4)	1618 (4.3)
Headache	973 (5.2)	304 (1.6)	1277 (3.4)
Gastrointestinal disorders	565 (3.0)	368 (2.0)	933 (2.5)
Diarrhoea	194 (1.0)	149 (0.8)	343 (0.9)
Nausea	216 (1.1)	63 (0.3)	279 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Subgroup analyses by age

16 and 17 years of age: the table below represents an FDA-generated summary of unsolicited AEs consistent with reactogenicity and AEs that occurred at ≥1% and higher in the BNT162b2 Vaccine Group, classified by MedDRA System Organ Class and Preferred Term.

Table 20. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 16 and 17 Years of Age

System Organ Class Preferred Term	BNT162b2 N=53 n (%)	Placebo N=50 n (%)	Total N=103 n (%)
General disorders and administration site conditions	7 (13.2)	3 (6.0)	10 (9.7)
Injection site pain	5 (9.4)	2 (4.0)	7 (6.8)
Pyrexia	5 (9.4)	0	5 (4.9)
Pain	2 (3.8)	0	2 (1.9)
Chills	1 (1.9)	0	1 (1.0)
Injury, poisoning and procedural complications	1 (1.9)	0	1 (1.0)
Concussion	1 (1.9)	0	1 (1.0)
Facial bones fracture	1 (1.9)	0	1 (1.0)
Road traffic accident	1 (1.9)	0	1 (1.0)
Investigations	1 (1.9)	0	1 (1.0)
Body temperature increased	1 (1.9)	0	1 (1.0)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

Table 21. Frequency of Unsolicited AEs with Occurrence in ≥1% of Participants in any Treatment Group from Dose 1 to 1 Month After Dose 2, Phase 2/3 Safety Population*, 65 Years and Older

System Organ Class Preferred Term	BNT162b2 (N=4058) n (%)	Placebo (N=4043) n (%)	Total (N=8101) n (%)
General disorders and administration site conditions	577 (14.2)	118 (2.9)	695 (8.6)
Injection site pain	361 (8.9)	39 (1.0)	400 (4.9)
Fatigue	175 (4.3)	44 (1.1)	219 (2.7)
Chills	143 (3.5)	19 (0.5)	162 (2.0)
Pyrexia	148 (3.6)	10 (0.2)	158 (2.0)
Pain	60 (1.5)	7 (0.2)	67 (0.8)
Musculoskeletal and connective tissue disorders	231 (5.7)	83 (2.1)	314 (3.9)
Myalgia	125 (3.1)	23 (0.6)	148 (1.8)
Arthralgia	42 (1.0)	21 (0.5)	63 (0.8)
Pain in extremity	33 (0.8)	10 (0.2)	43 (0.5)
Nervous system disorders	179 (4.4)	87 (2.2)	266 (3.3)
Headache	127 (3.1)	45 (1.1)	172 (2.1)
Gastrointestinal disorders	127 (3.1)	72 (1.8)	199 (2.5)
Diarrhea	49 (1.2)	26 (0.6)	75 (0.9)
Nausea	40 (1.0)	13 (0.3)	53 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
* Participants ≥16 years of age enrolled by October 9, 2020 and received at least 1 dose of vaccine or placebo.
Data analysis cutoff date: November 14, 2020.

FDA independently conducted standard MedDRA queries (SMQs) using FDA-developed software (MAED) to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions. The SMQs, conducted on the phase 2/3 all-enrolled safety population, revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137 [0.63%]) compared with the placebo group (111 [0.51%]). No imbalances between treatment groups were evident for any of the other SMQs evaluated.

Immediate AEs (phase 2/3 safety population)
The frequency of immediate AEs reported in the vaccine group was 0.4% after Dose 1 and <0.3% after Dose 2 and were mainly consistent with solicited reactogenicity events. In both study groups, the most frequently reported immediate AE was injection site pain (BNT162b2 vaccine 0.3%, placebo 0.2%).

Study Withdrawals due to an AE (all-enrolled population)
Of 43,448 enrolled participants, 37 (0.2%) vaccine recipients and 30 (0.1%) placebo recipients (0.1%), and no adolescents 16 to <18 years of age, withdrew from the study due to an AE. AEs in the SOC of General Disorders and Administration Site Conditions (7 vaccine, 3 placebo) was common, with injection site pain the most frequent (2 vaccine, 0 placebo).

Serious Adverse Events

Deaths

A total of six (2 vaccine, 4 placebo) of 43,448 enrolled participants (0.01%) died during the reporting period from April 29, 2020 (first participant, first visit) to November 14, 2020 (cutoff date). Both vaccine recipients were >55 years of age; one experienced a cardiac arrest 62 days after vaccination #2 and died 3 days later, and the other died from arteriosclerosis 3 days after vaccination #1. The placebo recipients died from myocardial infarction (n=1), hemorrhagic stroke (n=1) or unknown causes (n=2); three of the four deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

Non-fatal SAEs

In the all-enrolled population of (total N=43,448), the proportions of participants who reported at least 1 SAE during the time period from Dose 1 to the data cutoff date (November 14, 2020) were 0.6% in the BNT162b2 vaccine group and 0.5% in the placebo group. The most common SAEs in the vaccine group which were numerically higher than in the placebo group were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), and syncope (0.02%). Occurrence of SAEs involving system organ classes and specific preferred terms were otherwise balanced between treatment groups, including no imbalance overall in cardiovascular serious adverse events.

Appendicitis was reported as a SAE for 12 participants, and numerically higher in the vaccine group: 8 vaccine participants ([appendicitis [n=7], appendicitis perforated [n=1]) and 4 placebo participants (appendicitis [n=2], appendicitis perforated [n=1], complicated appendicitis [n=1]). All of the vaccine participants (n=8) and 2 placebo participants were younger than 65 years of age. The cases were considered unrelated to vaccination by the study investigators and occurred no more frequently than expected in the given age groups. FDA agrees that there is no clear basis upon which to suspect that this imbalance represents a vaccine-related risk.

Three SAEs reported in the BNT162 group were considered by the investigator as related to vaccine or vaccine administration: shoulder injury, ventricular arrhythmia, and lymphadenopathy. The investigator and the sponsor thought that the shoulder injury was related to vaccine administration. Two SAEs in the BNT162b2 group and none in the placebo group were considered by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally following vaccination (n=1). In FDA's opinion following review of the adverse event narratives, two of these events were considered as possibly related to vaccine: shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. For lymphadenopathy, the event was temporally associated and biologically plausible.

Among participants 16 to 17 years of age, there was 1 participant in the vaccine group who experienced an SAE of facial bones fracture, which was not considered related to study intervention by the investigator.

Suspected COVID-19 Cases

As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness. Two serious cases of suspected but unconfirmed COVID-19 were reported, both in the vaccine group, and narratives were reviewed. In one case, a 36-year-old male with no medical comorbidities experienced fever, malaise, nausea, headache and myalgias beginning on the day of Dose 2 and was hospitalized 3 days later for further evaluation of apparent infiltrates on chest radiograph and treatment of dehydration. A nasopharyngeal PCR test for SARS-CoV-2 was negative on the day of admission, and a chest CT was reported as normal. The participant was discharged from the hospital 2 days after admission. With chest imaging findings that are difficult to reconcile, it is possible that this event represented reactogenicity following the second vaccination, a COVID-19 case with false negative test that occurred less than 7 days after completion of the vaccination series, or an unrelated infectious process. In the other case, a 66-year-old male with no medical comorbidities experienced fever, myalgias, and shortness of breath beginning 28 days post-Dose 2 and was hospitalized one day later with abnormal chest CT showing a small left-sided consolidation. He was discharged from the hospital 2 days later, and multiple nasopharyngeal PCR tests collected over a 10-day period beginning 2 days after symptom onset were negative. It is possible, though highly unlikely, that this event represents a COVID-19 case with multiple false negative tests that occurred more than 7 days after completion of the vaccination regimen, and more likely that it represents an unrelated infectious process.

Among 3410 total cases of suspected but unconfirmed COVID-19 in the overall study population, 1594 occurred in the vaccine group vs. 1816 in the placebo group. Suspected COVID-19 cases that occurred within 7 days after any vaccination were 409 in the vaccine group vs. 287 in the placebo group. It is possible that the imbalance in suspected COVID-19 cases occurring in the 7 days postvaccination represents vaccine reactogenicity with symptoms that overlap with those of COVID-19. Overall though, these data do not raise a concern that protocol-specified reporting of suspected, but unconfirmed COVID-19 cases could have masked clinically significant adverse events that would not have otherwise been detected.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Female study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Twenty-three pregnancies were reported through the data cut-off date of November 14, 2020 (12 vaccine, 11 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (4 vaccine, 2 placebo), within 30 days after LMP in 8 participants (4 vaccine, 6 placebo), >30 days after LMP in 1 participant (0 vaccine, 2 placebo), and date of LMP not known in 5 participants (4 vaccine, 1 placebo). Unsolicited AEs related to pregnancy include spontaneous abortion and retained products of conception, both in the placebo group. Pregnancy outcomes are otherwise

unknown at this time.

Clinical Laboratory Evaluations

Clinical laboratory tests (hematology, chemistries) were assessed in study BNT162-01 and C4591001 phase 1. The only common laboratory abnormality reported throughout the studies was transient decreases in lymphocytes 1-3 days after Dose 1, which increased in frequency with increasing dose, were mostly Grade 1-2, generally normalized at the next laboratory assessment 6-8 days after Dose 1 and did not occur after Dose 2. Among C4591001 phase 1 participants who received the 30 µg dose of BNT162b2, transient decreases in lymphocytes post-Dose 1 occurred in 5 of 12 participants 18-55 years of age and in 4 of 12 participants 65-85 years of age. These transient hematological changes were not associated with clinical symptoms.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of BNT162b2 in the context of the proposed indication and population for intended use under EUA. The number of participants in the phase 2/3 safety population (N=37586; 18801 vaccine,18785 placebo) meets the expectations in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy, and the median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series meets the agency's expectations in FDA's Guidance on its Emergency Use Authorization for Vaccines to Prevent COVID-19. The all-enrolled population contained more participants >16 years of age, regardless of duration of follow-up (43448; 21720 vaccine, 21728 placebo). The demographic and baseline characteristics of the all-enrolled population and the safety population were similar. Although the overall median duration of follow-up in the all-enrolled population was less than 2 months, because the protocol was amended to include subpopulations such as individuals with HIV and adolescents, the data from both populations altogether provide a comprehensive summary of safety.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%); severe adverse reactions occurred in 0.0% to 4.6% of participants, were more frequent after Dose 2 than after Dose 1, and were generally less frequent in adults ≥55 years of age (≤2.8%) as compared to younger participants (≤4.6%). Among adverse events of special interest, which could be possibly related to vaccine, lymphadenopathy was reported in 64 participants (0.3%): 54 (0.5%) in the younger (16 to 55 years) age group; 10 (0.1%) in the older (>55 years) age group; and 6 in the placebo group. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff. Bell's palsy was reported by four vaccine participants. From Dose 1 through 1 month after Dose 2, there were three reports of Bell's palsy in the vaccine group and none in the placebo group. This observed frequency of reported Bell's palsy is consistent with the expected background rate in the general population. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2 vaccine.

A total of six deaths occurred in the reporting period (2 deaths in the vaccine group, 4 in placebo). In the vaccine group, one participant with baseline obesity and pre-existing atherosclerosis died 3 days after Dose 1, and the other participant experienced cardiac arrest

60 days after Dose 2 and died 3 days later. Of the four deaths in the placebo arm, the cause was unknown for two of them, and the other two participants died from hemorrhagic stroke (n=1) and myocardial infarction (n=1), respectively; three deaths occurred in the older group (>55 years of age). All deaths represent events that occur in the general population of the age groups where they occurred, at a similar rate.

The frequency of non-fatal serious adverse events was low (<0.5%), without meaningful imbalances between study arms. The most common SAEs in the vaccine arm which were numerically higher than in the placebo arm were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%), and in the placebo arm numerically higher than in the vaccine arm were pneumonia (0.03%), atrial fibrillation (0.02%), atrial fibrillation (0.02%) and syncope (0.02%). Appendicitis was the most common SAE in the vaccine arm. There were 12 participants with SAEs of appendicitis; 8 in the BNT162b2 group. Of the 8 total appendicitis cases in the BNT162b2 group, 6 occurred in the younger (16 to 55 years) age group and 2 occurred in the older (>55 years) age group (one of the cases in the older age group was perforated). One of the 6 participants with appendicitis in the younger age group also had a peritoneal abscess. Cases of appendicitis in the vaccine group were not more frequent than expected in the general population.

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

The Sponsor plans to offer vaccination to participants ⩾16 years of age who originally received placebo and who become eligible for receipt of BNT162b2 according to local or national recommendations. The Sponsor proposes that these participants will be unblinded upon request and will have the opportunity to receive BNT162b2 as part of the study. The Sponsor also proposes that all placebo recipients ⩾16 years of age will be offered BNT162b2 after completing 6 months of follow-up after Dose 2, if they did not request and receive vaccine previously. The participants will provide consent to receive vaccination and to continue follow-up. For these participants, the Sponsor plans a total follow up period of 18 months, with one visit 1-month postvaccination and subsequent phone contacts at 1, 6, and 18 months postvaccination. Safety and efficacy monitoring during this period will include collection of AEs, SAEs, and screening and diagnosing COVID-19 cases.

7. Pharmacovigilance Activities

Pfizer submitted a Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with Pfizer-BioNTech COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease as an important potential risk. Use in pregnancy and lactation and vaccine effectiveness are areas the Sponsor identified as missing information. In addition to the safety concerns specified by the Sponsor, FDA requested that the Sponsor update their PVP to include missing information in pediatric participants less than 16 years of age.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following three planned active surveillance studies. Of note, the Sponsor will submit plans for a clinical study to assess safety and immunogenicity in pregnant women and has proposed active surveillance studies designed to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA.

- Study Protocol Number C4591008. The Sponsor proposes to survey 20,000 U.S. health care workers enrolled in the COVID-19 HERO registry as well as health care workers in certain participating health care facilities about adverse events of special interest, and other clinically significant events of interest after vaccination with the Pfizer-BioNTech COVID-19 Vaccine. Incidence rates of these events in this cohort will be compared to expected rates. The respondents would receive follow-up surveys for a 30-month period.
- Study Protocol Number C4591011. This study is an active safety surveillance evaluation conducted within the Department of Defense Health System Databases using data derived from electronic health records and medical service claims among covered U.S. military and their families. Rates of safety events of interest in vaccinated participants will be compared to unvaccinated comparators. The study will be conducted for 30 months.
- Study Protocol Number C4591012. This study is an active surveillance study for adverse events of special interest and other clinically significant events associated with the Pfizer-BioNTech COVID-19 Vaccine using the Veteran's Health Administration electronic medical record database. Vaccinated participants will be compared to unvaccinated participants or to recipients of seasonal influenza vaccine. The study will be conducted for 30 months.

Currently, the primary objective of all three proposed studies above is descriptive, and the list of adverse events in the studies has not been finalized. FDA will provide feedback on these studies after further review.

Reporting to VAERS and Pfizer, Inc.

Providers administering the Pfizer-BioNTech COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to Pfizer the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1. Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2
- Reduction in the risk of confirmed COVID-19 after Dose 1 and before Dose 2
- Reduction in the risk of confirmed severe COVID-19 any time after Dose 1

The protocol-specified 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 7 days after completion of the vaccination regimen. Additional primary efficacy analyses in the all-available efficacy population, including participants who had protocol violations, showed consistency with outcomes in the primary analysis population. Efficacy findings were also consistent across various subgroups, including racial and ethnic minorities, participants aged 65 years and older, and those with one or more of the following conditions: obesity, diabetes, hypertension, and chronic cardiopulmonary diseases. While limited, available data suggest that individuals with previous SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination.

Among participants with no evidence of COVID-19 prior to vaccination, the vaccine was effective in reducing the risk of COVID-19 and severe COVID-19 after Dose 1. Fewer severe cases were also observed in the vaccine recipients relative to recipients of placebo during the follow up period after Dose 1. The findings post Dose 1, from a post-hoc analysis, cannot be the basis to assess the potential efficacy of the vaccine when administered as a single dose because the period of observation is limited by the fact that most participants received a second dose three weeks after the first one.

8.2. Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subset of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) is too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

The primary endpoint was evaluated in individuals without prior evidence of COVID-19 disease, and very few cases of confirmed COVID-19 occurred among participants with evidence of infection prior to vaccination (although more cases occurred in the placebo group compared with the vaccine group). Therefore, available data are insufficient to make conclusions about benefit in individuals with prior SARS-CoV-2 infection. However, available data, while limited, do suggest that previously infected individuals can be at risk of COVID-19 (i.e., reinfection) and could benefit from vaccination.

Effectiveness in pediatric populations

The representation of pediatric participants in the study population is too limited to adequately evaluate efficacy in pediatric age groups younger than 16 years. No efficacy data are available from participants ages 15 years and younger. Although adolescents 16 to 17 years of age were included in the overall efficacy analysis, only one confirmed COVID-19 case was reported in this age group. However, it is biologically reasonable to extrapolate that effectiveness in ages 16 to 17 years would be similar to effectiveness in younger adults. Efficacy surveillance continued beyond November 14, 2020, and the Sponsor has represented that additional data will be provided in a BLA.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27 to November 14, 2020, in various geographical locations. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine against asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[11-14] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3. Known Risks

The vaccine has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%). Adverse reactions characterized as reactogenicity were generally mild to moderate. The number of subjects reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (137 [0.63%] vs. 111 [0.51%]). Severe adverse reactions occurred in 0.0-4.6% of participants, were more frequent after Dose 2 than after Dose 1 and were generally less frequent in older adults (>55 years of age) (≤2.8%) as compared to younger participants (≤4.6%). Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination.

Serious adverse events, while uncommon (<1.0%), represented medical events that occur in the general population at similar frequency as observed in the study. Three SAEs in the BNT162b2 group were considered related by the investigator, but not the Sponsor, as related to study vaccination: shoulder injury (n=1), ventricular arrhythmia in a participant with known cardiac conditions (n=1), and lymphadenopathy temporally related following vaccination (n=1). We considered two of the events as possibly related to vaccine: the shoulder injury possibly due to vaccine administration or the vaccine itself and lymphadenopathy. Lymphadenopathy was temporally associated and biologically plausible.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection. Although participants 16 to 17 years of age were enrolled in the phase 3 trial, safety data for this age group is limited. However, available data are consistent with the safety profile in the adult population, and it is biologically reasonable to extrapolate the greater safety experience in adults, in particular younger adults, to the oldest pediatric age group of 16 to 17 years.

8.4. Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 16 years of age, pregnant and lactating individuals, and immunocompromised individuals.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of nearly 44,000 participants over the period of follow up at this time. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

A numerically greater number of appendicitis cases occurred in the vaccine group but occurred no more frequently than expected in the given age groups and do not raise a clear concern at this time for a causal relationship to study vaccination. Although the safety database revealed an imbalance of cases of Bell's palsy (4 in the vaccine group and none in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

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10. Appendix A. Study BNT162-01

Design

Study BNT162-01 is an ongoing, first-in-human, phase 1 dose-level finding study conducted in Germany to evaluate the safety and immunogenicity of several different candidate vaccines, including BNT162b2. Twelve adults 18 to 55 years of age received 30ug BNT162b2.

Secondary and exploratory objectives were specified to describe the immune response, measured by functional antibody titer, antibody binding assay, and cell-mediated immune responses (cytokines associated with Th1 and Th2 responses to assess for the induction of a balanced versus Th1 or Th2 dominant immune response) at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as in study C4591001.

Results

No SAEs were reported in the BNT162-01 safety database included in the EUA submission, and the safety profile for BNT162b2 in this study was similar to that in the much larger study, C4591001.

Evaluable ELISPOT data were available from 39 participants across dose levels of BNT162b2 (data cutoff date was 17 September 2020). Evaluable intracellular cytokine staining and FACS data were available from 36 participants across dose levels of BNT162b2 (cutoff date was 04 September 2020). Data for serology results for serum neutralizing titers were available for 45 participants across dose levels of BNT162b2 (data cutoff date was 18 September 2020). Most participants who received both doses of BNT162b2 had evidence of SARS-CoV-2 S protein-specific CD4+ (39/39, 100%) and CD8+ (35/39, 89.7%) T cell responses. These T cell responses were directed against different parts of the antigen, including epitopes in the RBD, indicating the induction of multi-epitope responses by BNT162b2. Functionality and polarization of S-specific BNT162b2-induced SARS-CoV-2 T cells were assessed by intracellular accumulation of cytokines IFNγ, IL-2, and IL-4 measured after stimulation with overlapping peptide pools representing the full-length sequence of the whole SARS-CoV-2 S protein. For benchmarking, PBMC fractions from 15 convalescent patients with virologically confirmed COVID-19 were used. The Th1 polarization of the T helper response was characterized by the IFNγ and IL-2 production, and only minor IL-4, production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation. The SARS-CoV-2 neutralizing geometric mean titer (GMTs) increased over baseline after Dose 1, with a boost effect after Dose 2 that was most pronounced at the 30 µg dose level.

Thus, the immunogenicity results from Study BNT162-01 showed evidence of antibody-mediated SARS-CoV-2 neutralization and a Th1 polarization in the cell-mediated cellular immune responses in healthy adults 18 to 55 years of age, which supports the final dose selection and prospect of benefit for the enrollment of larger numbers of participants in Study C4591001.

11. Appendix B. Charlson Comorbidity Index

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, HIV/AIDS.

Reference: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

12. Appendix C. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19

Emergency Use Authorization for Vaccines to Prevent COVID-19

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Vaccines and Related Biological Products Advisory Committee Meeting
December 17, 2020

FDA Briefing Document

Moderna COVID-19 Vaccine

Sponsor:
ModernaTX, Inc.

Moderna COVID-19 Vaccine
VRBPAC Briefing Document

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Glossary

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
mRNA	messenger RNA
NAAT	nucleic acid amplification-based test
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On November 30, 2020, ModernaTX (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (mRNA-1273) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is 2 doses, 100 µg each, administered 1 month apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3 randomized, double-blinded and placebo-controlled trial of mRNA-1273 in approximately 30,400 participants. The primary efficacy endpoint is the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2. In an interim analysis conducted using a data cutoff of November 7, 2020, a total of 27,817 participants randomized 1:1 to vaccine or placebo with a median 7 weeks of follow-up post-dose 2 were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to vaccination. Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5.0% (95% CI 86.5%, 97.8%) with 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 (11 protocol-defined severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group), in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for some of these outcomes did not allow for firm conclusions. Efficacy data from the final scheduled analysis of the primary efficacy endpoint (data cutoff of November 21, 2020, with a median follow-up of >2 months post-dose 2) demonstrated a VE of 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group and was consistent with results obtained from the interim analysis. The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to <65 years of age and 86.4% (95% CI: 61.4%, 95.5%) for participants ⩾65 years of age. A final secondary efficacy analysis also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 cases in the vaccine group.

Safety data from a November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomized 1:1 to vaccine or placebo with a median of 7 weeks of follow-up after the second dose supported a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. These safety data are the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Key safety data from this later submission, including death, other serious adverse events, and unsolicited adverse events of interest were independently verified and confirmed not to change the safety conclusions from the interim safety analysis.

The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and

chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ≥65 years of age as compared to younger participants. Among unsolicited adverse events of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff, lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Lymphadenopathy (axillary swelling and tenderness of the vaccination arm) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there were three reports of facial paralysis (Bell's palsy) in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

The frequency of serious adverse events was low (1.0% in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

With the exception of more frequent, generally mild to moderate reactogenicity in participants <65 years of age, the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations on whether, based on the totality of scientific evidence available, the benefits of the mRNA-1273 COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of December 11, 2020, has caused more than 71 million cases of COVID-19 and claimed the lives of more than 1.6 million people worldwide. In the United States, more than 16 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 296,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S.

President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is the main target for neutralizing antibodies, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

2.2 EUA Request for the Moderna COVID-19 Vaccine mRNA-1273

ModernaTX, Inc. (Sponsor) is developing a vaccine to prevent COVID-19 that is based on the pre-fusion stabilized SARS-CoV-2 spike glycoprotein (S) antigen encoded by mRNA and formulated in a lipid nanoparticle (LNP). The Moderna COVID-19 Vaccine (also referred to as mRNA-1273) is a 2-dose series of 100-µg intramuscular injections administered 1 month apart. The vaccine is supplied as a multi-dose vial (10 doses) containing a frozen suspension -25° to -15°C) of mRNA-1273 that must be thawed prior to administration. The vaccine does not contain a preservative.

A Phase 3 randomized and placebo-controlled trial using mRNA-1273 in approximately 30,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. A prespecified interim efficacy analysis from 27,817 participants using a data cutoff date of November 7, 2020, demonstrated vaccine efficacy (VE) of 94.5% (95% CI: 86.5%, 97.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. At the time of this interim analysis, the median efficacy follow-up was 7 weeks post completion of the 2-dose series. Safety data from a November 11, 2020, interim analysis with a median of 7 weeks follow-up after the second dose of vaccine were reported to demonstrate an acceptable tolerability profile with no significant safety concerns. On November 30, 2020, ModernaTX submitted an EUA request to FDA, based on the interim analyses described above, for use of mRNA-1273 to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

On December 7, 2020, the Sponsor submitted an amendment to the EUA request with additional accrued safety data on all participants with a median of 2 months (9 weeks) follow-up after the second dose, using a data cutoff date of November 25, 2020, and data from the prespecified final efficacy analysis using a data cutoff of November 21, 2020, which met the median follow-up of 2 months after dose 2 and demonstrated vaccine efficacy of 94.1% (95%

CI: 89.3%, 96.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. Although the complete datasets and analyses from the primary efficacy analysis and associated safety analyses submitted on December 7, 2020, have not been independently verified by the FDA to the same extent as the data for the interim efficacy analyses and associated safety analyses submitted on November 30, 2020, based on comprehensive independent review of the data from the interim analysis, and the consistency of findings across the two analysis time points, FDA considers that the totality of available data are sufficient to support an evaluation of this product for EUA.

2.3 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and would continue under further investigation (under an Investigational New Drug Application). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4 Alternatives for Prevention of COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. However, the Pfizer-BioNTech COVID-19 vaccine is not an approved product, and furthermore is not available in quantity sufficient to vaccinate all persons in the U.S. for whom the vaccine is authorized for use. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use authorization, but not FDA approved, for treatment of COVID-19. Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.5 Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6]

2.6 Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.7 Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Regardless of when vaccination of placebo recipient would occur, there may be advantages to maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[9-11]

2.8 Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session to discuss, in general, the development, authorization, and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents
- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine

- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
  - Further evaluate safety, effectiveness and immune markers of protection
  - Evaluate the safety and effectiveness in specific populations.

On December 10, 2020, the VRBPAC met in open session to discuss the EUA request of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age older. Topics discussed at the meeting but not voted upon included Pfizer's plan for continuation of blinded, placebo-controlled follow-up in ongoing trials in the event that the vaccine is made available under EUA and gaps in plans for further evaluation of vaccine safety and effectiveness in populations that receive the Pfizer-BioNTech Vaccine under an EUA. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the proposed vaccine outweigh its risks for use in individuals 16 years of age and older.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on December 17, 2020, to discuss and provide recommendations on whether based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The Committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

4. Moderna COVID-19 Vaccine (mRNA-1273)

4.1 Vaccine Composition, Dosing Regimen

The Moderna COVID-19 Vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

The Moderna COVID-19 Vaccine is provided as a frozen suspension [stored between -25° to -15°C (-13° to 5°F)] multi-dose vial containing 10 doses. The vaccine must be thawed prior to administration. After thawing, a maximum of 10 doses (0.5 mL each) can be withdrawn from each vial. Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F) and discarded after 6 hours.

The Moderna COVID-19 Vaccine, mRNA-1273 (100 µg) is administered intramuscularly as a series of two doses (0.5 mL each), given 28 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2 Proposed Use Under EUA

The proposed use of the vaccine under an EUA is for the prevention of COVID-19 in adults 18 years of age and older.

5. FDA Review of Clinical Safety and Effectiveness Data

5.1 Overview of Clinical Studies

Table 1

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Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Moderna COVID-19 Vaccine mRNA-1273

Study Number	Type of Study (Efficacy, Safety, Nonclinical)	Participants randomized (N)	Study Design & Type of Control	Test Product(s); Dosing Regimens	Study Status
P301	Efficacy, Safety	30418	A Phase 3, randomized, stratified, observer-blind, placebo-controlled study	mRNA-1273 100 µg	Ongoing-vaccine efficacy demonstrated at the 1st interim analysis
P201	Safety, Immunogenicity	600	A Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study	mRNA-1273 50ug,100µg	Ongoing-Day 57 primary analysis have completed
20-0003*	Safety, Immunogenicity	120	A Phase 1 Open-label dose-ranging study	mRNA-1273 25ug 50ug,100ug 250ug	Ongoing-Day 119 (25ug, 100ug, 250ug), Day 57 (50ug)

*Sponsor: Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health

5.2 Study mRNA-1273-P301

5.2.1 Design

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 years of age and older. The study took place in 99 sites in the United States. Participants (N=30,351) were randomized 1:1 to receive intramuscular injections of either 100 µg of mRNA-1273 vaccine (n=15,181) or placebo

(n=15,170) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19, 18 to <65 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 41.4% of the study population. Participants were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. The study included 24,907 (82.1%) participants considered at occupational risk for acquiring SARS-CoV-2 infection, of whom 7,613 (25.1%) were healthcare workers. Other essential workers were also represented. The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS CoV-2 at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (Viracor; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the final scheduled efficacy analysis. Two interim analysis timepoints were pre-specified; the first upon accrual of 53 cases and the second upon accrual of 106 cases. The expected duration of study participation is approximately 25 months.

Primary Efficacy Endpoint

The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). The primary analysis was based on the Per-Protocol Set, defined as all randomized, baseline SARS-CoV-2 negative participants who received planned doses per schedule and have no major protocol deviations. For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was defined as:

- At least TWO of the following systemic symptoms: Fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), or
- At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; and
- NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Vaccine efficacy was defined as the percent reduction (mRNA-1273 vs. placebo) in the hazard of the primary endpoint, i.e. VE =1 – Hazard Ratio (HR). A stratified Cox proportional hazard (PH) model using Efron's method to handle ties and with treatment group as the independent variable was used to estimate the HR, where the same stratification factor used for randomization was applied. The primary objective would be met if the null hypothesis of H0: VE ≤30% is rejected at any of the interim or primary analyses at the respective significance level.

The final scheduled efficacy analysis of the primary endpoint was planned when a total of 151 adjudicated cases occurring at least 14 days after the second injection had been accrued. In addition, two interim analyses were planned when 35% (53 cases) and 70% (106 cases) of the

total target number of cases had been accrued. The Lan-DeMets spending function was used for approximating O'Brien-Fleming efficacy bounds to preserve the overall Type I error rate at a one-sided α =0.025, yielding nominal one-sided α of 0.0002, 0.0073, and 0.0227 at the first and second interim and the primary analyses, respectively. As conducted, the first and only interim analysis in the study occurred at 95 adjudicated cases of the primary endpoint, where the null hypothesis of H0: VE ≤30% was evaluated at a one-sided alpha of 0.0047.

Secondary Efficacy Endpoints

Secondary endpoints based on the Per-Protocol Set included the VE of mRNA-1273 to prevent the following:

- Severe COVID-19 (as defined below)
- COVID-19 based on a less restrictive definition of disease (defined below) occurring at least 14 days after the second dose of vaccine
- Death due to COVID-19
- COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the second dose)

One additional secondary endpoint was based on the Full Analysis Set (FAS): VE of mRNA-1273 to prevent COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection.

One of the secondary efficacy endpoints assessed COVID-19 as defined by a less restrictive definition: a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR **and** one of the following systemic symptoms:

- fever (temperature ≥38°C), or
- chills,
- cough,
- shortness of breath or difficulty breathing,
- fatigue,
- muscle aches or body aches,
- headache,
- new loss of taste or smell,
- sore throat,
- nasal congestion or rhinorrhea,
- nausea or vomiting, or diarrhea

Another secondary endpoint assessed cases of severe COVID-19, defined as a case of confirmed COVID-19 plus at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg);
- Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death

Vaccine efficacy of secondary endpoints was estimated from the Cox proportional-hazards model when the primary endpoint reached statistical significance. Estimates based on the Per-Protocol Set were presented with nominal two-sided 95% confidence intervals.

Analysis Populations

For the purposes of analysis, the following populations are defined:

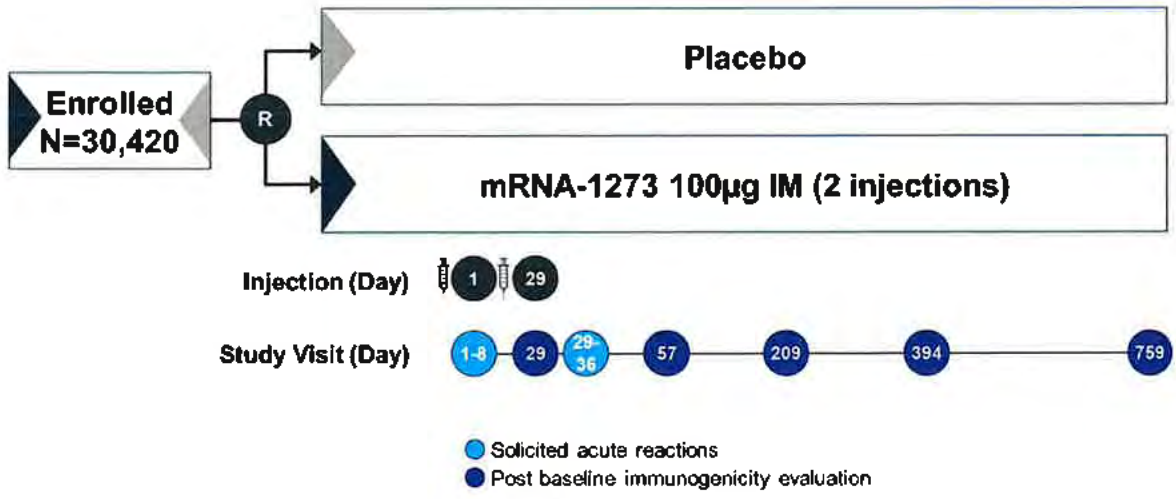
Table 2. Efficacy Set Definitions

Population	Description
Randomized	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set	All randomized participants who received at least one dose of Investigational Product (IP).
mITT Set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 (i.e., negative NP swab test at Day 1 and/or bAb against SARS-CoV-2 nucleocapsid below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1 before the first dose of IP.
Per Protocol Set	All participants in the mITT Set who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to DBL and unblinding, that impact critical or key study data.
Safety Set	All randomized participants who received at least one dose of IP.
Solicited Safety Set	All randomized participants who received at least one dose of IP and contributed any solicited adverse reaction data.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of mRNA-1273 after 1 or 2 doses. In all studies, participants recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from dose 1 to 28 after the last dose and medically attended adverse events (MAAEs) and serious AEs (SAEs) from dose 1 to the end of the study. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study 301



Safety assessments included the following:

- Solicited local and systemic adverse reactions (AR) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR.
- AEs leading to discontinuation from vaccination and/or study participation from Day 1 through Day 759 or withdrawal from the study.
- Medically Attended Adverse Events (MAAE) from Day 1 through Day 759 or withdrawal from the study.
- Serious Adverse Events (SAEs) from Day 1 through Day 759 or withdrawal from the study.
- Abnormal vital sign measurements.
- Physical examination findings.
- Pregnancy and accompanying outcomes.

Safety laboratory evaluations were not assessed in Study P301 but were collected in the phase 2 Study P201. See Appendix A on page 53.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. Such illnesses were evaluated and reported as SAEs.

Monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

The table below shows the Phase 3 safety analyses populations that were used to determine the proportions of study participants who experienced adverse events, including solicited adverse reactions after each dose, unsolicited adverse events, medically attended adverse events, and serious adverse events.

Table 3. Safety Set Definitions

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants treatment status in the study.
Safety Set	All randomized participants who received at least one dose of investigational product. The safety set was used for all analyses of safety except solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set	All randomized participants who received at least one dose of investigational product and contributed any solicited adverse reaction data. The solicited safety set was used for the analyses of solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set-1st Injection	All randomized participants who received the 1st dose and provided any solicited reaction data.

Population	Description
Solicited Safety Set-2nd Injection	All randomized participants who received the 2nd dose and provided any solicited reaction data.

5.2.2 FDA Assessment of Phase 3 Follow-Up Duration

As of the interim analysis cutoff (November 7, 2020, for efficacy, November 11, 2020, for safety), the proportion of participants across groups who received one dose of vaccine or placebo was 100%, and the proportion of participants who received two doses was 91.9% (92.1% vaccine, 91.7% placebo). The median follow-up after dose 2 was 7 weeks across groups. (For participants who did not receive a second dose of vaccine or placebo, follow-up after dose 2 was zero. Among participants who received dose 2, the median follow-up after the second dose was 50.0 days.) The proportion of participants with at least 1 month of follow-up after dose 2 was 76.7% (77.2% vaccine, 76.2% placebo) and with at least 2 months follow-up after dose 2 was 25.3% (25.7% vaccine, 24.9% placebo). FDA has completed its independent validation and evaluation of the datasets from which the Sponsor's interim safety and efficacy analyses were derived.

A second safety data cutoff was performed on November 25, 2020, and final efficacy analysis performed with a data cutoff of November 21, 2020, when 196 primary endpoint cases accrued. These data include a median follow-up of 2 months (9 weeks) for both efficacy and safety. The proportion of participants with at least 1 month of follow-up after dose 2 was 87.9% (88.2% vaccine, 87.7% placebo) and with at least 2 months follow-up after dose 2 was 53.6% (53.8% vaccine, 53.5% placebo). The Sponsor submitted analyses from the final efficacy analysis (Tables, Figures and Listings) on December 4, 2020, and safety analyses (Tables, Figures and Listings) on December 7, 2020, for FDA review under the EUA. Datasets were also submitted on December 7, 2020 and validated by FDA by December 8, 2020. The review of the second dataset submission for the final scheduled efficacy analysis and safety data through November 25, 2020, was not as comprehensive as that of the interim efficacy data and safety data first submitted in support of the EUA. However, preliminary assessments of safety and efficacy data and analyses from second data cutoff do not demonstrate any notable differences compared with the efficacy and safety analyses from November 7, 2020, and November 11, 2020, respectively, and key safety and efficacy data (e.g., the primary analysis, cases of severe COVID-19, and serious adverse events) from the December 7, 2020, submission were verified. FDA therefore considers the totality of submitted data to satisfy the expectation of a median of 2 months follow-up after completion of the full vaccination regimen.

5.2.3 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 4 (Per-Protocol Set) and Table 5 (Safety Set). The proportion of participants excluded from the Per-Protocol Set was balanced between treatment groups, with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the per protocol population, 26.3% of vaccine recipients and 25.7% of placebo recipients completed at least 2 months follow-up after dose 2.

Table 4. Efficacy Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Full Analysis Set	15180 (99.8)	15170 (99.7)	30350 (99.8)
Modified Intent-to-Treat Set	14312 (94.1%)	14370 (94.5%)	28682 (94.3)
Participants excluded from PP set	1274 (8.4%)	1327 (8.7%)	2601 (8.6%)
Randomized but received no Investigational Product (IP)	28 (0.2%)	40 (0.3%)	68 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	868 (5.7%)	800 (5.3%)	1668 (5.5)
Received IP other than what the participant was randomized to	5 (<0.1)	7 (<0.1)	12 (<0.1)
Discontinued study or study vaccine without receiving the second dose	136 (0.9)	203 (1.3)	339 (1.1)
Did not receive second dose of IP	144 (0.9)	155 (1.0)	299 (1.0)
Received vaccine out of window	81 (0.5)	98 (0.6)	179 (0.6)
Major protocol deviation	12 (<0.1)	24 (0.2)	36 (0.1)
Per Protocol Set		13883 (91.3)	27817 (91.4)
Completed 1 dose**	13934 (100)	13883 (100)	27817 (100)
Completed 2 doses**	13218 (94.9)	13164 (94.8)	26382 (94.8)
Completed at least 7 weeks follow-up after dose 2**	7293 (52.3)	7304 (52.6)	14597 (52.5)
Completed at least 2 months follow-up after dose 2**	3669 (26.3)	3568 (25.7)	7237 (26.0)
Discontinued from Study**	24 (0.2)	34 (0.2)	58 (0.2)
Reason for Discontinuation**			
Adverse Event	0	0	0
Death	0	1 (<0.1)	1 (<0.1)
Withdrawal by Participant	18 (0.1)	22 (0.2)	
Lost to Follow-up	2 (<0.1)	9 (<0.1)	11 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	2 (<0.1)	0	2 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2
[a] EUA request (interim analysis): November 11, 2020 cutoff
*Percentage based on number of participants in the Safety Set
**Percentage based on number of participants in the Per-Protocol Set

Based on the November 11, 2020 safety data cutoff, an overview of participant disposition is presented in the table below. The proportion of randomized participants who discontinued from the study was 0.9% (288 participants) across study groups, with a greater number in the placebo group (168) compared with the vaccine group (120). The most frequently reported reason was withdrawal of consent (67 participants in the vaccine group, 120 in the placebo group). In addition, 51 participants were lost to follow-up (20 in the vaccine group, 31 in the placebo group). In the vaccine group, 3 participants withdrew due to an adverse event (<0.1%, including 1 participant who withdrew due to a SAE) and 3 participants died during the study. In the placebo group, no participants withdrew due to an adverse event, and 4 participants died during the study.

Table 5. Safety Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Completed 1 dose	15180 (99.8)	15170 (99.7)	30350 (99.8)
Completed 2 doses	13982 (91.9)	13916 (91.5)	27898 (91.7)
Exposed (Safety Set)	15184	15166	30350 (99.8)
Discontinued from Study	120 (0.8)	168 (1.1)	288 (0.9)
Reason for Discontinuation			
Adverse Event	3 (<0.1)	0	3 (<0.1)
Death	3 (<0.1)	4 (<0.1)	7 (<0.1)
Withdrawal by Participant	67 (0.4)	120 (0.8)	187 (0.6)
Lost to Follow-up	20 (0.1)	31 (0.2)	51 (0.2)
Protocol Deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician Decision	17 (0.1)	2 (<0.1)	19 (<0.1)
Other	9 (<0.1)	10(<0.1)	19 (<0.1)
Completed ≥1 month f/up*	14354 (94.5)	14345 (94.6)	28700 (94.6)
Completed ≥2 months f/up*	12021 (79.2)	11974 (79.0)	23995 (79.1)
Completed ≥1 month f/up after dose 2*	11717 (77.2)	11559 (76.2)	23276 (76.7)
Completed ≥2 months f/up after dose 2*	3894 (25.7)	3773 (24.9)	7667 (25.3)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2.
[a] EUA request (interim analysis): November 11, 2020 cutoff

5.2.4 Demographics and Other Baseline Characteristics

The Per-Protocol Set included 47.4% females and 25.3% of individuals ≥65 years of age. There were 36.5% of participants considered as representing communities of color with 9.7% African American, 4.7% Asian, and <3% from other racial groups; 20% of participants were Hispanic/Latino. A majority of the participants (82%) were considered at occupational risk for SARS-CoV-2 exposure, with 25.4% of participants being healthcare workers. At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.3% of participants, and 4% of participants had two or more high risk conditions. The protocol-specified risk factors were those conditions that placed an individual at increased risk for severe complications of COVID-19 and were selected based on CDC recommendations[12] from March 2020. These conditions included the following:

- Chronic lung disease (e.g., emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- HIV infection

There was a similar distribution of demographic characteristics between the treatment groups as well as between the all randomized population, Full Analysis Set, and the Per-Protocol Set.

Table 6. Demographic Characteristics[a], Per-Protocol Set

Characteristic	Vaccine Group (N=13934) n (%)	Placebo Group (N=13883) n (%)	Total (N=27817) n (%)
Sex			
Female	6661 (47.8)	6514 (46.9)	13175 (47.4)
Male	7273 (52.2)	7369 (53.1)	14642 (52.6)
Age (years)			
Mean (SD)	51.6 (15.45)	51.5 (15.55)	51.6 (15.50)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age- subgroups (years)			
18 to <65	10407 (74.7)	10384 (74.8)	20791 (74.7)
65 and older	3527 (25.3)	3499 (25.2)	7026 (25.3)
Race			
American Indian or Alaska Native	107 (0.8)	110 (0.8)	217 (0.8)
Asian	616 (4.4)	684 (4.9)	1300 (4.7)
Black or African American	1369 (9.8)	1338 (9.6)	2707 (9.7)
Native Hawaiian or Other Pacific Islander	33 (0.2)	30 (0.2)	63 (0.2)
White	11078 (79.5)	11005 (79.3)	22083 (79.4)
Other	298 (2.1)	293 (2.1)	591 (2.1)
Ethnicity			
Hispanic or Latino	2783 (20.0)	2769 (19.9)	5552 (20.0)
Not Hispanic or Latino	11019 (79.1)	10987 (79.1)	22006 (79.1)
Race and Ethnicity			
Non-Hispanic white	8858 (63.6)	8755 (63.1)	17613 (63.3)
Communities of color	5054 (36.3)	5102 (36.7)	10156 (36.5)
Occupational Risk*	11397 (81.8)	11408 (82.2)	22805 (82.0)
Healthcare worker	3541 (25.4)	3531 (25.4)	7072 (25.4)
High Risk Condition**			
No high risk condition	11820 (77.9)	11788 (77.7)	23608 (77.8)
One high risk condition present	3116 (22.4)	3075 (22.1)	6191 (22.3)
Two or more high risk conditions present	561 (4.0)	554 (4.0)	1115 (4.0)
Age and Health Risk for Severe COVID-19***			
18 to <65 years and not at risk	8309 (59.6)	8323 (60.0)	16632 (59.8)
18 to <65 years and at risk	2098 (15.1)	2061 (14.8)	4159 (15.0)
≥65 years	3527 (25.3)	3499 (25.2)	7026 (25.3)

Source: Sponsor's Table14.1.3.4.2. [a] EUA request (interim analysis): November 11, 2020 data cutoff.
Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.
* High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
** Age and health risk for severe COVID-19 is used as stratification factor for randomization.

The demographic characteristics among vaccine and placebo participants in the safety population were similar. There were no significant imbalances in demographic and other baseline characteristics between the per-protocol population and the safety population, with median 7-week follow-up.

Table 7. Demographic Characteristics[a], Safety Set

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Sex			
Female	7255 (47.8)	7100 (46.8)	14355 (47.3
Male	7929 (52.2)	8065 (53.2)	15995 (52.7)
Age (years)			
Mean (SD)	51.4 (15.50)	51.3 (15.60)	51.4 (15.55)
Median	53.0	52.0	52.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
≥18 to <65	11414 (75.2)	11415 (75.3)	22830 (75.2)
65 and older	3770 (24.8)	3750 (24.7)	7520 (24.8)
Race			
American Indian or Alaska Native	110 (0.7)	120 (0.8)	230 (0.8)
Asian	653 (4.3)	732 (4.8)	1385 (4.6)
Black or African American	1562 (10.3)	1528 (10.1)	3090 (10.2)
Native Hawaiian or other Pacific islander	34 (0.2)	32 (0.2)	66 (0.2)
White	12032 (79.2)	11990 (79.1)	24023 (79.2)
Other	321 (2.1)	315 (2.1)	636 (2.1)
Multiracial	315 (2.1)	319 (2.1)	634 (2.1)
Ethnicity			
Hispanic or Latino	3121 (20.6)	3112 (20.5)	6234 (20.5)
Not Hispanic or Latino	11920 (78.5)	11914 (78.6)	23834 (78.5)
Race and Ethnicity			
Non-Hispanic White	9534 (62.8)	9458 (62.4)	18992 (62.6)
Communities of color	5624 (37.0)	5680 (37.5)	11305 (37.2)
Occupational Risk*	12420 (81.8)	12487 (82.3)	24907 (82.1)
Healthcare worker	3787 (24.9)	3826 (25.2)	7613 (25.1)
High Risk Condition**			
One high risk condition present	3360 (22.1)	3382 (22.3)	6742 (22.2)
No high risk condition	11824 (77.9)	11783 (77.7)	23608 (77.8)
Age and Health Risk for Severe COVID-19***			
≥18 to <65 years and not at risk	8889 (58.5)	8884 (58.6)	17773 (58.6)
≥18 to <65 years and at risk	2530 (16.7)	2534 (16.7)	5065 (16.7)
≥65 years	3765 (24.8)	3747 (24.7)	7512 (24.8)

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Baseline SARS CoV-2 status****			
Negative	14316 (94.3%)	14366 (94.7)	26862 (94.5%)
Positive	341 (2.2%)	334 (2.2%)	675 (2.2%)
Missing	527 (3.5%)	465 (3.5%)	993 (3.3%)

Source: Sponsor's Table 14.1.3.2.2 [a] EUA request (interim analysis): November 11 2020 cutoff.
* Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.**
**High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human immunodeficiency virus (HIV) infection

The following table provides the proportions of participants randomized to each of the protocol-specified strata based on presence or absence of protocol-defined risk factors for severe COVID-19 disease, including age ⩾65 years. The presence of these risk factors was assessed at screening via review of the participants medical history. The protocol specified that at least 25% (and up to 50%) of enrolled participants were to be either ⩾65 years of age or 18 through <65 years of age with a protocol-defined risk factor. As of the November 11, 2020 cutoff, ~25% of participants were age ⩾65 years, and 16.7% of participants were age 18 to <65 years with a protocol-defined risk factor. The remainder of participants (58.6%) were age 18 to <65 years without risks. The proportions of participants in each of these three strata randomized to vaccine or placebo are shown in the table below.

Table 8. Protocol-Defined Risk for Severe COVID-19 Disease, Safety Seta

Participants Risk Categories	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Without Any Protocol Risk for Severe COVID-19	11824 (77.9)	11783 (77.7)	23608 (77.8)
With Any Protocol Risk for Severe COVID-19	3360 (22.1)	3382 (22.3)	6742 (22.2)
Chronic Lung Disease	707 (4.7)	741 (4.9)	1448 (4.8)
Significant Cardiac Disease	742 (4.9)	741 (4.9)	1483 (4.9)
Severe Obesity	986 (6.5)	978 (6.4)	1964 (6.5)
Diabetes	1427 (9.4)	1431 (9.4)	2858 (9.4)
Liver Disease	100 (0.7)	96 (0.6)	196 (0.6)
HIV Infection	90 (0.6)	86 (0.6)	176 (0.6)

Source: Sponsor's Table 14.1.3.2.2. [a] EUA request (interim analysis): November 11, 2020 cutoff

5.2.5 Vaccine Efficacy

Interim Primary Efficacy Analysis

The interim primary efficacy analysis was based on the Per-Protocol Set, which consisted of all participants with negative baseline SARS-CoV-2 status (i.e., negative RT-PCR for SARS-CoV-2 at Day 1 and/or negative serology against SARS-CoV-2 nucleocapsid) and who received 2 doses of investigational product per schedule with no major protocol deviations. The primary efficacy endpoint was vaccine efficacy (VE) in preventing protocol defined COVID-19 occurring at least 14 days after dose 2. Cases were adjudicated by a blinded committee. The primary

efficacy success criterion would be met if the null hypothesis of VE ≤30% was rejected at the O'Brien Fleming boundary at either the interim or primary analysis. The efficacy analysis presented is based on the data at the first pre-specified interim analysis timepoint consisting of 95 adjudicated cases. As shown in Table 9, in participants ≥18 years of age, there were 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group, with a VE of 94.5%, a lower bound of the 95% CI of 86.5%, and a one-sided p-value of <0.0001 for testing H0: VE ≤30%, which met the pre-specified success criterion. In participants ≥65 years of age in the Per-Protocol Set, there were no COVID-19 cases in the vaccine group and 15 COVID-19 cases in the placebo group.

Table 9. Interim Analysis[a] for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
All participants	5 (<0.1) 1.840	90 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1.
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose. All potential COVID-19 cases starting 14 days after the 2nd dose in the clinical database as of 07-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (07-Nov-2020 is the data cutoff date for efficacy). One case (in the placebo group) was assessed as a case by the adjudication committee but did not meet case definition based on statistical analysis plan (participant had body aches, nasal congestion, rhinorrhea, which were not protocol defined symptoms).
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/placebo) and 95% CI from the stratified Cox proportional hazard model.
**The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary: the one-sided nominal alpha of 0.0049 based on 95 cases using the Lan-DeMets O'Brien-Fleming spending function.

There were an additional 18 COVID-19 cases which met the protocol-defined primary efficacy endpoint but were not able to be adjudicated in time for the interim analysis. Of these 18 cases, one was in the vaccine group, and 17 were in the placebo group. Vaccine efficacy for the primary efficacy endpoint including these unadjudicated cases was similar to the results presented above.

Interim Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the primary efficacy endpoint include VE based on age, sex, race and ethnicity, risk factor, and baseline SARS-CoV-2 status and provide additional information on the applicability of these results across the general population. In general, VE among the subgroups are similar to the VE seen in the overall study population. The small number participants and cases in some subgroups, such as participants ≥75 years of age and participants in certain racial subgroups, limits the interpretability of the individual VE results, but are displayed for completeness.

Table 10. Subgroup Analyses of Vaccine Efficacy[a], COVID-19 14 Days After Dose 2 Per Adjudication Committee Assessments, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Age (years)			
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)
65 to <75	0 / 2904	12/ 2823 (0.4) 20.883	100%
75 and older	0 / 623	3 / 676 (0.4) 21.726	100%
Age and risk for severe COVID-19**			
18 and <65 and not at risk	4 / 8309 (<0.1) 2.524	57 / 8323 (0.7) 36.034	93.0% (80.8%, 97.5%)
18 and <65 and at risk	1 / 2098 (<0.1) 2.428	18 / 2061 (0.9) 44.673	94.6% (59.4%, 99.3%)
≥65	0 / 3527	15 / 3499 (0.4) 21.046	100%
Sex			
Female	3 / 6661 (<0.1) 2.271	45 / 6514 (0.7) 34.991	93.5% (79.2%, 98.0%)
Male	2 / 7273 (<0.1) 1.433	45 / 7369 (0.6) 31.883	95.5% (81.5%, 98.9%)
Race and Ethnicity			
Non-Hispanic white	5 / 8858 (<0.1) 2.657	70 /8755 (0.8) 37.721	93.0% (82.6%, 97.2%)
Communities of color	0 / 5054	20 / 5102 (0.4) 23.892	100%
Ethnicity			
Hispanic or Latino	0 / 2783	12 / 2769 (0.4) 26.346	100%
Not Hispanic or Latino	5 / 11019 (<0.1) 2.243	77 / 10987 (0.7) 34.729	93.6% (84.1 %, 97.4%)
Race			
American Indian or Alaska Native	0 / 107	0 / 110	
Asian	0 / 616	3 / 684 (0.4) 26.549	100%
Black or African American	0 / 1,369	4 / 1338 (0.3) 18.566	100%
Native Hawaiian or Other Pacific Islander	0 / 33	0 / 30	
White	5 /11078 (<0.1) 2.215	80 / 11005 (0.7) 35.821	93.8% (84.8%, 97.5%)
Multiple	0 / 293	1 / 304 (0.3)	100%

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Other	0 / 298	2 / 293 (0.7) 45.645	100%

Source: Sponsor's Table 14.2.2.1.1.6.1.1, Table 14.2.2.1.1.6.3.1, Table 4.2.2.1.1.6.7.1, Table 14.2.2.1.1.6.10.1, Table 14.2.2.1.1.6.4.1, Table 14.2.2.1.1.6.2.1, Table 14.2.2.1.1.6.5.1, Table 14.2.2.1.1.6.6.1
[a] EUA request (interim analysis): November 7, 2020 data cutoff.
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic f ibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
**used as stratification factor for randomization

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 11.

Table 11. Demographic Characteristics[a], Participants With COVID-19 Starting 14 Days After Dose 2, Per Adjudication Committee Assessments, Per-Protocol Set

Characteristic	Vaccine (N[a] =5) N[b] (%)	Placebo (N[a] =90) N[b] (%)	Total (N[a] =95) N[b] (%)
Sex			
Female	3 (60)	45 (50)	48 (50.5)
Male	2 (40)	45 (50)	47 (49.5)
Age group			
18 to <65 years	5 (100)	75 (83.3)	80 (84.2)
≥65 to <75 years	0	12 (13.3)	12 (12.6)
≥75 years	0	3 (3.3)	3 (3.2)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	3 (3.3)	3 (3.2)
Black or African American	0	4 (4.4)	4 (4.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	5 (100)	80 (88.9)	80 (84.2)
Multiracial	0	1 (1.1)	1 (1.1)
Other	0	2 (2.2)	2 (2.1)
Ethnicity			
Hispanic or Latino	0	12 (13.3)	12 (12.6)
Not Hispanic or Latino	5 (100)	77 (85.6)	82 (86.3)
Not reported	0	1 (1.1)	1 (1.1)
At risk for severe COVID-19			
Yes	1 (20)	24 (26.7)	25 (26.3)
No	4 (80)	66 (73.3)	70 (73.7)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. [a] EUA request (interim analysis): November 07 2020 efficacy data cutoff. [a] EUA request (interim analysis): November 07 2020 cutoff.
[b] n = Number of participants with the specified characteristic.

Only 2.2% of participants had evidence of prior infection at study enrollment, and there was only one COVID-19 case starting 14 days after dose 2 reported from this subgroup, which was in a participant in the placebo group. There is insufficient data to conclude on the efficacy of the vaccine in previously infected individuals.

Table 12. Vaccine Efficacy by Baseline SARS-CoV-2 Status[a]: First COVID-19 From 14 Days After Dose 2 Per Adjudication Committee Assessment, Full Analysis Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6/15180	92/15170	93.5% (85.2, 97.2)
Positive	0/341	1/334 (0.3) 17.038	100%
Negative	6/14312 (<0.1) 2.154	90/14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0/527	1/465 (0.2)	100%

* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

Additional subgroup analyses of the interim primary efficacy analysis were conducted to evaluate the vaccine efficacy, by risk factor for severe COVID-19. VE point estimates were consistent with the efficacy observed for the overall study population, though interpretation of the results is limited by small numbers of participants and cases.

Table 13. Vaccine Efficacy by Risk Factor: First COVID-19 Occurrence From 14 Days After Dose 2, Per Adjudication Committee Assessment, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
At risk for severe COVID-19 due to comorbidity, regardless of age			
Yes	1 / 3116 (<0.1) 1.604	24 / 3075 (0.8) 39.177	95.9% (69.7%, 99.4%)
Chronic Lung Disease	0/661	6/673 (0.9) 42.950	100%
Significant Cardiac Disease	0/686	3/678 (0.4) 21.463	100%
Severe Obesity (BMI ≥40 kg/m^2)	1/901 (0.1) 5.524	11/884 (1.2) 62.851	91.2% (32.0%, 98.9%)
Diabetes	0/1338	7/1309 (0.5) 27.148	100%
Liver Disease	0/93	0/90	
HIV infection	0/80	1/76 (1.3) 91.108	100%
No	4 / 10818 (<0.1) 1.911	66 / 10808 (0.6) 31.657	94.0% (83.5%, 97.8%)
Obesity (BMI >30 kg/m^2)**	2/5269 (<0.1%)	46/5207 (0.9)	95.8% (82.6, 99.0)

[a] EUA request (interim analysis): November 7, 2020 efficacy data cutoff
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
** Post hoc analysis.

Interim Secondary Efficacy Analyses

Severe COVID-19 Cases

All 11 cases of severe COVID-19 at least 14 days after second dose as assessed by the adjudication committee were in the placebo group. Of these 11 participants, 5 had risk factors for severe COVID-19 and 6 did not. Three severe COVID-19 cases resulted in hospitalization and 8 did not. Nine of these cases met the severe COVID-19 case definition based on low oxygen saturation ≤93% on room air without any other severe disease criteria. One participant had low oxygen saturation as well as systolic blood pressure <90 mmHg. One participant had low oxygen saturation and missing data on whether other criteria were met. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 14.

Table 14. Severe COVID-19 Cases Starting 14 Days After Second Dose Based on Adjudication Committee Assessment, Per-Protocol Set

	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)*
Severe COVID-19	0	11 (<0.1); 4.072	100%

[a] EUA request (interim analysis): Novemer 07 2020 efficacy data cutoff.
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented when the lower bound was not evaluable by the statistical methods used for the analysis.

One participant in the mRNA-1273 group, a participant >65 years of age who had risk factors for severe COVID-19, was hospitalized due to oxygen saturation of 88% on room air 2 months after receiving the second dose of vaccine. There was a verbal report of a positive SARS-CoV-2 RT-PCR test 3 days prior to hospitalization; however, NP swab collected during hospitalization was negative for SARS-CoV-2. Due to absence of a confirmed RT-PCR result at the time of data snapshot, this case was not referred for adjudication and not captured. The pre-hospitalization RT-PCR result was later reported to be positive from an external CLIA-certified laboratory and may represent a severe COVID-19 case with hospitalization in the vaccine group.

There were 4 additional severe COVID-19 cases which met the protocol-defined severe COVID-19 endpoint but were not able to be adjudicated in time for the interim analysis. All 4 cases were in the placebo group.

Other Secondary Efficacy Endpoints

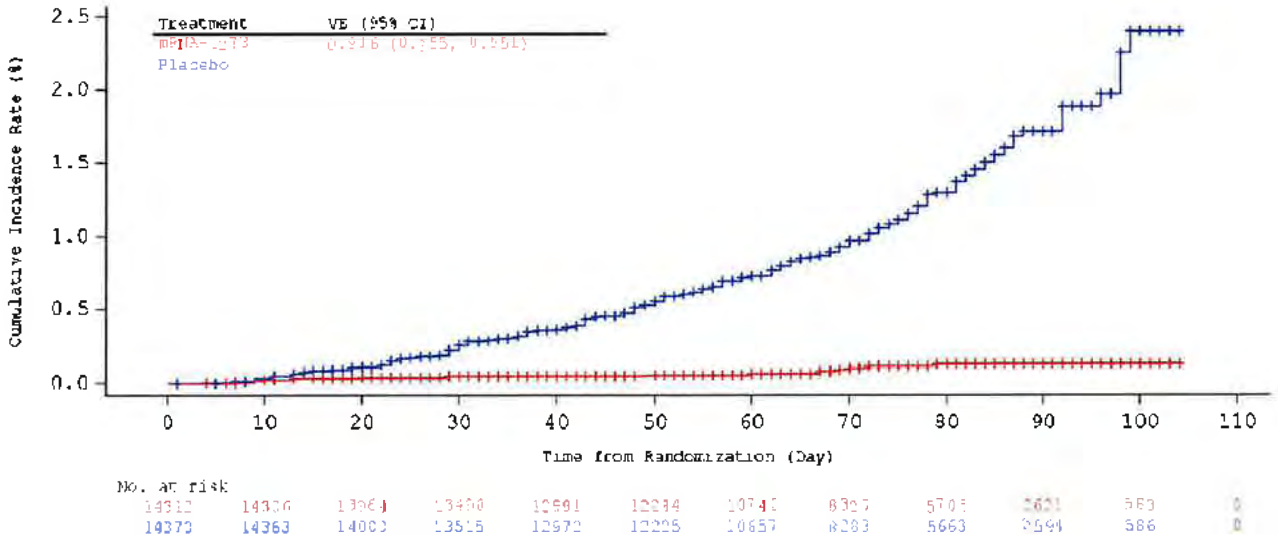
The secondary efficacy endpoint of VE of mRNA-1273 for the prevention of COVID-19 disease based on a less restrictive definition of COVID-19 disease from 14 days after dose 2 showed similar case splits and VE to the primary efficacy endpoints described above. Efficacy against COVID-19 occurring at least 14 days after the first dose of vaccine, including cases that occurred after the second dose, was also similar to the primary endpoint. There were no deaths due to COVID-19 at the time of the interim analysis to enable an assessment of vaccine efficacy against death due to COVID-19.

Cumulative Incidence Curves – Interim Efficacy Analysis

Based on the cumulative incidence curve for cases in the mITT efficacy population after randomization (same as date of dose 1), COVID-19 cases appear to have occurred similarly at low rates for both the mRNA-1273 and placebo groups until around Day 14 after dose 1. The

curves then diverge, with more cases accumulating in the placebo group than the mRNA-1273 group.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



Additional Interim Efficacy Analyses

Additional analyses were done to assess efficacy against COVID-19 after one dose of mRNA-1273. In participants in the mITT set who only received one dose of the vaccine at the time of the interim analysis, VE after one dose was 80.2% (95% CI 55.2%, 92.5%). These participants had a median follow-up time of 28 days (range: 1 to 108 days). The small, non-random sample and short median follow-up time limits the interpretation of these results. There appears to be some protection against COVID-19 disease following one dose; however, these data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Table 15. Vaccine Efficacy[a] of mRNA-1273 to Prevent COVID-19 From Dose 1 by Time Period in Participants Who Only Received One Dose, mITT Set

First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Case n (%)	Placebo Group N=1079 Case n (%)	VE (%) (95% CI)*
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (68.8%, 99.1%)

Surveillance time in person years for given endpoint across all participants within each group at risk for the endpoint
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years
**Participants who were not at risk (cases or censored at prior time period) are excluded from this analysis
[a] Based on interim analysis: November 7, 2020 efficacy data cutoff.

A similar analysis was conducted to look at vaccine efficacy against severe COVID-19 after one dose. In participants in the mITT group who received only one vaccine, 2 participants in the mRNA-1273 group and 4 participants in the placebo group developed severe COVID-19. Both participants in the vaccine group met the case definition for severe COVID-19 based on oxygen saturation ≤93% on room air. These results should be interpreted cautiously given the small sample size and case number and the short follow-up duration.

Table 16. Vaccine Efficacy[a] of mRNA-1273 to Prevent Severe COVID-19 After Dose 1 in Participants Who Only Received One Dose in mITT Set

	Vaccine Group N=996 Case n (%)	Control Group N=1079 Case n (%)	Vaccine Efficacy (95% CI)
Number of participants with severe COVID-19 starting after dose 1	2 (0.2)	4 (0.4)	42.6% (-300.8, 94.8)

[a] Based on interim analysis : EUA request (interim efficacy analysis): November 7, 2020 efficacy data cutoff.

Final Scheduled Efficacy Analysis

Data from the final scheduled efficacy analysis were submitted as an amendment to the EUA request on December 7, 2020. Analyses of efficacy endpoints beyond those presented below have not been independently verified by the FDA. The median efficacy and safety follow-up for participants in the study at of the time of the final scheduled efficacy analysis (November 21, 2020 efficacy data cutoff) was 9 weeks. Vaccine efficacy against COVID-19 starting 14 days after the second dose was 94.1% (95% CI 89.3%, 96.8%) and was consistent with results obtained from the interim analysis. The VE in participants ≥65 years of age appears to be lower than in younger adults 18 to <65 years (86.4% compared to 95.6%) and lower than observed in the interim analysis (100% based on a total of 15 cases).

Table 17. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence Rate per 1,000 person-years)*	Placebo Group N=13883 Cases n (%) (Incidence Rate per 1,000 person-years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All participants	11 (<0.1) 3.328	185 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years[1]	7/10551 (<0.1) 2.875	156/10521 (1.5) 64.625	95.6%; (90.6%, 97.9%)	NA
65 years and older[2]	4/3583 (0.1); 4.595	29/3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose. All potential COVID-19 cases starting 14 days after the second dose in the clinical database as of 21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy). One case (in the vaccine group) was adjudicated as a COVID-19 case by the committee but did was meet the case definition per statistical analysis plan due to documented symptoms and positive PCR being more than 14 days apart.
21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy).
* Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
**VE and 95% CI from the stratified Cox proportional hazard model
***The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary.
[1] Percentage based on number of participants in the 18 to <65 years of age group.
[2] Percentage based on number of participants in the ≥65 years of age group.

Severe COVID-19 Cases

In the primary efficacy analysis, there were an additional 19 cases of severe COVID-19 (one of which resulted in death from COVID-19), for a total of 30 severe COVID-19 cases starting 14 days after dose 2, per adjudication committee assessment. All 30 cases were in the placebo group. Nine of the total 30 severe COVID-19 cases resulted in hospitalization. Of the 19 additional severe cases since the interim analysis, 12 cases met the severe case definition due to low oxygen saturation ≤93% with no other criteria met. The remaining participants met the definition based on the following reasons: death (1 participant), ARDS requiring ECMO (1 participant), low oxygen saturation and renal and neurologic dysfunction (1 participant), low oxygen saturation and low blood pressure (2 participants), need for high flow oxygen (1 participant), low blood pressure only (1 participants). The COVID-19 case which resulted in death was in a 54-year-old participant with diabetes. The possible severe COVID-19 case in a mRNA-1273 vaccine recipient described with the interim efficacy analysis (negative SARS-CoV-2 PCR per the study central laboratory but reported positive PCR per a CLIA-certified external lab) is not included in the per-protocol analysis below.

Table 18. Secondary Efficacy Analysis, Severe COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All participants	0	30 (0.2) 9.138	100%

* EUA request (primary analysis): November 21, 2020 efficacy data cutoff.

Efficacy Summary

The data from the planned interim efficacy analysis, with a cutoff date of November 7, 2020, and median follow-up for efficacy of 7 weeks post-dose 2, met the prespecified success criteria established in the study protocol. Efficacy of the vaccine to prevent COVID-19 occurring at least 14 days after dose 2 was 94.5%, (95% CI 86.5%; 97.8%) in participants without prior evidence of SARS-CoV-2 infection. VE was >93% in the group of participants with or without prior infection, although interpretation of data in participants with positive SARS-CoV-2 status at baseline is limited by the small sample size and case numbers in this subgroup. Efficacy outcomes across demographic subgroups were consistent with the efficacy seen in the overall study population. All 11 cases of severe COVID-19 occurring 14 days after the second dose

were in the placebo group, although one severe COVID-19 may have occurred in the vaccine group but did not meet criteria for the protocol-specified case definition. Among participants in the mITT set who only received one dose of vaccine or placebo at the time of the interim analysis, efficacy against COVID-19 starting after dose 1 was 80.2% (95% CI: 55.2%, 92.5%). The efficacy observed after dose 1 and before dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the numbers of participants and time of observation are limited. The trial did not have a single-dose arm to make an adequate comparison.

Data from a final efficacy analysis (data cutoff November 21, 2020) was submitted as an amendment after the initial EUA request. The FDA has not independently verified the complete efficacy data from this dataset, beyond those analyses presented above. The final scheduled efficacy analysis on the primary endpoint, demonstrating a VE point estimate of 94.1% (95% CI: 89.3%, 96.8%), appear to align with the data obtained from the interim analysis, except for a lower efficacy observed in participants ≥65 years of age compared to that in younger adults 18 to <65 years of age and compared to the efficacy estimate from the interim analysis.

5.2.6 Safety

The safety analyses presented in this review are largely derived from the November 11, 2020 dataset that was the basis for the November 30, 2020 EUA request. FDA has not independently verified the complete safety dataset and analyses from the cutoff date of November 25, 2020. However, all new deaths, SAEs, unsolicited adverse events of interest, and pregnancies were reviewed using the cutoff date of November 25, 2020. No additional safety concerns were raised based on the additional data reviewed by FDA or analyses presented by the Sponsor. The safety analyses from the November 25, 2020 cutoff date, as presented by the Sponsor, appear to align with results from the interim analysis in terms of overall rates and types of solicited and unsolicited adverse events.

Adverse events were reported in a higher proportion of vaccine recipients than placebo recipients, and this imbalance was driven by reactogenicity (solicited AEs) reported in the 7 days following each dose of vaccine. The proportions of participants with SAEs, death, and withdrawals due to adverse events were balanced across the study groups. Overall, rates of AEs were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. The tables below provide an overview of the rates of AEs by treatment groups and baseline SARS-CoV-2 status.

Table 19. Participants Reporting at Least One Adverse Event, Among All Participants and by Baseline SARS-COV2 Status (Safety Set)[a]

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set	**N=15176**	**N=15162**
Solicited adverse reactions after any injection	14338/15176 (94.5)	9027/15162 (59.5)
Baseline SARS-COV-2 negative	13566/14309 (94.8%)	8576/14363 (59.7)
Baseline SARS-COV-2 positive	279 /340 (82.1%)	151/334 (45.2)
Solicited local adverse reaction	13,962/15176 (92.0)	4,381/15161 (28.9)
Baseline SARS-COV-2 negative	13211/14309 (92.3)	4147/14362 (28.9)
Baseline SARS-COV-2 positive	268/340 (78.8)	74/334 (22.2)
Grade 3 solicited injection site reaction[a]	1386/15176 (9.1)	143/15161 (0.9)
Baseline SARS-COV-2 negative	1307/14309 (9.1)	131/14362 (0.9)
Baseline SARS-COV-2 positive	23/340 (6.8)	5/334 (1.5)
Solicited systemic adverse reaction	12553/15176 (82.7)	8032/15,162 (53.0)
Baseline SARS-COV-2 negative	11893/14309 (83.1)	7628/14363(53.1)
Baseline SARS-COV-2 positive	237/340 (69.7)	137/334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction	2,501/15,176 (16.5)	560/15,162 (3.7)
Baseline SARS-COV-2 negative	2383/14309 (16.7)	529/14363 (3.7)
Baseline SARS-COV-2 positive	37/340 (10.9)	13/334 (3.9)
Safety Set	**N=15184**	**N=15165**
Unsolicited adverse event up to 28 days after any injection	3325/15184 (21.9)	2949/15165 (19.4)
Baseline SARS-COV-2 negative	3204/14316 (22.4)	2846/14366 (19.8)
Baseline SARS-COV-2 positive	49/341 (14.4)	56/334 (16.8)
Unsolicited adverse event	3283/15184 (21.6)	2902/15165 (19.1)
Grade 3 unsolicited adverse event	187/15184 (1.2)	148/15165 (1.0)
Related** unsolicited adverse events	1127/15184 (7.4)	609/15165 (4.0)
Baseline SARS-COV-2 negative	1095/14316 (7.6)	585/14366 (4.1)
Baseline SARS-COV-2 positive	16/341 (4.7)	14/334 (4.2)
Related** Grade 3 unsolicited adverse event	69/15184 (0.5)	28/15165 (0.2)
Medically attended adverse Event	1215/15184 (8.0)	1276/15165 (8.4)
Baseline SARS-COV-2 negative	1167/14316 (8.2)	1243/14366 (8.7)
Baseline SARS-COV-2 positive	19/341 (5.6)	18/334 (5.4)
Related** medically attended adverse events	122/15184 (0.8)	73/15165 (0.5)
Baseline SARS-COV-2 negative	118/14316 (0.8)	68/14366 (0.5)
Baseline SARS-COV-2 positive	0/341	5/334 (1.5)
Serious adverse event	82/15184 (0.5)	86/15165 (0.6)
Baseline SARS-COV-2 negative	79/14316 (0.6)	82/14366 (0.6)
Baseline SARS-COV-2 positive	0/341	3/334 (0.9)
Related** serious adverse event	5/15184 (<0.1)	4/15165 (<0.1)
Baseline SARS-COV-2 negative	5/14316 (<0.1)	4/14366 (<0.1)
Baseline SARS-COV-2 positive	0/341	0/334
Death*	4/15184 (<0.1)	4/15165 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	41/15184 (0.3)	71/15165 (0.5)
Baseline SARS-COV-2 negative	34/14316 (0.2)	68/14366 (0.5)
Baseline SARS-COV-2 positive	4/341 (1.2)	3/334 (0.9)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7
[a] There were no reports of Grade 4 injection site adverse reactions
[a] EUA request (interim analysis)-November 11, 2020
**Related as assessed by investigator

In subgroup analyses of adults ≥65 years of age, rates of solicited reactions (any, Grade 3 or higher) and all other unsolicited adverse events (AEs) (all and related) were comparable to those observed in all participants. Table 20 below summarizes AEs in participants ≥65 years of age, irrespective of baseline serostatus (as less than 1% of ≥65-year-olds were seropositive at baseline).

Table 20. Adverse Events Among Adults ≥65 Years of Age (Safety Set)[a]

Participants Reporting at Least One	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set		
Solicited adverse reactions after any injection	3497/3766 (92.9)	2010/3750 (53.6)
Solicited local adverse reaction	3337/3766 (88.6)	859/3750 (22.9)
Grade 3 solicited local adverse reaction	279/3766 (7.4)	66/3750 (1.8)
Solicited systemic adverse reaction	2922/3766 (77.6)	1754/3750 (46.8)
Grade 3 or 4 solicited systemic adverse reaction	444/3766 (11.8)	119/3750 (3.2)
Safety Set		
Unsolicited Adverse Event up to 28 days after any	872/3770 (23.1)	734/3750 (19.6)
Related** unsolicited adverse events	261/3770 (6.9)	138/3750 (3.7)
Medically Attended Adverse Event	336/3770 (8.9)	376/3750 (10.0)
Related** medically attended adverse events	22/3770 (0.6)	13/3750 (0.3)
Serious Adverse Event	36/3770 (1.0)	42/3750 (1.1)
Related** serious adverse event	2/3770 (<0.1)	1/3750 (<0.1)
Death	1/3768 (<0.1)	2/3752 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	12/3770 (0.3)	17/3750 (0.5)
Related** AE leading to discontinuation of the vaccine	3/3370 (<0.1)	4/3750 (0.1)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7. [a] EUA request (interim analysis)-November 11 2020. Data provided in response to Information Request (IR),- received December 7 2020
**Related as assessed by investigator

Solicited Adverse Reactions

Solicited local and systemic adverse reactions with onset within 7 days after each dose were assessed across groups and are presented in the tables below stratified by age (18 to 64 years; ≥65 years) for all participants. Solicited adverse reactions (AR) were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling, and lymphadenopathy) and systemic reactions (fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting).

Local Adverse Reactions

Solicited local AR were reported by the majority of vaccine recipients and at higher rates than placebo recipients. Vaccine recipients reported higher rates of local reactions after dose 1 than dose 2. The proportions of participants reporting any local AR were 84.2% and 88.8% after dose 1 and dose 2 in vaccine recipients, compared to 19.8% and 18.8% after dose 1 and dose 2 in placebo recipients, respectively. The proportions reporting at least one grade 3 local AR were 3.5% and 7.0% after dose 1 and dose 2, respectively in vaccine recipients and 0.5% after any dose in placebo recipients. There were no reports of Grade 4 local reactions after any dose across groups. The majority of vaccine recipients (57.6%) reported onset of local AR on Day 1 while at home, and the median duration was 2 days after dose and 3 days after dose 2.

Overall across both age cohorts, the most frequently reported local AR was pain, reported by 83.7% vs 19.8% of vaccine/placebo recipients after the first dose (2.8% vs 0.4% reported as Grade 3) and 88.4% vs 17.0% of vaccine/placebo recipients after dose 2 (4.1% vs 0.3% reported as Grade 3). The median durations for pain were 2 days and 3 days after dose 1 and dose 2, respectively. The highest rates of pain were in participants 18 to <64 years after dose 2, with 90.1% reporting any pain and 4.6% reporting Grade 3 pain.

Axillary lymphadenopathy (vaccination arm) was the second most frequently reported local AR overall. It was reported in 10.2% vs 4.8% of vaccine/placebo recipients after dose 1 and 14.0% vs 3.9% of vaccine/placebo recipients after dose 2 respectively. Grade 3 axillary lymphadenopathy was reported in 0.3% vs 0.2% vaccine/placebo recipients after dose 1 and in 0.5% vs 0.1% of vaccine/placebo recipients after dose 2. The median duration after dose 1 was 1 day and after dose 2 was 2 days. The highest rates of axillary lymphadenopathy were reported by participants 18 to 64 years of age after dose 2, with 16.0% reporting any severity lymphadenopathy and 0.4% reporting Grade 3 lymphadenopathy.

Local reactions that persisted beyond 7 days after any dose were reported by both vaccine recipients and placebo recipients. Local reactions that persisted were reported by 3.7% of vaccine recipients and 1.3% of placebo recipients across both age cohorts. In the younger age cohort, 4.2% of vaccine recipients and 1.4% of placebo recipients reported a local reaction that persisted beyond 7 days, of which 0.6% of vaccine recipients and <0.1% of placebo recipients reported a Grade 3 reaction that persisted. In the older age cohort, 2.3% of vaccine recipients compared to 1.1% of placebo recipients reported a local reaction that persisted, including 0.5% of vaccine recipients, and <0.1% of placebo recipients reporting Grade 3 local reactions. Frequently reported local reactions persisting beyond 7 days in the younger age cohort in vaccine/placebo recipients were pain (1.5%/0.6%) and axillary lymphadenopathy (2.5%/0.7%), and in the older age cohort pain (1.2%/0.6%) and erythema (0.7%/<0.1%).

Table 21. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18 to <64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	9960/11401 (87.4)	2432/11404 (21.3)	9371/10357 (90.5)	2134/10317 (20.7)
Grade 3	452/11401 (4.0)	39/11404 (0.3)	766/10357 (7.4)	41/10317 (0.4)
Pain[a]	9908/11401 (86.9)	2179/11404 (19.1)	9335/10357 (90.1)	1942/10317 (18.8)
Grade 3	367/11401 (3.2)	23/11404 (0.2)	479/10357 (4.6)	21/10317 (0.2)
Erythema[b] (Redness)	345/11401 (3.0)	46/11404 (0.4)	928/10357 (9.0)	42/10317 (0.4)
Grade 3	34/11401 (0.3)	11/11404 (<0.1)	206/10357 (2.0)	12/10317 (0.1)
Swelling[b] (Hardness)	768/11401 (6.7)	33/11404 (0.3)	1309/10357 (12.6)	35/10317 (0.3)
Grade 3	62/11401 (0.5)	3/11404 (<0.1)	176/10357 (1.7)	4/10317 (<0.1)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Lymphadenopathy[c]	1322/11401 (11.6)	567/11404 (5.0)	1654/10357 (16.0)	444/10317 (4.3)
Grade 3	36/11401 (0.3)	13/11404 (0.1)	45/10357 (0.4)	10/10317 (<0.1)

Source: Sponsor's Table 14.3.1.1.4, Table 14.3.1.1.5
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose
[a] EUA request (interim analysis)-November 11 2020
Note: Adverse reaction data were collected on the electronic diary (eDiary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
c: Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e. lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
Note: No grade 4 solicited local adverse reactions were reported.

Table 22. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	2805/3762 (74.6)	566/3746 (15.1)	3010/3587 (83.9)	473/3549 (13.3)
Grade 3	77/3762 (2.0)	39/3746 (1.0)	212/3587 (5.9)	29/3549 (0.8)
Pain[a]	2782/3762 (74.0)	481/3746 (12.8)	2990/3587 (83.4)	421/3549 (11.9)
Grade 3	50/3762 (1.3)	32/3746 (0.9)	96/3587 (2.7)	17/3549 (0.5)
Erythema[b] (Redness)	86/3761 (2.3)	19/3746 (0.5)	265/3587 (7.4)	13/3549 (0.4)
Grade 3	8/3761 (0.2)	2/3746 (<0.1)	75/3587 (2.1)	3/3549 (<0.1)
Swelling[b] (Hardness)	166/3761 (4.4)	19/3746 (0.5)	386/3587 (10.8)	13/3549 (0.4)
Grade 3	20/3761 (0.5)	3/3746 (<0.1)	69/3587 (1.9)	7/3549 (0.2)
Lymphadenopathy[c]	231/3761 (6.1)	155/3746 (4.1)	302/3587 (8.4)	90/3549 (2.5)
Grade 3	12/3761 (0.3)	14/3746 (0.4)	21/3587 (0.6)	8/3549 (0.2)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5]
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
[a] EUA request (interim analysis)-November 11 2020.
Note: Adverse reaction data were collected on the electronic diary by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
c: Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e. lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
Note: No grade 4 solicited local adverse reactions were reported.

Systemic Adverse Reactions

Solicited systemic AR were reported for the majority of vaccine recipients and at higher rates than for placebo recipients. Vaccine recipients had higher rates of systemic reactions after the second dose than the first dose. The proportions of vaccine and placebo participants reporting systemic AR were as follows: reporting any grade was 54.9% vs 42.2% after dose 1 and 79.3% vs 36.5% after dose 2, and reporting Grade 3 was 2.9% vs. 2.0% after dose 1 and 15.7% vs. 2.0% after dose 2, respectively. Across groups and doses <0.1% reported a Grade 4 systemic reaction (mainly fever > 104 °F). The majority of vaccine recipients reported onset of systemic AR while at home either on Day 1 (33.7%) or on Day 2 (37.0%), and the median duration after any dose was 2 days.

Overall, the most frequently reported systemic AR was fatigue, reported by 68.5% of vaccine recipients and 36.1% of placebo recipients. After any dose, Grade 3 fatigue was reported by 9.6% of vaccine participants and 1.3% of placebo recipients. Grade 4 fatigue was reported by 1 participant in the vaccine group and none in the placebo group. After dose 1, any/Grade 3 fatigue was reported by 37.2%/1.0% of vaccine recipients and after dose 2 any/Grade 3 fatigue was reported by 65.2%/9.7% of vaccine recipients. The median duration for fatigue in vaccine recipients was 2 days after any dose. The highest rates of fatigue were reported by participants 18 to 64 years after the 2nd dose, with 67.6% reporting any fatigue, 10.6% reporting Grade 3, and 1 participant reporting Grade 4 (after Dose 1).

Rates of other solicited systemic AR were: headache 63.0% vaccine group vs. 36.5% placebo group; myalgia 59.6% vaccine group vs. 20.1% placebo group; arthralgia 44.8% vaccine group vs. 17.2% placebo group; and chills 43.4% vaccine group vs. 9.5% placebo group. The rates of Grade 3 AR were: headache 5.5% vaccine group vs. 2.2% placebo group; myalgia 8.6% vaccine group vs. 0.6% placebo group; arthralgia 5.1% vaccine group vs. 0.5% placebo group; and chills 1.3% vaccine group vs. 0.2% of placebo group. The median duration was 1 day after dose 1 and 1 to 2 days after dose 2. The highest rates of solicited reactions were observed in participants 18 to 64 years after dose 2 and included the following: headache 62.8% (5.0% reported Grade 3), myalgia 61.3% (10.0% Grade 3), arthralgia 45.2% (5.8% Grade 3), and chills 45.8% (1.5% Grade 3). There was one vaccine recipient in the younger age cohort who also reported Grade 4 arthralgia after dose 1.

Fever was reported after any dose by 14.8% of vaccine participant and 0.6% of placebo recipients. Fever was reported after dose 1 in 0.8% of vaccine recipients and 15.6% of vaccine recipients after dose 2. Grade 3 (≥102.1 °F) was reported by <0.1% (11 participants) of vaccine recipients after Dose 1 and 1.3% (186 participants) of vaccine recipients after dose 2. Grade 4 (≥104.0 °F) fever were reported by 4 vaccine recipients after dose 1 and 11 vaccine recipients after dose 2. In participants 18 to 64 years after dose 2, any fever, Grade 3 fever, and Grade 4 fever were reported in 1,806 participants (17.4%), 168 participants (1.6%), and 10 participants (<0.1%), respectively.

Systemic reactions persisting longer than 7 days were reported in both age cohorts of vaccine and placebo recipients after any dose. In the vaccine group, 11.9% of participants reported a solicited reaction that persisted beyond 7 days compared to 9.5% of placebo participants. In the younger age cohort, 9.8% of vaccine recipients and 8.9% of placebo recipients reported a systemic reaction that persisted beyond 7 days; and 2.0% of vaccine recipients and 1.2% of placebo recipients reported Grade 3 or 4 systemic reaction that persisted beyond 7 days. In the older age cohort, 9.4% of vaccine recipients and 8.1% of placebo recipients reported a systemic reaction that persisted; 1.7% of vaccine recipients (63 participants) and 0.8% of placebo

recipients (31 participants) reported a Grade 3 or 4 reaction that persisted. The most frequently reported systemic reactions that persisted beyond 7 days in vaccine recipients/placebo recipients 18 to 64 years were fatigue (5.7%/5.0%), headache (4.8%/4.0%), myalgia (2.7%/2.7%), and arthralgia (2.6%/2.8%); in the older cohort were fatigue (5.8%/4.5%), arthralgia (3.7%/3.8%), myalgia (2.9%/2.7%), and headache (2.8%/2.7%).

Fever persisted beyond 7 days in 7 vaccine recipients and 4 placebo recipients, all of whom were in the younger age cohort. There were 2 vaccine recipients who reported grade 3 fever that persisted, and none in the placebo group.

Table 23. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18-64 years, Solicited Safety Set[*a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	6503/11405 (57.0)	5063/11406 (44.4)	8484/10358 (81.9)	3967/10320 (38.4)
Grade 3	363/11405 (3.2)	248/11406 (2.2)	1801/10358 (17.4)	215/10320 (2.1)
Grade 4	5/11405 (<0.1)	4/11406 (<0.1)	10/10358 (<0.1)	2/10320 (<0.1)
Fever	105/11403 (0.9)	39/11404 (0.3)	1806/10352 (17.4)	38/10315 (0.4)
Grade 3	10/11403 (<0.1)	1/11404 (<0.1)	168/10352 (1.6)	1/10315 (<0.1)
Grade 4	4/11403 (<0.1)	4/11404 (<0.1)	10/10352 (<0.1)	2/10315 (<0.1)
Headache	4031/11401 (35.4)	3303/11404 (29.0)	6500/10357 (62.8)	2617/10317 (25.4)
Grade 3	219/11401 (1.9)	162/11404 (1.4)	515/10357 (5.0)	124/10317 (1.2)
Fatigue	4384/11401 (38.5)	3282/11404 (28.8)	7002/10357 (67.6)	2530/10315 (24.5)
Grade 3	120/11401 (1.1)	83/11404 (0.7)	1099/10357 (10.6)	81/10315 (0.8)
Grade 4	1/11401 (<0.1)	0	0	0
Myalgia	2698/11401 (23.7)	1626/11404 (14.3)	6353/10357 (6.1)	1312/10316 (12.7)
Grade 3	73/11401 (0.6)	38/11404 (0.3)	1032/10357 (10.0)	39/10316 (0.4)
Arthralgia	1892/11401 (16.6)	1327/11404 (11.6)	4685/10357 (45.2)	1087/10315 (10.5)
Grade 3	47/11401 (0.4)	29/11404 (0.3)	603/10357 (5.8)	36/10315 (0.3)
Grade 4	1/11401 (<0.1)	0	0	0
Nausea/Vomiting	1069/11401 (9.4)	908/11404 (8.0)	2209/10357 (21.3)	754/10315 (7.3)
Grade 3	6/11401 (<0.1)	8/11404 (<0.1)	8/10357 (<0.1)	8/10315 (<0.1)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Chills	1051/11401 (9.2)	730/11404 (6.4)	5001/10357 (48.3)	611/10315 (5.9)
Grade 3	17/11401 (0.1)	8/11404 (<0.1)	151/10357 (1.5)	14/10315 (0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis)-November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ⩾39.0 – ⩽40.0°C or ⩾102.1 – ⩽104.0° F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Table 24. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 Years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	1818/3761 (48.3)	1335/3748 (35.6)	2580/3589 (71.9)	1102/3549 (31.1)
Grade 3	84/3761 (2.2)	63/3748 (1.7)	387/3589 (10.8)	58/3549 (1.6)
Grade 4	0	0	2/3589 (<0.1)	1/3549 (<0.1)
Fever	10/3760 (0.3)	7/3748 (0.2)	366/3587 (10.2)	5/3549 (0.1)
Grade 3	1/3760 (<0.1)	1/3748 (<0.1)	18/3587 (0.5)	0
Grade 4	0	2/3748 (<0.1)	1/3587 (<0.1)	1/3549 (<0.1)
Headache	921/3761 (24.5)	724/3745 (19.3)	1665/3587 (46.4)	635/3549 (17.9)
Grade 3	52/3761 (1.4)	34/3745 (0.9)	107/3587 (3.0)	32/3549 (0.9)
Fatigue	1251/3761 (33.3)	851/3745 (22.7)	2094/3587 (58.4)	695/3549 (19.6)
Grade 3	30/3761 (0.8)	23/3745 (0.6)	248/3587 (6.9)	20/3549 (0.6)
Myalgia	743/3761 (19.8)	443/3745 (11.8)	1683/3587 (46.9)	385/3549 (10.8)
Grade 3	17/3761 (0.5)	9/3745 (0.2)	201/3587 (5.6)	10/3549 (0.3)
Arthralgia	618/3761 (16.4)	456/3745 (12.2)	1252/3587 (34.9)	381/3549 (10.7)
Grade 3	13/3761 (0.3)	8/3745 (0.2)	122/3587 (3.4)	7/3549 (0.2)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Nausea/Vomiting	194/3761 (5.2)	166/3745 (4.4)	425/3587 (11.8)	129/3549 (3.6)
Grade 3	4/3761 (0.1)	4/3745 (0.1)	10/3587 (0.3)	3/3549 (<0.1)
Grade 4	0	0	1/3587 (<0.1)	0
Chills	202/3761 (5.4)	148/3745 (4.0)	1099/3587 (30.6)	144/3549 (4.1)
Grade 3	7/3761 (0.2)	6/3745 (0.2)	27/3587 (0.8)	2/3549 (<0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis) November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ≥39.0 – ≤40.0°C or ≥102.1 – ≤104.0°F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Unsolicited AEs

Unsolicited AEs from the November 11, 2020 data cutoff include safety data from participants who had at least 1 month of follow-up after dose 2 (76.7% of all participants) those who had at least 2 months of follow-up after dose 2 (25.3% of all participants). The median study duration following dose 2 was 7 weeks across study groups. Table 25 below shows unsolicited AEs reported through the first data cutoff. Treatment emergent adverse events (AEs) were defined as any event that occurred during the study and was not present before exposure (study vaccine or placebo), any event that occurred during the study and was not present before exposure, or any event already present that worsened after exposure. The following unsolicited adverse events were specified in the protocol:

- Unsolicited AEs observed or reported during the 28 days following each vaccine or placebo dose
- AEs leading to discontinuation from vaccination and/or study participation through Day 759 (study completion) or withdrawal from the study
- Serious adverse events and medically attended adverse events through Day 759 (study completion) or withdrawal from study

Determination of severity for all unsolicited AE were made by the investigators based on medical judgement and definitions of severity as mild, moderate, or severe.

The overall proportions of participants who reported an unsolicited adverse event were generally similar, with numerically slightly higher rates of unsolicited AEs in the vaccine group compared to placebo group for some categories of unsolicited nonserious AEs.

Table 25. Summary of Unsolicited AEs Regardless of Relationship to the Investigational Vaccine, Through 28 Days After Any Vaccination, Study 301, Safety Set

Event Type	Nov 11 Dataset[a] mRNA-1273 (N=15184) n (%)	Nov 11 Dataset[a] Placebo (N=15165) n (%)	Nov 25 Dataset[b] mRNA-1273 (N=15185) n (%)	Nov 25 Dataset[b] Placebo (N=15166) n (%)
All unsolicited AEs	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Medically-attended	1215 (8.0)	1276 (8.4)	1372 (9.0)	1465 (9.7)
Severe unsolicited AEs	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)	50 (0.3)	80 (0.5)
Serious	82 (0.5)	86 (0.6)	93 (0.6)	89 (0.6)
Death	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)

Source:
Abbreviation: AE = adverse event.
Note: An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages were based on the number of safety participants.
[a] EUA request (interim analysis)-November 11 2020
[b] Primary efficacy analysis-November 25, 2020

Unsolicited Adverse Events

The table below shows rates of unsolicited AEs that occurred within 28 days of any vaccination and at rates of ≥1% in the vaccine group through the November 11, 2020 data cutoff. The proportion of vaccine recipients who reported an unsolicited AE was 21.9% (3325 participants) compared to 19.4% of placebo participants. A higher frequency of unsolicited adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local and systemic reactogenicity following vaccination.

Table 26. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants, by MedDRA Primary System Organ Class and Preferred Term (Safety Analysis Set)[a]

System Organ Class Preferred Term	Vaccine N=15184 n (%) Any	Vaccine N=15184 n (%) Severe	Placebo N=15165 n (%) Any	Placebo N=15165 n (%) Severe
Infections and infestations	521 (3.4)	13 (<0.1)	621 (4.1)	25 (0.2)
Vascular disorders	149 (1.0)	28 (0.2)	138 (0.9)	39 (0.3)
Nervous system disorders	624 (4.1)	27 (0.2)	552 (3.6)	21 (0.1)
Headache	435 (2.9)	19 (0.1)	409 (2.7)	13 (<0.1)
Respiratory, thoracic and mediastinal disorders	480 (3.2)	8 (<0.1)	522 (3.4)	9 (<0.1)
Cough	148 (1.0)	1 (<0.1)	143 (0.9)	1 (<0.1)
Oropharyngeal pain	137 (0.9)	1 (<0.1)	184 (1.2)	3 (<0.1)
Gastrointestinal disorders	426 (2.8)	14 (<0.1)	387 (2.6)	16 (0.1)
Diarrhea	178 (1.2)	2 (<0.1)	147 (1.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	213 (1.4)	4 (<0.1)	158 (1.0)	2 (<0.1)
Musculoskeletal and connective tissue disorders	586 (3.9)	24 (0.2)	521 (3.4)	18 (0.1)
Arthralgia	174 (1.1)	10 (<0.1)	152 (1.0)	2 (<0.1)
Myalgia	172 (1.1)	11 (<0.1)	138 (0.9)	0

System Organ Class Preferred Term	Vaccine N=15184 n (%)	Vaccine N=15184 n (%)	Placebo N=15165 n (%)	Placebo N=15165 n (%)
General disorders and administration site	894 (5.9)	43 (0.3)	560 (3.7)	13 (<0.1)
Fatigue	344 (2.3)	12 (<0.1)	307 (2.0)	7 (<0.1)
Injection site pain	147 (1.0)	6 (<0.1)	49 (0.3)	1 (<0.1)
Injury, poisoning and procedural complications	238 (1.6)	16 (0.1)	262 (1.7)	13 (<0.1)

Source: Sponsor's Tables 14.3.1.8.1 and 14.3.1.17.1
n (%)=number (percentage) of participants reporting the adverse event at least once
[a] EUA request (interim analysis): November 11, 2020 data cutoff.

Unsolicited AEs considered related by the investigator to study vaccination were reported by 7.4% of vaccine recipients and 4.0% of placebo recipients. The proportion of participants who reported severe unsolicited AEs was 1.4% following any vaccine dose (275 participants) and 1.3% following any placebo dose (225 participants). The most frequently reported severe AEs that occurred in greater numbers of vaccine than placebo recipients were headache, myalgia, arthralgia, injection site erythema, and injection site pain (Table 26).

Medically attended adverse events (MAAE) from dose 1 through 28 day following any dose were reported for 8.0% of participants in the vaccine group (1,839 events in 1,215 participants) and 8.4% of those in the placebo group (1,837 events in 1,276 participants). The majority of these events were considered not related to study vaccinations and were primarily attributed to local and systemic reactogenicity following vaccinations.

FDA conducted standard MedDRA queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited adverse events with onset following dose 1 through the November 11, 2020 cutoff. The SMQs were conducted on adverse event Preferred Terms that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune disorders. FDA assessment of additional safety data accrued through the November 25, 2020 cutoff is ongoing, though specific SMQ of adverse events of clinical interest were assessed.

A SMQ evaluating lymphadenopathy-related events (including injection site lymphadenopathy, lymph node pain, and lymphadenitis) through the November 25, 2020 data cut demonstrated a numerical imbalance across study groups, with 1.1% of vaccine recipients (191 events in 173 vaccine recipients) compared to 0.63% of placebo recipients (109 events in 95 participants) reporting such events in the Safety Set. The rates reported in the older cohort (≥65 years) were 0.74% (28 events in 28 participants) in vaccine recipients compared to 0.35% (16 events in 13 participants) in placebo recipients. The rates reported in the younger cohort (18-64 years) were 1.3% (163 events in 145 participants) in vaccine recipients and 0.72% (93 events in 82 participants) in placebo recipients. These events support a plausible relationship to study vaccination and were also reported in the evaluation of solicited local adverse reactions. Local axillary swelling/tenderness was reported in approximately 19% of participants during the 7 days following any dose in the Solicited Safety Set. The median duration following any dose was 1 to 2 days, and <1% reported Grade 3 axillary swelling/tenderness.

A SMQ evaluating hypersensitivity-related adverse events through the November 25, 2020 data cutoff demonstrated a numerical imbalance across study groups, with 1.5% of vaccine recipients (258 events in 233 participants) and 1.1% of placebo recipients (185 events in 166 participants) reporting such events in the Safety Set. In the older cohort (age ≥65 years) which

comprised 24.8% of the Safety Set, the rates of hypersensitivity were 1.8% (74 events in 68 participants) in vaccine recipients and 1% (45 events in 38 participants) in placebo recipients. In the younger age cohort (18-64 years), the rates were 1.5% (184 events in 165 participants) in vaccine recipients compared to 1.1% (140 events in 128 participants). Overall, the most frequently reported AEs in the hypersensitivity SMQ were injection site rash (0.24% vaccine, 0.01% placebo), injection site urticaria (0.1% vaccine, 0% placebo), and rash maculo-papular (0.07% vaccine, 0.01% placebo). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

A query of specific adverse events of clinical interest in the Safety Set through November 25, 2020 demonstrated a small imbalance in the number of participants reporting Bell's palsy (facial paralysis), with 3 vaccine recipients and 1 placebo recipient reporting this MAAE. One case of Bell's palsy in the vaccine group was considered a SAE; a 67-year-old female with diabetes was hospitalized for stroke due to new facial paralysis 32 days after vaccination. This case was reported as resolving. Another Bell's palsy case in the vaccine group occurred 28 days after vaccination in a 30-year-old female who reported an upper respiratory infection 27 days prior to onset of her facial paralysis. This case was reported as resolved. An additional case of Bell's palsy in the vaccine group was reported with the primary analysis safety data (November 25, 2020 data cutoff) and occurred 22 days after vaccination in a 72-year-old female; this event was still ongoing at the time of safety report. The case in the placebo group, reported as resolving, occurred 17 days post injection in a 52-year-old-male. Causality assessment is confounded by predisposing factors in these participants. However, considering the temporal association and biological plausibility, a potential contribution of the vaccine to the manifestations of these events of facial palsy cannot be ruled out. FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to the Moderna COVID-19 vaccine.

Immediate Adverse Events

Immediate solicited reactions occurring within 30 minutes of vaccination were infrequent and there does not appear to be an imbalance between the treatment groups. Review of unsolicited AEs that occurred within 30 minutes of vaccination demonstrated comparable rates across study groups (0.6% vaccine, 0.6% placebo), and none of the events reported in the vaccine group were considered serious.

Study Withdrawals due to an Adverse Event (Safety Set)

Adverse events that led to discontinuation of vaccination were reported in 0.3% in the vaccine group and 0.5% in the placebo group. Following the November 25, 2020 cutoff, 4 participants were withdrawn from the study due to an adverse event (2 vaccine recipients and 2 placebo recipients). The two AEs reported in the vaccine group were acute pancreatitis and road traffic accident, and the two AEs reported in the placebo group were incarcerated hernia and duodenal ulcer hemorrhage. FDA's review of data through this latter time point is ongoing.

Serious Adverse Events

Deaths

As of December 3, 2020, 13 deaths were reported (6 vaccine, 7 placebo). Two deaths in the vaccine group were in participants >75 years of age with pre-existing cardiac disease; one

participant died of cardiopulmonary arrest 21 days after dose 1, and one participant died of myocardial infarction 45 days after dose 2. Another two vaccine recipients were found deceased at home, and the cause of these deaths is uncertain: a 70-year-old participant with cardiac disease was found deceased 57 days after dose 2, and a 56-year-old participant with hypertension, chronic back pain being treated with opioid medication died 37 days after dose 1 (The official cause of death was listed as head trauma). One case was a 72-year-old vaccine recipient with Crohn's disease and short bowel syndrome who was hospitalized for thrombocytopenia and acute kidney failure due to obstructive nephrolithiasis 40 days after dose 2 and developed complications resulting in multiorgan failure and death. One vaccine recipient died of suicide 21 days after dose 1. The placebo recipients died from myocardial infarction (n=3), intra-abdominal perforation (n=1), systemic inflammatory response syndrome in the setting of known malignancy (n=1), COVID-19 (n=1), and unknown cause (n=1). These deaths represent events and rates that occur in the general population of individuals in these age groups.

Non-fatal Serious Adverse Events

Among participants who received at least one dose of vaccine or placebo (N=30,351), the proportion of participants who reported at least one SAE from dose 1 to the primary analysis cutoff date (November 25, 2020) was 1% in the mRNA-1273 group and 1% in the placebo group. The most common SAEs occurring at higher rates in the vaccine group than the placebo group were myocardial infarction (0.03% in vaccine group, 5 cases vs. 3 cases in placebo group), cholecystitis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group), and nephrolithiasis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group). The small numbers of cases of these events do not suggest a causal relationship. The most common SAEs occurring at higher rates in the placebo arm than the vaccine arm, aside from COVID-19 (0.1% in placebo group), were pneumonia (0.05% in placebo group) and pulmonary embolism (0.03% in placebo group). Occurrence of other SAEs, including cardiovascular SAEs, were otherwise balanced between treatment groups.

As of November 25, 2020, 7 SAEs (4.8%) in the mRNA-1273 group and 5 (3.3%) in the placebo group were assessed by the investigator as related to study vaccination (Table 27). Of the 7 SAEs in the mRNA-1273 group, the Sponsor assessed 4 as related and 3 as unrelated to the vaccine.

Table 27. SAEs Considered Related by Investigator

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Intractable nausea and vomiting	1	65 F; history of headaches and severe nausea requiring hospitalization	Resolved	Yes/Yes
mRNA-1273	Facial swelling	1	46 F; dermal filler cosmetic injection 6 months prior	Resolved	Yes/Yes
mRNA-1273	Facial swelling	2	51 F; dermal filler cosmetic injection 2 weeks prior	Resolved	Yes/Yes
mRNA-1273	Rheumatoid arthritis	14	57 M; hypothyroid	Unresolved	Yes/Yes
mRNA-1273	Dyspnea with exertion, peripheral edema	8	66 F; diabetes, hypertension	Resolving	Yes/No

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Autonomic dysfunction	24	46 F; hypothyroid; possible sinus infection	Unresolved	Yes/No
mRNA-1273	B-cell lymphocytic lymphoma	31	75 F; history of metastatic lung cancer, breast cancer	Unresolved	Yes/No
Placebo	Polymyalgia rheumatica	15	83 M; chronic low back pain	Resolving	Yes/Yes
Placebo	Facial swelling, paresthesia, anxiety	7	41 F; dental procedure 2 weeks prior	Resolved	Yes/No
Placebo	Procedural hemorrhage	16	52 M; aortic stenosis, hyperlipidemia; aspirin intake	Resolved	Yes/No
Placebo	Pulmonary embolism	24	59 M; smoking	Unresolved	Yes/No
Placebo	Pneumonia and myocardial infarction	29	70 M; coronary artery disease, chronic kidney disease, diabetes	Resolved	Yes/No

There was one event of lip angioedema 2 days after vaccination in a 29-year-old female participant in the vaccine group which was classified as medically significant but not considered an SAE. The participant has a history of dermal filler injection in the lips (unknown how long prior to vaccination). She reported having a similar reaction after receipt of an influenza vaccine in the past. Taken in context with the SAEs of facial swelling which occurred in 2 participants who had previous history of cosmetic filler injections, it is possible the localized swelling in these cases is due to an inflammatory reaction from interaction between the immune response after vaccination and the dermal filler. This phenomenon has been reported after natural infection (e.g., after an influenza-like illness).

In FDA's opinion following review of the narratives, 3 SAEs are considered likely related, including the one report of intractable nausea/vomiting and 2 reports of facial swelling. The possibility that the vaccine contributed to the SAE reports of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction cannot be excluded. The vaccine was unlikely to have contributed to the other SAEs assessed by the investigator as related. As described in detail in a previous section, there was one report of Bell's palsy in the vaccine arm which occurred 32 days after vaccination; both the investigator and the Sponsor assessed this event as unrelated to the study vaccine, but in FDA's assessment a causal relationship cannot be definitively excluded.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or

before vaccination and not detected by pre-vaccination screening tests. Thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (2 vaccine, 3 placebo), within 30 days after LMP in 5 participants (2 vaccine, 3 placebo), >30 days after LMP in 2 participants (1 vaccine, 1 placebo), and date of LMP not known in 1 participant (1 vaccine, 0 placebo). Unsolicited AEs related to pregnancy include a case of spontaneous abortion and a case of elective abortion, both in the placebo group. One participant in the placebo group is lost to follow-up. Pregnancy outcomes are otherwise unknown at this time.

A combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats was submitted to FDA on December 4, 2020. FDA review of this study concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of the mRNA-1273 vaccine in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 3 safety population (N=30,350; 15,184 vaccine,15,165 placebo) meets the expectations described in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The initial EUA request was based on data from the pre-specified interim analysis (November 11, 2020 data cutoff) with a median follow-up duration of 7 weeks after dose 2; this interim analysis data is the primary basis of this EUA review and conclusions. Data and analyses from a November 25, 2020 data cut with a median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series was submitted as an amendment to the EUA request on December 7, 2020. The FDA has not independently verified the complete safety data from the primary analysis, aside from all new deaths (including those reported through December 3, 2020) and SAEs. No new safety concerns have been identified. The rates and types of solicited adverse reactions and unsolicited adverse events are unlikely to change significantly with an additional 2 weeks of follow-up. The totality of the data package submitted in the EUA request meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); 0.2% to 9.7% were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in adults ≥65 years of age as compared to younger participants. Among adverse events of clinical interest, lymphadenopathy was reported in 173 participants (1.14%) in the vaccine group and 95 participants (0.63%) in the placebo group. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the Safety Set. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there has been three reports of Bell's palsy in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-

1273.

As of December 3, 2020, there were a total of 13 deaths reported in the study (6 vaccine, 7 placebo). These deaths represent events and rates that occur in the general population of individuals in these age groups. The frequency of non-fatal serious adverse events was low and without meaningful imbalances between study arms (1% in the mRNA-1273 group and 1% in the placebo group). The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

ModernaTX expects that participants, including approximately 25% who are healthcare workers, may request unblinding to receive mRNA-1273 or another vaccine potentially available under EUA external to the trial. More extensive participant-driven crossover would be expected to alter the composition of the trial population, with greatly increased participant dropout due to a large proportion of participants belonging to priority vaccination groups desiring to be vaccinated with vaccine made available under EUA. ModernaTX is evaluating the opportunity to amend the protocol to proactively reconsent participants who received placebo to be offered mRNA-1273 vaccination and to remain in the trial, enabling ModernaTX to continue to collect the relevant safety and effectiveness data over the entire two years of follow-up while increasing the likelihood of retaining participants on trial. Adverse events among those vaccinated within the trial will be captured, regardless of the treatment group to which the participants were originally allocated, over the entire follow-up period of 24 months.

7. Pharmacovigilance Activities

The Sponsor submitted a Pharmacovigilance Plan to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease (which includes but is not limited to vaccine-associated enhanced respiratory disease) and anaphylactic reactions (including anaphylaxis) as important potential risks. Use in the pediatric population, use in pregnant and breast-feeding women, immunogenicity in participants with immunosuppression, concomitant administration with non-COVID vaccines, long-term safety and long-term effectiveness are areas the Sponsor identified as missing information.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and proposed to submit periodic safety reports at quarterly intervals, or at another interval specified by FDA. FDA has

requested that periodic reports be submitted monthly. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following three planned surveillance studies.

- Pregnancy Cohort: The Sponsor plans to establish a passive pregnancy registry to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA, and to submit a protocol for FDA review and approval.

- Active Follow-up for Safety: This study is an active safety surveillance activity conducting retrospective analyses of medical and pharmacy claims data to address three objectives; estimation of background rates of 23 prespecified adverse events of special interest (AESI), descriptive analyses of observed versus expected rates, and self-controlled risk interval analyses that will be conducted if certain criteria are met from the descriptive analyses. The planned study duration is through December 2022.

- Real World Effectiveness Study: This study is a prospective cohort study to be conducted at Kaiser Permanente Southern California to evaluate vaccine effectiveness in preventing the following outcomes: laboratory confirmed and clinical COVID-19 infection, hospitalization, and mortality for COVID-19. Vaccinated participants will receive Moderna COVID-19 Vaccine between January 1, 2021 and December 31, 2021, and the comparator group will be age matched, unvaccinated KPSC members. The planned study duration is through December 31, 2023.

FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

Reporting to VAERS and ModernaTX, Inc.

Providers administering the Moderna COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to ModernaTX the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports

medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1 Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 14 days after the second dose of vaccine
- Reduction in the risk of confirmed severe COVID-19 occurring at least 14 days after the second dose of vaccine

The 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 14 days after receipt of the second dose. Secondary efficacy analyses showed consistency with outcomes in the primary efficacy analysis; the vaccine was effective in preventing COVID-19 using a less restrictive definition of the disease and considering all cases starting 14 days after the first injection. Efficacy findings in the interim analysis were also consistent across various subgroups, including racial and ethnic minorities, participants ages 65 years and older, and those at risk for severe COVID-19 disease due to obesity, diabetes, cardiac disease, liver disease, chronic lung disease, mild to severe asthma, and infection with HIV, although the efficacy estimate in participants ages 65 years and older was slightly lower in the primary efficacy analysis.

8.2 Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) are too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

Limited data suggest that individuals with prior SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination. Regarding the benefit of the mRNA-1273 for individuals with prior infection with SARS-CoV2, participants with a known history of SARS-CoV-2 infection were excluded from the Phase 3 study, and there was only one case of COVID-19 among study participants with positive SARS-COV-2 infection status at baseline. Thus, the study was not designed to assess the benefit in individuals with prior SARS-CoV-2 infection.

Effectiveness in pediatric populations

No efficacy data are available from participants ages 17 years and younger.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27, 2020 to November 21, 2020, in sites across the United States. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine in preventing asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[13-16] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3 Known Risks

The vaccine elicited increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were pain at injection site (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). Adverse reactions characterized as reactogenicity were generally mild to moderate; 0.2% to 9.7% of these events were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in older adults (≥65 years of age) as compared to younger participants. Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination. The number of participants reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (258 events in 233 participants [1.5%] vs. 185 events in 166 participants [1.1%]). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

Serious adverse events, while uncommon (1.0% in both treatment groups), represented medical events that occur in the general population at similar frequency as observed in the study. Of the 7 SAEs in the mRNA-1273 group that were considered as related by the investigator, FDA considered 3 as related: intractable nausea and vomiting (n=1), facial swelling (n=2). For the serious adverse events of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction, a possibility of vaccine contribution cannot be excluded. For the event of B-cell lymphoma, an alternative etiology is more likely. An SAE of Bell's palsy occurred in a vaccine recipient, for which a causal relationship to vaccination cannot be concluded at this time.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

8.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 18 years of age, pregnant and lactating individuals, and immunocompromised individuals.

FDA review of a combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in female rats concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of approximately 30,000 participants over the period of follow-up at this time. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Although the safety database revealed an imbalance of cases of Bell's palsy (3 in the vaccine group and 1 in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

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10. Appendix A. Phase 1 and 2 Studies

Study DMID Protocol 20-0003

Study Design
DMID Protocol 20-0003 is an ongoing Phase 1, open-label, first-in-human, dose-ranging study to evaluate the safety and immunogenicity of mRNA-1273 in healthy adults 18 years of age and older. A total of 120 participants without risk factors for progression to severe COVID-19 were enrolled into one of 10 age and dose cohorts to receive 2 injections of 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273 given 28 days apart. The study included 60 participants 18 through 55 years of age, 30 participants 56 through 70 years of age, and 30 participants 71 years and older. Participants will be followed safety and immunogenicity for 12 months after last vaccination.

Study Objectives/Endpoints Relevant to the EUA
The immunogenicity objectives are to evaluate the binding antibody (bAb) concentrations for spike IgG as measured by ELISA and neutralizing antibody (nAb) titers as measured by PsVNA for all dose levels at baseline and at various time points after vaccination. The study also evaluated T-cell responses elicited by the mRNA-1273 vaccine as assessed by an intracellular cytokine stimulation assay. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study, and all results were descriptive.

Study Results

The study showed a dose response in participants across all age groups as measured by both binding and neutralizing antibodies after 2 doses. There was a comparable response between the 100-µg and 250-µg dose groups, and both were greater compared to the 25-µg group. The bAb and nAb levels seen after 2 doses of 100 µg or 250 µg of mRNA-1273 were similar in magnitude compared to those seen in pooled convalescent sera from patients recovered from COVID-19. All dose levels elicited CD4+ T-cell responses that were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. This Th1-dominant profile was clinically reassuring in terms of risk of developing vaccine-induced disease. These results, along with the interim safety data showing a lower incidence of reactogenicity in the 100ug group compared to the 250ug group, led to the selection of the 100ug dose to advance to Phase 2 and 3. Preliminary safety data from this Phase 1 study show a similar profile to that observed in the Phase 3 study. No SAEs or severe COVID-19 cases have been reported from this study as of November 16, 2020.

Study mRNA-1273-P201

Study Design
Study mRNA-1273-P201 is an ongoing phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in healthy adults 18 years and older. The study enrolled 600 participants, consisting of 300 participants 18 to <55 years old and 300 participants 55 years and older, who

were randomized equally to receive either 2 doses of 50ug of mRNA-1273, 100ug of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months post last vaccination.

Study Objectives/Endpoints Relevant to the EUA
The immunogenicity objectives are to evaluate the immunogenicity of 2 doses of mRNA-1273 at the 2 dose levels (50 µg and 100 µg) administered 28 days apart as assessed by level of bAb and by nAb titers at baseline and at various time points after vaccination. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study and all results were descriptive.

Study Results

The immune response as assessed by bAb and nAb after 2 doses were comparable in the 50-µg and 100-µg dose groups, with an overall geometric mean fold rise (GMFR)>20-fold in bAB as measured by ELISA and >50-fold in nAb as measured by microneutralization assay at 28 days post-dose 2. In the 100-µg dose group, the older age cohort (≥55 years) had slightly lower bAb response when compared to the younger age cohort (18 to <55 years) at 28 days post-dose 2, but the nAb response was similar between both age groups

Safety profile was similar to that reported in the Phase 3 study. Laboratory evaluations (including complete blood count, liver function tests, kidney functions tests, and coagulation studies) were conducted for participants ≥55 years of age (N=100) at baseline and at 1 month after the second dose (Day 29, Day 57). According to narratives that the Sponsor provided to FDA on December 6, 2020, there were 2 participants in the 100-µg group who experienced Grade 3 decreases in hemoglobin (Grade 0 reported at baseline), but both Grade 3 values were within normal range and not clinically significant. The overall event rates were not provided.

As of December 6, 2020, there were 3 SAEs reported in the vaccine group: a 65-year-old participant with community acquired pneumonia 25 days after vaccination, a 72-year-old participant with arrhythmia after being struck by lightning 28 days after vaccination, and an 87-year-old participant with worsening of chronic bradycardia 45 days after vaccination. On FDA review of the narratives, none of these SAEs are assessed as related. There were no cases of severe COVID-19 reported in the study.

This is Exhibit "G" to the Affidavit of
Bonnie Mallard, sworn before me on
this 15th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B , LL.M.

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FINAL REPORT

Test Facility Study No. 185350
Sponsor Reference No. ALC-NC-0552

A Tissue Distribution Study of a [^{3}H]-Labelled Lipid Nanoparticle-mRNA Formulation Containing ALC-0315 and ALC-0159 Following Intramuscular Administration in Wistar Han Rats

TEST FACILITY:
(b) (4)

SPONSOR:
Acuitas Therapeutics Inc.
6190 Agronomy Road, Suite 402
Vancouver, British Columbia
V6T 1Z3 Canada

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FDA-CBER-2021-5683-0013962

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1 COMPLIANCE STATEMENT

Study Title: A Tissue Distribution Study of a [^{3}H]-Labelled Lipid Nanoparticle-mRNA Formulation Containing ALC-0315 and ALC-0159 Following Intramuscular Administration in Wistar Han Rats

GLP regulations are not applicable to studies of this nature therefore no claim of GLP compliance is made. Nevertheless, as Study Director, I confirm that this study was conducted in a GLP compliant facility and that the practices and procedures adopted during its conduct were consistent with the OECD Principles of Good Laboratory Practice as incorporated into the United Kingdom Statutory Instrument for GLP.

The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained.

DocuSigned by:
(b) (4)
Signer Name: (b) (4)
Signing Reason: I approve this document
Signing Time: 05-Nov-2020 | 11:52:33 EST
CD262FA0424043DEB85DE525652AC3BD

(b) (4)
Study Director

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2 QUALITY ASSURANCE STATEMENT

Study Title: A Tissue Distribution Study of a [^{3}H]-Labelled Lipid Nanoparticle-mRNA Formulation Containing ALC-0315 and ALC-0159 Following Intramuscular Administration in Wistar Han Rats

This study has not been subjected to any study specific Quality Assurance procedures.

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3 RESPONSIBLE PERSONNEL

Study Director:	(b) (4)
Sponsor Representative:	(b) (6)
Test Facility Management:	(b) (4)

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4 SUMMARY

The test item, 08-A01-C01, is an aqueous dispersion of lipid nanoparticles (LNP), comprised of a proprietary mixture of lipid components (including ALC-0315, ALC-0159, distearoylphosphatidylcholine, and cholesterol) and mRNA. The mRNA encodes a model protein (luciferase) and is not pharmacologically active. The test item contains trace amounts of radiolabelled [Cholesteryl-1,2-^{3}H(N)]-Cholesteryl Hexadecyl Ether ([^{3}H]-CHE), a non-exchangeable, non-metabolisable lipid marker used to monitor the disposition of the lipid nanoparticles (containing encapsulated mRNA). Once intracellular, the [^{3}H]-CHE does not recirculate and therefore allows assessment of distribution of the particles.

The objectives of this study were to:

1. Characterise the disposition of 08-A01-C01 containing a radiolabelled lipid marker in male and female Wistar Han rats following a single intramuscular administration.

2. Determine the concentration and content of radioactivity in blood, plasma and tissues of rats (expressed as µg lipid eq/mL (or per g for tissue), and % administered (injected dose)/tissue, where appropriate).

Wistar Han rats (21 male and 21 female) each received a single intramuscular dose of [^{3}H]-08-A01-C01 at a target mRNA total dose of 50 µg/animal (1.29 mg/animal total lipid dose). The content and concentration of total radioactivity in blood, plasma and tissues were determined at pre-defined time points following administration.

Whole blood and tissue samples were collected at 0.25 1, 2, 4, 8, 24 and 48 hours post-dose (three animals/sex/timepoint) and plasma was subsequently separated from blood by centrifugation. The concentration of total radioactivity was measured by liquid scintillation counting (LSC).

Following intramuscular administration of [^{3}H]-08-A01-C01 to male and female Wistar Han rats at a target dose level of 50 µg/animal (1.29 mg/animal total lipid dose), the greatest mean concentration was found remaining in the injection site at each time point in both sexes. Outside the injection site, low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, [^{3}H]-08-A01-C01 distributed mainly to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of [^{3}H]-08-A01-C01 outside the injection site was greatest in the liver (up to 21.5%) and was much less in spleen (≤1.1%), adrenal glands (≤0.1%) and ovaries (≤0.1%). The mean concentrations and tissue distribution pattern were broadly similar between the sexes.

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Blood:plasma ratios were generally between 0.5-0.6, indicating that the majority of the total radioactivity is associated with the plasma fraction and that [^{3}H]-08-A01-C01 does not undergo appreciable accumulation in red blood cells.
In conclusion, the distribution of [^{3}H]-08-A01-C01 (monitoring the [^{3}H]-CHE lipid label) in blood, plasma and selected tissues was determined in male and female Wistar Han rats over 48 hours after a single intramuscular injection at 50 µg mRNA/animal (1.29 mg/animal lipid dose). The concentrations of [^{3}H]-08-A01-C01 were greatest in the injection site at all time points, with levels peaking in the plasma by 1-4 hours post-dose and distribution mainly into liver, adrenal glands, spleen and ovaries over 48 hours. Total recovery of radioactivity outside of the injection site was greatest in the liver, with much lower total recovery in spleen, and very little recovery in adrenals glands and ovaries. The mean plasma, blood and tissue concentrations and tissue distribution patterns were broadly similar between the sexes and [^{3}H]-08-A01-C01 did not associate with red blood cells.

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5 INTRODUCTION

The objectives of this study were to:

1. Characterise the disposition of 08-A01-C01 containing a radiolabelled lipid marker in male and female Wistar Han rats following a single intramuscular administration

2. Determine the concentration and content of radioactivity in blood, plasma and tissues of rats (expressed as µg lipid eq/g (or per mL for plasma) and % injected dose/tissue, where appropriate)

The Wistar Han rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies and has been used in all regulatory toxicology studies by the Sponsor.

The study was designed to be appropriate for submission to regulatory authorities. However, it is recognised that no detailed test guidelines for the conduct of drug distribution and pharmacokinetic studies are currently available.

Initially, 21 male rats were dosed at 100 µg mRNA/animal. Some adverse clinical signs were observed after approximately 24 hours post-dose and a subsequent review of the data showed concentrations were well detected in tissues. After discussions with the Sponsor, the target dose level was lowered to 50 µg mRNA/animal by amendment for the remainder of the study. Reference is made to the 100 µg mRNA /animal group in some sections of the report, however, the results are not discussed.

5.1 Study Location

The study was carried out at (b) (4) (b) (4) according to (b) (4) Protocol No. 185350 and Amendments 1 and 2.

5.2 Study Dates The study was conducted according to the following timetable:

Study Initiation:	16 July 2020
Experimental Start Date:	17 July 2020
Experimental Completion Date:	24 September 2020
Study Completion Date:	See compliance page for date of Study Director's signature.

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5.3 Archiving

All raw data generated and recorded during this study will be stored in the Scientific Archive of (b) (4) for 2 years after issue of the final report. After the 2-year period the Sponsor will be consulted regarding the disposal, transfer, or continued storage of the raw data. Electronic data generated by the Test Facility were archived as noted above, except reporting files stored on Shared Document Management System (SDMS), which were archived at the (b) (4)

The original signed copy of the final report will be stored indefinitely in the Scientific Archive of (b) (4)

The residual [^{3}H]-08-A01-C01 dose (approximately 5 MBq) will be retained and stored in a fridge set to maintain 4°C at (b) (4)

Biological samples generated during the course of this study were held deep frozen until issue of the final report. (b) (4) will contact the Sponsor to discuss the fate of the samples (disposal, return or retain at (b) (4)) on issue of the final report. Samples will be disposed of unless (b) (4) receives written instruction regarding shipment of the samples to the Sponsor or continued storage at (b) (4)

6 EXPERIMENTAL PROCEDURE

6.1 Test Item

Identification:	[^{3}H]-08-A01-C01
Supplier:	Acuitas Therapeutics Inc
Lot Number:	NC-0552-1
Expiration Date:	July 7, 2021
Physical Description:	White to off-white, homogenous, opalescent liquid; no foreign particles
Concentration (mRNA):	1.0 mg/mL
Radioactive Concentration	0.864 mCi/mL, 1,900,000 dpm/µL

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Concentration (Total Lipid)	25.7 mg/mL
Molecular weight	Not applicable for LNP
Purity:	94%
Radiochemical Purity	>97%
Specific Activity (mRNA):	0.864 mCi/mg (32.0 MBq/mg)
Correction Factor	None
Storage Conditions:	Frozen (-60°C to -90°C)

The test item contains trace amounts of radiolabelled [Cholesteryl-1,2-^{3}H(N)]-Cholesteryl Hexadecyl Ether ([^{3}H]-CHE), a non-exchangeable, non-metabolisable lipid marker used to monitor the disposition of the lipid nanoparticles (containing encapsulated mRNA). Per the manufacturer's information, the radiochemical purity of [^{3}H]-CHE was found to be >97% and the rate of decomposition is initially 2% for 6 months from the date of purification (16 December 2019). No radiochemical purity assessments were made as part of this study.

The Certificates of Analysis for [^{3}H]-08-A01-C01 and [^{3}H]-CHE are presented in Appendix 1

6.2 Other Materials

AquaSafe 500 Plus liquid scintillation fluid was obtained from Zinsser Inc.

Monophase® was used in conjunction with the Perkin Elmer Model 307 Automatic Sample Oxidiser and was supplied by Perkin Elmer Life Science and Analytical Instruments Inc, UK.

Spec-Chec™-^{3}H used to estimate efficiencies of combustion was also obtained from Perkin Elmer Life Science and Analytical Instruments Inc, UK.

All other materials and chemicals used were of analytical grade where available and supplied by standard commercial suppliers.

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6.3 Animals and Husbandry

Forty-two male and 21 female Wistar Han rats (8-11 weeks and body weight 179-270 g at the time of dosing) were used in the study and were supplied by [redacted]. The animals were acclimatised to the experimental unit for at least 5 days prior to use on the study. During the acclimatisation periods, the animals were closely observed by the animal technicians to ensure that they were in good health and suitable for inclusion in the study. During the study period the animals were closely observed twice daily by the animal technicians to ensure that they were in good health.

During the study period, the rats were housed in groups in polycarbonate and stainless steel cages with wire mesh floors. Animals used for excretion collection were housed singly in all-glass metabolism cages for the separate collection of urine and faeces.

A standard laboratory diet of known formulation (SDS Rat and Rat Maintenance Diet No.1, Special Diet Services, 1 Stepfield, Witham, Essex) and domestic mains tap water were available *ad libitum*.

Holding and study areas had automatic control of light cycles and temperature. Automatic 12 hours light and 12 hours dark. Ranges of temperature and humidity measured during the study were 21-23°C and 44-67%, respectively, with the exception of 31 July 2020 where the room temperature reached a maximum of 25°C.

6.4 Specific Activity

The specific activity value of 1.24 MBq/mg lipid (as calculated from the 0.864 mCi/mg mRNA specific activity value supplied and converted to per mg lipid) was used to calculate the amount of [^{3}H]-08-A01-C01 dispensed in the dose formulation.

6.5 Dose Formulation

[^{3}H]-08-A01-C01 was provided in PBS/sucrose buffer at the required dose concentration (1 mg mRNA/mL). No dilutions were therefore required. Four dose formulation vials were provided (3 x 1.5 mL and 1 x 1.2 mL).

The appropriate number of vials for each dosing occasion were defrosted for at least 30 minutes prior to dosing. Prior to use, each vial was inverted 3 times to mix. Once dosing was complete, each vial was stored in a fridge within 4 hours of removal from the -80°C freezer.

The radioactive concentration of the supplied dose formulation was determined by the removal of triplicate aliquots (50 µL) prior to and after the first dosing occasion. Appropriate

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dilutions of each aliquot were prepared in distilled water and duplicate aliquots of each dilution were analysed by liquid scintillation counting (LSC).

The radioactive concentration determined by LSC was within 10% of the target value provided in the supplied Certificate of Analysis and was used in the dose determination calculations.

6.6 Dose Administration and Determination

Each animal received a single (one site) intramuscular administration of [^{3}H]-08-A01-C01 at either 50 or 100 µL volume for the 50 and 100 µg mRNA/animal dose groups, respectively (target doses of 1.29 or 2.57 mg total lipid/animal, respectively).

The actual dose received by each animal was determined with reference to the dose concentration, the volume of dose administered and the specific activity of [^{3}H]-08-A01-C01 in the formulated dose. Any undosed residue was also taken in to account. The actual dose received by each animal is documented in Appendix 2.

6.7 Collection of Biological Samples

Three male and three female rats were sacrificed at the following times:

0.25, 1, 2, 4, 8, 24 and 48 hours post dose

From each animal, a terminal blood sample (*ca.* 5-10 mL) was collected by cardiac puncture into heparinised tubes. A portion (*ca.* 0.5 mL) was retained and plasma separated from the remainder of each sample by centrifugation (3000 rpm for 10 minutes in a centrifuge set to maintain a temperature of 4°C). Blood cells were discarded.

The following tissues were collected (where relevant for sex)

Adipose tissue	Ovaries
Adrenal glands	Pancreas
Bladder	Pituitary gland
Bone (femur)	Prostate
Bone marrow (femur)	Salivary glands
Brain	Skin
Eyes	Muscle
Heart	Small intestine
Injection site	Spinal cord
Kidneys	Spleen
Large intestine	Stomach
Liver	Testes
Lung	Thymus
Lymph node (mandibular)	Thyroid

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Lymph node (mesenteric)	Uterus

Additionally, for animals 043M, 045M, 046M, 048M, 051M, 052M, 055M and 058M, the tibia/fibula bone was also collected but not analysed (refer to Section 6.11).

6.8 Sample Storage

Samples not analysed immediately were stored frozen in a freezer set to maintain a temperature of -20°C until taken for analysis, with the exception of urine and faeces samples which were stored at -80°C. After analysis, samples were returned to storage in a freezer set to maintain a temperature of -20°C.

Samples of cage wash, dose determinations and dose residues were stored at room temperature prior to and following analysis. These samples were discarded at the Study Director's discretion following acceptance of the study results.

6.9 Preparation of Samples for Total Radioactivity Analysis

Volumes or weights of all samples were measured where appropriate

6.9.1 Dose Formulation

Duplicate aliquots (0.1 mL) of each dilution of the dose formulation were diluted with water and dissolved in scintillation fluid (Aquasafe 500 Plus, Zinsser Inc.) and analysed directly by liquid scintillation counting.

6.9.2 Blood and Plasma

Duplicate weighed aliquots of whole blood (2 x *ca.* 0.15 g) were taken and then combusted using a Perkin Elmer Model 307 Sample Oxidiser. The resultant $^{3}H_2O$ generated was collected by absorption in Monophase® (15 mL).

Duplicate aliquots (100 µL) of plasma were allowed to air dry, diluted with water and dissolved in scintillation fluid (Aquasafe 500 Plus, Zinsser Inc.) and analysed directly by LSC.

6.9.3 Tissues

Tissue samples were finely chopped with scissors and duplicate, where appropriate, portions were combusted using a Perkin Elmer Model 307 Sample Oxidiser. Smaller tissues were aliquoted directly. The resultant $^{3}H_2O$ generated was collected by absorption in Monophase® S (15 mL).

Combustion of standards showed that recovery efficiencies were in excess of 95% throughout.

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6.9.4 Urine, Faeces and Cage Wash

Urine, faeces and cage wash samples were collected but not analysed for total radioactivity. Urine and faeces sample weights were taken prior to storage. Urine and faeces samples were retained at -80°C for possible analysis of specific lipids by LC-MS/MS conducted and reported separately. The sample weights are presented in Appendix 3.

6.10 Quantification of Radioactivity

6.10.1 Liquid Scintillation Counting

All samples prepared in scintillation fluid were subjected to liquid scintillation counting for 5 min, together with representative blank samples, using a Liquid Scintillation Analyser with automatic quench correction by an external standard method. Prior to analysis, samples were allowed to stabilise with regard to light and temperature. Self-normalisation and calibration (SNC) were conducted once a day. An unquenched tritium standard was used to initially calibrate the system to obtain optimal performance by adjusting the voltage on the photo-multiplier tubes. Representative blank sample values were subtracted from sample count rates to give net disintegrations per minute (dpm) per sample. A limit of reliable measurement of 30 counts per minute (cpm) above background was instituted in these laboratories. Any results arising from data below the limit of reliable measurement were noted in the Results section of the report. Sample repeat analysis were in accordance with Standard Operating Procedures.

6.10.2 Data Presentation

Levels of radioactivity in all samples were quantified by LSC and the data captured into DEBRA® management software, Version 5.7 (LabLogic Ltd, UK). Plasma, blood and tissues concentrations of radioactivity in dpm/g and mass eq/g were calculated based on the measured specific activity (1.24 MBq/mg lipid) of radiolabelled test item in the dose formulation.

Individual and mean data were tabulated. The following information was reported:

- Radioactive content in tissues where a total organ weight is applicable was calculated as % administered (injected) dose
- Radioactive content in tissues, whole blood and plasma as µg equiv/g (or mL).
- Blood/plasma ratio

Data presented in results tables are computer generated in DEBRA and rounded appropriately for inclusion in the report. As a consequence, calculation of individual and mean values from data presented will, in some instances, yield slight differences from the results presented.

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6.11 Protocol Deviations

Due to the unavailability of rats within specification at [redacted] the rat supplier used in this study was Envigo, UK, deviating from Section 11 of the Protocol. In the opinion of the Study Director this had no impact on the study outcome since the correct age and strain of rats were used on this study.

In error, tibia/fibula bone were collected at necropsy for animals 043M, 045M, 046M, 048M, 051M, 052M, 055M, and 058M instead of femur bone, deviating from Section 14.1 of the Protocol. Once noticed, the femur bone was retrieved from the residual carcass stored in the -20°C freezer pending disposal and analysed after discussions with the Sponsor. The results appeared similar to the other animals in each timepoint and therefore this had no impact on the study outcome.

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7 RESULTS

7.1 Clinical Observations

In the 100 µg mRNA male group, approximately 24 h following administration, animal 021M was noted to have decreased activity, ungroomed, brown staining on muzzle and irregular respiration. A decrease in bodyweight was noted in all remaining animals (approximately 16 g, equivalent to *ca.* 7% reduction of bodyweight) and food hoppers appeared untouched. By approximately 30 hours post-dose, animal 021M was also piloerect, hunched, and was hypersensitive to noise stimulus. Animal 021M was humanely killed and the diagnostic necropsy carried out showed one finding in the liver (prominent lobular architecture). Additionally, animals 019M and 020M were hunched and piloerect from approximately 30 h post-dose onwards.

In the 50 µg mRNA male group, following administration and for the duration of the study, no adverse effects were noted in any animal.

In the 50 µg mRNA female group, approximately 30 h following administration, animal 042F was noted to have decreased activity, and irregular respiration. At 48 h post dose animal 042F was additionally hunched and piloerect.

7.2 Body Weights

At the time of dosing, body weights were in the range of 217-270 g (males) and 179-224 g (females).

7.3 Tissue Distribution Following Intramuscular Administration

The mean (sex combined) concentration and recovery of total radioactivity in whole blood, plasma, injection site and tissues following a single intramuscular administration of [^{3}H]-08-A01-C01 to Wistar Han rats at a target dose level of 50 µg mRNA/animal (1.29 mg/animal lipid) is presented in Table 1. The mean concentration of total radioactivity in whole blood, plasma, injection site and tissues following a single intramuscular administration of [^{3}H]-08-A01-C01 to male and female Wistar Han rats at a target dose level of 50 µg mRNA/animal (1.29 mg/animal lipid) is presented in Table 2. The mean recovery in male and female individual tissues is presented in Table 3.

Individual male and female concentration data is presented in Appendix 4 and Appendix 5, respectively. Individual male and female recovery data is presented in Appendix 6 and Appendix 7, respectively. The male 100 µg data is presented in Appendix 8.

When analysing the injection site, there was often high inter-animal variability in concentration and % injected dose values at each time point. This may have been due to

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difficulty in collecting the entirety of this sample since the total area that the injected bolus dose migrated to within the muscle was not visible. When dosing the male 50 µg mRNA group, the injection site was circled using a marker pen to help aid dissection of the injection area. The overall injection site concentrations and % dose values were higher in males than in females. Since concentrations in other tissues were broadly similar between the sexes, it is likely that the higher injection site values in males were a result of its more consistent identification and collection in males.

Following a single intramuscular administration of [^{3}H]-08-A01-C01, the greatest mean tissue concentration and, in most instances, % of injected dose was found remaining in the injection site at each time point in both sexes. The injection site mean concentration and equivalent % dose values are presented in the table below.

Timepoint (h)	Injection site (µg equiv lipid/g)		Injection site (% dose)	
	Male	Female	Male	Female
0.25	219.940	36.566	32.887	6.815
1	587.670	199.950	68.829	36.411
2	529.210	93.144	39.053	24.094
4	619.850	56.227	47.710	9.056
8	299.590	125.930	18.731	24.993
24	267.170	122.540	31.957	26.295
48	268.770	61.088	32.823	16.426

The highest mean recovery of total radioactivity observed was 68.8% of the administered dose at 1-hour post-dose in males.

Low levels of radioactivity were detected in most tissues from the first time point (0.25 h), with the greatest level found circulating in plasma between 1-4 hours post-dose. The plasma and blood mean concentrations and blood:plasma ratios are presented in the table below.

Timepoint (h)	Blood (µg equiv lipid/g)		Plasma (µg equiv lipid/mL)		Blood:plasma ratio	
	Male	Female	Male	Female	Male	Female
0.25	3.003	0.936	6.035	1.894	0.48	1.15
1	2.809	5.928	5.379	10.884	0.49	0.54
2	4.028	6.773	8.714	9.091	0.46	0.64
4	3.400	2.698	8.755	4.251	0.42	0.60
8	2.000	0.628	3.573	1.147	0.56	0.55
24	1.274	0.544	2.621	0.945	0.49	0.57
48	0.535	0.305	1.085	0.524	0.50	0.58

Mean plasma concentrations peaked by 4 hours post-dose in males (8.755 µg equiv lipid/mL) and by 1 hour post-dose in females (10.884 µg equiv lipid/mL), before steadily decreasing. Concentrations were higher in plasma than in blood, with mean blood:plasma ratios generally

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ca. 0.5-0.6, indicating that the majority of the total radioactivity is associated with the plasma fraction.

Over 48 hours, [^{3}H]-08-A01-C01 distributed from the injection site to most tissues, with the majority of tissues exhibiting low levels of radioactivity. The highest mean concentrations observed, and the equivalent % dose, are presented in the tables below.

Timepoint (h)	Values expressed as µg equiv lipid/g)						
	Liver		Spleen		Adrenal glands		Ovaries
	Male	Female	Male	Female	Male	Female	Female
0.25	1.151	0.323	0.354	°0.313	0.302	°0.240	°0.104
1	4.006	5.244	2.140	2.801	0.580	2.388	1.339
2	9.574	12.370	5.255	10.213	1.206	4.232	1.638
4	18.525	14.569	8.945	11.646	2.569	3.206	2.341
8	27.916	25.172	24.434	19.747	6.387	7.218	3.088
24	23.360	15.119	22.819	17.341	19.948	7.595	5.240
48	18.164	30.411	19.550	27.155	21.476	14.942	12.261

=Mean includes results calculated from data less than 30 cpm above background

Timepoint (h)	Liver		Spleen		Adrenal glands		Ovaries
	Male	Female	Male	Female	Male	Female	Female
0.25	0.995	0.209	0.014	°0.011	0.001	°0.001	°0.001
1	2.834	2.907	0.087	0.098	0.002	0.012	0.009
2	7.629	7.030	0.232	0.418	0.005	0.015	0.008
4	15.027	8.699	0.351	0.419	0.012	0.018	0.016
8	21.519	14.580	1.118	0.845	0.026	0.043	0.025
24	19.901	10.977	0.957	0.685	0.083	0.049	0.037
48	13.953	18.357	0.914	1.146	0.104	0.108	0.095

=Mean includes results calculated from data less than 30 cpm above background

Maximum concentrations (C_{max}) in liver and spleen were observed at 8 hours post-dose in males and 48 hours post dose in females, but were broadly similar and appeared to plateau at 8 hours post-dose when considering variability. The greatest mean concentration outside the injection site was observed in the liver, with values of 27.916 µg equiv lipid/g (equivalent to 21.5 % dose) in males and 30.411 µg equiv lipid/g (equivalent to 18.4 % dose) in females. In the spleen the highest concentrations were 24.434 µg equiv lipid/g in males and 27.155 µg equiv lipid/g (equivalent to 1.1% dose in both sexes).

In the adrenal glands and ovaries, the highest mean concentrations were observed at 48 hours post-dose. The highest mean concentrations in the adrenal glands were 21.476 and 14.942 µg equiv lipid/g in males and females, respectively (equivalent to 0.1% dose in both sexes). The highest mean ovaries concentration was 12.261 µg equiv lipid/g (equivalent to 0.1 % dose).

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8 CONCLUSIONS

In conclusion, the distribution of [^{3}H]-08-A01-C01 (monitoring the [^{3}H]-CHE lipid label) in blood, plasma and selected tissues was determined in male and female Wistar Han rats over 48 hours after a single intramuscular injection at 50 µg mRNA/animal (1.29 mg/animal lipid dose). The concentrations of [^{3}H]-08-A01-C01 were greatest in the injection site at all time points, with levels peaking in the plasma by 1-4 hours post-dose and distribution mainly into liver, adrenal glands, spleen and ovaries over 48 hours. Total recovery of radioactivity outside of the injection site was greatest in the liver, with much lower total recovery in spleen, and very little recovery in adrenals glands and ovaries. The mean plasma, blood and tissue concentrations and tissue distribution patterns were broadly similar between the sexes and [^{3}H]-08-A01-C01 did not associate with red blood cells.

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9 TABLES

Table 1 **Mean (Sexes-Combined) Concentration and Recovery of Total Radioactivity in Whole Blood, Plasma and Tissues Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Wistar Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as total lipid concentration (µg lipid equiv/g (mL)) and % of administered dose

Sample	Total Lipid Concentration (µg lipid equiv/g (or mL))							% of Administered Dose						
	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	-	-	-	-	-	-	-
Adrenal glands	0.271	1.484	2.719	2.888	6.803	13.772	18.209	0.001	0.007	0.010	0.015	0.035	0.066	0.106
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	-	-	-	-	-	-	-
Bone marrow (femur)	0.479	0.960	1.237	1.236	1.836	2.492	3.771	-	-	-	-	-	-	-
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
Heart	0.282	1.029	1.402	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030
Injection site	128.253	393.810	311.177	338.039	212.760	194.855	164.929	19.851	52.620	31.574	28.383	21.862	29.126	24.625
Kidneys	0.391	1.161	2.046	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
Large intestine	0.013	0.048	0.093	0.287	0.649	1.104	1.338	0.008	0.025	0.065	0.192	0.405	0.692	0.762
Liver	0.737	4.625	10.972	16.547	26.544	19.240	24.288	0.602	2.871	7.330	11.863	18.050	15.439	16.155
Lung	0.492	1.210	1.834	1.497	1.151	1.039	1.093	0.052	0.101	0.178	0.169	0.122	0.101	0.101
Lymph node (man)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	-	-	-	-	-	-	-
Lymph node (mes)	0.050	0.146	0.530	0.489	0.689	0.985	1.366	-	-	-	-	-	-	-
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	-	-	-	-	-	-	-
Ovaries (females)	0.104	1.339	1.638	2.341	3.088	5.240	12.261	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	-	-	-	-	-	-	-

- =Partial tissue taken therefore not applicable

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Table 1 (Continued) **Mean (Sexes-Combined) Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Wistar Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as total lipid concentration (µg lipid equiv/g (mL)) and % of administered dose

Sample	Total Lipid Concentration (µg lipid equiv/g (or mL))							% of Administered Dose						
	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h
Small intestine	0.030	0.221	0.476	0.879	1.279	1.302	1.472	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.471	7.734	10.296	22.091	20.080	23.353	0.013	0.093	0.325	0.385	0.982	0.821	1.030
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.000	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.970	4.369	5.401	3.049	1.314	0.909	0.420	-	-	-	-	-	-	-
Plasma	3.965	8.132	8.903	6.503	2.360	1.783	0.805	-	-	-	-	-	-	-
Blood:plasma ratio	0.815	0.515	0.550	0.510	0.555	0.530	0.540	-	-	-	-	-	-	-

- =Partial tissue taken therefore not applicable/not applicable

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Table 2 **Mean Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Wistar Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	0.25 min		1 h		2 h		4 h		8 h		24 h		48 h	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Adipose tissue	0.040	°0.073	0.050	0.149	0.070	0.182	0.093	0.163	0.116	0.069	0.126	0.042	0.129	0.232
Adrenal glands	0.302	°0.240	0.580	2.388	1.206	4.232	2.569	3.206	6.387	7.218	19.948	7.595	21.476	14.942
Bladder	0.049	°0.033	0.095	0.165	0.137	0.155	0.227	0.106	0.211	0.085	0.323	0.171	0.340	0.389
Bone (femur)	0.126	0.056	0.148	0.241	0.235	0.296	0.335	0.217	0.502	0.177	0.504	0.180	0.520	0.854
Bone marrow (femur)	0.761	°0.196	0.910	1.010	1.136	1.337	1.557	0.915	2.397	1.274	3.579	1.405	3.690	3.851
Brain	0.073	°0.016	0.083	0.117	0.143	0.133	0.155	0.075	0.101	0.045	0.090	0.047	0.083	0.052
Eyes	0.014	°0.006	0.027	0.043	0.046	0.058	0.095	0.038	0.088	0.030	0.129	0.052	0.127	0.097
Heart	0.419	°0.144	0.631	1.426	1.122	1.682	1.049	0.925	1.189	0.391	0.583	0.318	0.672	0.420
Injection site	219.940	36.566	587.670	199.950	529.210	93.144	619.850	56.227	299.590	125.930	267.170	122.540	268.770	61.088
Kidneys	0.511	0.271	0.630	1.692	1.124	2.967	1.033	0.814	0.837	0.342	0.504	0.348	0.482	0.368
Large intestine	0.017	°0.008	0.031	0.065	0.080	0.106	0.350	0.224	0.690	0.608	1.741	0.466	1.426	1.249
Liver	1.151	0.323	4.006	5.244	9.574	12.370	18.525	14.569	27.916	25.172	23.360	15.119	18.164	30.411
Lung	0.737	0.247	0.845	1.574	1.594	2.074	1.772	1.222	1.674	0.628	1.316	0.762	1.288	0.898
Lymph node (man)	0.090	°0.038	0.154	0.223	0.217	0.362	0.424	0.391	0.695	0.372	0.744	0.363	0.820	0.633
Lymph node (mes)	0.052	°0.048	0.095	0.196	0.229	0.831	0.441	0.536	0.649	0.729	1.106	0.863	1.057	1.675
Muscle	°0.029	0.012	0.039	0.082	0.067	0.100	0.075	0.130	0.101	0.091	0.098	0.092	0.280	0.104
Ovaries (females)	-	°0.104	-	1.339	-	1.638	-	2.341	-	3.088	-	5.240	-	12.261
Pancreas	0.125	0.037	0.153	0.261	0.423	0.404	0.361	0.398	0.349	0.239	0.396	0.320	0.587	0.611
Pituitary gland	0.537	°0.141	0.446	0.844	0.781	0.955	1.249	0.458	0.669	0.141	0.656	0.300	0.543	0.845
Prostate (males)	0.061	-	0.091	-	0.128	-	0.157	-	0.150	-	0.183	-	0.170	-
Salivary glands	0.114	°0.054	0.148	0.237	0.214	0.295	0.270	0.169	0.176	0.094	0.243	0.096	0.297	0.231
Skin	°0.016	0.010	0.028	0.387	0.054	0.263	0.085	0.204	0.122	0.116	0.195	0.118	0.209	0.297

°=Mean includes results calculated from data less than 30 cpm above background

Table 2 (Continued) **Mean Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Wistar Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	0.25 min		1 h		2 h		4 h		8 h		24 h		48 h	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Small intestine	0.038	°0.021	0.194	0.247	0.471	0.481	0.919	0.838	1.525	1.033	1.878	0.726	1.630	1.314
Spinal cord	0.061	°0.024	0.072	0.122	0.166	0.172	0.375	0.124	0.168	0.044	0.121	0.048	0.162	0.062
Spleen	0.354	°0.313	2.140	2.801	5.255	10.213	8.945	11.646	24.434	19.747	22.819	17.341	19.550	27.155
Stomach	0.018	°0.015	0.039	0.091	0.104	0.126	0.186	0.101	0.410	0.126	0.222	0.081	0.235	0.195
Testes (males)	0.031	-	0.042	-	0.079	-	0.129	-	0.146	-	0.304	-	0.320	-
Thymus	0.106	°0.069	0.187	0.298	0.220	0.459	0.461	0.209	0.292	0.100	0.255	0.159	0.296	0.366
Thyroid	0.217	°0.093	0.391	0.680	0.575	1.109	1.097	0.604	0.781	0.307	0.820	0.335	1.344	0.655
Uterus (females)	-	°0.043	-	0.203	-	0.305	-	0.140	-	0.287	-	0.289	-	0.456
Whole Blood	3.003	0.936	2.809	5.928	4.028	6.773	3.400	2.698	2.000	0.628	1.274	0.544	0.535	0.305
Plasma	6.035	1.894	5.379	10.884	8.714	9.091	8.755	4.251	3.573	1.147	2.621	0.945	1.085	0.524
Blood:plasma ratio	0.48	1.15	0.49	0.54	0.46	0.64	0.42	0.60	0.56	0.55	0.49	0.57	0.50	0.58

°=Mean includes results calculated from data less than 30 cpm above background

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Table 3 **Mean Recovery of Total Radioactivity in Tissues Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Wistar Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	0.25 min		1 h		2 h		4 h		8 h		24 h		48 h	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Adrenal glands	0.001	°0.001	0.002	0.012	0.005	0.015	0.012	0.018	0.026	0.043	0.083	0.049	0.104	0.108
Bladder	0.000	°0.000	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.000	0.002	0.001	0.002	0.002
Brain	0.011	°0.002	0.010	0.016	0.021	0.019	0.021	0.011	0.014	0.007	0.012	0.007	0.011	0.007
Eyes	0.000	°0.000	0.000	0.001	0.001	0.001	0.002	0.001	0.002	0.001	0.002	0.001	0.003	0.002
Heart	0.028	°0.008	0.032	0.079	0.065	0.102	0.067	0.052	0.061	0.022	0.035	0.018	0.039	0.020
Injection site	32.887	6.815	68.829	36.411	39.053	24.094	47.710	9.056	18.731	24.993	31.957	26.295	32.823	16.426
Kidneys	0.069	0.030	0.077	0.171	0.149	0.272	0.136	0.082	0.109	0.040	0.068	0.039	0.071	0.042
Large intestine	0.011	°0.004	0.018	0.032	0.054	0.075	0.236	0.148	0.463	0.346	1.091	0.293	0.810	0.714
Liver	0.995	0.209	2.834	2.907	7.629	7.030	15.027	8.699	21.519	14.580	19.901	10.977	13.953	18.357
Lung	0.082	0.022	0.085	0.117	0.189	0.167	0.226	0.112	0.180	0.064	0.136	0.065	0.131	0.070
Ovaries (females)	-	°0.001	-	0.009	-	0.008	-	0.016	-	0.025	-	0.037	-	0.095
Pancreas	0.005	0.001	0.006	0.008	0.015	0.012	0.013	0.017	0.014	0.016	0.013	0.009	0.015	0.023
Pituitary gland	0.000	°0.000	0.000	0.001	0.000	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.001
Prostate (males)	0.001	-	0.001	-	0.002	-	0.003	-	0.003	-	0.004	-	0.003	-
Salivary glands	0.004	°0.002	0.005	0.008	0.007	0.009	0.009	0.006	0.007	0.003	0.008	0.003	0.010	0.007
Small intestine	0.032	°0.015	0.124	0.135	0.353	0.285	0.623	0.462	0.972	0.580	1.275	0.536	0.971	0.698
Spinal cord	0.001	°0.000	0.001	0.002	0.001	0.002	0.003	0.002	0.001	0.001	0.001	0.001	0.001	0.001
Spleen	0.014	°0.011	0.087	0.098	0.232	0.418	0.351	0.419	1.118	0.845	0.957	0.685	0.914	1.146
Stomach	0.008	°0.003	0.016	0.022	0.033	0.035	0.037	0.022	0.055	0.024	0.054	0.020	0.049	0.029
Testes (males)	0.007	-	0.010	-	0.017	-	0.030	-	0.034	-	0.074	-	0.074	-
Thymus	0.005	°0.002	0.006	0.008	0.008	0.012	0.018	0.006	0.012	0.003	0.009	0.004	0.008	0.007
Thyroid	0.000	°0.000	0.000	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.001	0.000	0.001	0.001
Uterus (females)	-	°0.002	-	0.011	-	0.015	-	0.008	-	0.016	-	0.018	-	0.022

°=Mean includes results calculated from data less than 30 cpm above background

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Court File No./N° du dossier du greffe : CV-22-00691880-0000

10 APPENDICES

Appendix 1 Certificates of Analysis for [^{3}H]-08-A01-C01 and [^{3}H]-CHE

Confidential

ACUITAS

R&D Formulation Characterization Report

Batch ID	LNP ID	Specific Activity	[Lipid]	Encaps	Encapsulated mRNA	Yield	mRNA/Lipid Ratio	Particle Diameter	Poly-dispersity
		dpm/uL	mg/mL	%	mg/mL	mg	mg/mg	nm	
NC-0552-1	08-A01-001	1,900,000	25.7	94	1.0	6.05	0.039	89	0.062

Notes

Formulated July 6, 2020 for NC-0552 using BioNTech mRNA (AnSo luc 1041 CorVac) and trace labeled with 3H-CHE. Endotoxin below detection limit (<0.5 EU/mL). Sterile filtered using 0.2 µm pore-size filters.

Stored at -70°C. Thaw at room temperature and dilute on the day of use.

(b) (6)

(b) (6)

08-July-20
Date

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ACD-008.01

Appendix 1 (continued) **Certificates of Analysis for [^{3}H]-08-A01-C01 and [^{3}H]-CHE**

TECHNICAL DATA SHEET ^{3}H

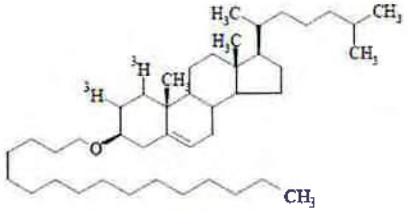
Research Use Only. Not for use in diagnostic procedures

CHOLESTERYL HEXADECYL ETHER, [CHOLESTERYL-1,2-^{3}H(N)]-

Product Number: NET859

LOT SPECIFIC INFORMATION

Lot Number:	2656317	
Specific Activity:	51.9	Ci/mmol
	1920	GBq/mmol
Production Date:	16-Dec-2019	



M.W. 611.1
$C_{43}H_{78}O$

PACKAGING: 1.0 mCi/ml (37 MBq/ml) in toluene, under argon in an ampoule. Shipped on dry ice.

STABILITY AND STORAGE RECOMMENDATIONS: When cholesteryl hexadecyl ether, [cholesteryl-1,2-^{3}H(N)]- is stored at -20°C in its original solvent and at its original concentration, the rate of decomposition is initially 2% for 6 months from date of purification. Stability is nonlinear and not correlated to isotope half-life. Lot to lot variation may occur.

SPECIFIC ACTIVITY RANGE: 40-60 Ci/mmol (1480-2220 GBq/mmol)

RADIOCHEMICAL PURITY: This product was initially found to be greater than 97% when determined by the following methods. The rate of decomposition can accelerate. It is advisable to check purity prior to use:

High pressure liquid chromatography on a Zorbax C-8 column using the following mobile phase:
acetonitrile : isopropanol, (35:65).

Thin layer chromatography on silica gel using the following solvent system:
toluene : hexane, (1:9).

QUALITY CONTROL: The radiochemical purity of cholesteryl hexadecyl ether, [cholesteryl-1,2-^{3}H(N)]- is checked at appropriate intervals using the first listed chromatography method.

The precursor used in the synthesis of NET-859 is synthetic.

HAZARD INFORMATION: WARNING: This product contains a chemical known to the state of California to cause cancer.

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NET859-REV-02

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Appendix 2 Individual Animal Dosing Summary

Males

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Animal ID	Body weight (g)	Dose Received		
		mg mRNA	mg lipid	MBq
043M	270	0.0514	1.32	1.63
044M	264	0.0518	1.33	1.65
045M	244	0.0521	1.34	1.66
046M	263	0.0525	1.35	1.68
047M	232	0.0514	1.32	1.64
048M	228	0.0525	1.35	1.67
049M	259	0.0514	1.32	1.64
050M	249	0.0518	1.33	1.66
051M	257	0.0533	1.37	1.70
052M	258	0.0521	1.34	1.66
053M	249	0.0529	1.36	1.69
054M	235	0.0525	1.35	1.68
055M	247	0.0502	1.29	1.60
056M	256	0.0514	1.32	1.64
057M	266	0.0521	1.34	1.66
058M	263	0.0521	1.34	1.66
059M	243	0.0525	1.35	1.67
060M	248	0.0518	1.33	1.65
061M	240	0.0521	1.34	1.66
062M	259	0.0521	1.34	1.66
063M	238	0.0521	1.34	1.66

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Appendix 2 (continued) **Individual Animal Dosing Summary**

Females

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Animal ID	Body weight (g)	Dose Received		
		mg mRNA	mg lipid	MBq
022F	215	0.0521	1.34	1.66
023F	206	0.0529	1.36	1.68
024F	206	0.0514	1.32	1.64
025F	212	0.0533	1.37	1.70
026F	213	0.0525	1.35	1.68
027F	207	0.0529	1.36	1.69
028F	198	0.0529	1.36	1.68
029F	208	0.0529	1.36	1.69
030F	214	0.0518	1.33	1.64
031F	204	0.0537	1.38	1.71
032F	207	0.0533	1.37	1.70
033F	209	0.0521	1.34	1.66
034F	224	0.0510	1.31	1.62
035F	179	0.0482	1.24	1.53
036F	211	0.0467	1.20	1.49
037F	205	0.0506	1.30	1.61
038F	225	0.0502	1.29	1.60
039F	213	0.0525	1.35	1.67
040F	199	0.0533	1.37	1.69
041F	218	0.0529	1.36	1.69
042F	193	0.0533	1.37	1.70

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Appendix 2 (continued) **Individual Animal Dosing Summary**

Males

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Animal ID	Body weight (g)	Dose Received		
		mg mRNA	mg lipid	MBq
001M	240	0.104	2.66	3.30
002M	243	0.106	2.73	3.38
003M	277	0.107	2.74	3.40
004M	247	0.106	2.72	3.37
005M	243	0.107	2.76	3.42
006M	237	0.107	2.74	3.39
007M	245	0.107	2.75	3.41
008M	237	0.106	2.73	3.39
009M	248	0.106	2.73	3.39
010M	227	0.101	2.60	3.22
011M	267	0.105	2.71	3.36
012M	237	0.106	2.72	3.37
013M	241	0.105	2.69	3.34
014M	264	0.107	2.76	3.42
015M	264	0.105	2.71	3.36
043M	241	0.106	2.73	3.39
017M	252	0.106	2.73	3.39
018M	263	0.105	2.70	3.35
019M	248	0.106	2.72	3.37
020M	246	0.106	2.73	3.39
021M	217	0.107	2.75	3.41

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Appendix 3 Urine and Faeces Sample Weights

Males

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed in g

Sample	Timepoint	061M	062M	063M
Urine	Pre-dose	6.860	18.617	14.228
	6 h	6.139	8.101	8.153
	24 h	21.208	29.766	40.276
	48 h	28.317	28.566	36.902
Faeces	Pre-dose	11.324	7.893	6.070
	24 h	4.716	14.327	8.659
	48 h	6.968	8.398	7.007

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Appendix 3 (continued) **Urine and Faeces Sample Weights**

Females

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed in g

Sample	Timepoint	040F	041F	042F
Urine	Pre-dose	3.963	9.453	7.513
	6 h	4.844	5.664	9.719
	24 h	20.736	29.176	21.294
	48 h	30.371	33.928	23.141
Faeces	Pre-dose	6.110	2.679	6.010
	24 h	8.887	9.193	5.619
	48 h	4.565	6.139	4.834

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Appendix 3 (continued) **Urine and Faeces Sample Weights**

Males

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed in g

Sample	Timepoint	019M	020M	021M
Urine	Pre-dose	7.519	4.094	13.159
	6 h	8.883	8.835	10.517
	24 h	29.916	22.983	12.664
	48 h	37.860	35.653	*6.931
Faeces	Pre-dose	9.491	9.292	4.882
	24 h	11.197	14.005	8.769
	48 h	6.950	8.229	*2.449

Note that for animal 021M the collection period was approximately 24-31 h.

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Appendix 4 **Individual Male Concentration Data**

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 0.25 min Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	043M	044M	045M	Mean	SD
Adipose tissue	0.056	0.045	0.019	0.040	0.019
Adrenal glands	0.380	0.480	0.046	0.302	0.227
Bladder	0.096	0.045	0.007	0.049	0.045
Bone (femur)	0.172	0.085	0.119	0.126	0.044
Bone marrow (femur)	0.775	0.326	1.182	0.761	0.428
Brain	0.093	0.092	0.033	0.073	0.034
Eyes	0.025	0.013	0.005	0.014	0.010
Heart	0.710	0.474	0.074	0.419	0.322
Injection site	436.090	159.310	64.429	219.940	193.100
Kidneys	0.808	0.600	0.123	0.511	0.351
Large intestine	0.020	0.027	0.003	0.017	0.012
Liver	2.035	1.226	0.193	1.151	0.923
Lung	1.050	0.826	0.334	0.737	0.366
Lymph node (Man)	0.152	0.069	0.049	0.090	0.055
Lymph node (Mes)	0.087	0.054	0.016	0.052	0.036
Muscle	0.049	0.035	*0.003	°0.029	°0.024
Pancreas	0.156	0.201	0.019	0.125	0.095
Pituitary gland	0.962	0.535	0.115	0.537	0.424
Prostate	0.098	0.074	0.012	0.061	0.044
Salivary glands	0.169	0.145	0.028	0.114	0.076
Skin	0.030	0.015	*0.002	°0.016	°0.014
Small intestine	0.064	0.043	0.008	0.038	0.028
Spinal cord	0.108	0.063	0.013	0.061	0.047
Spleen	0.519	0.450	0.094	0.354	0.228
Stomach	0.022	0.027	0.005	0.018	0.012
Testes	0.053	0.036	0.006	0.031	0.024
Thymus	0.119	0.169	0.030	0.106	0.071
Thyroid	0.292	0.307	0.053	0.217	0.142
Whole Blood	5.631	2.526	0.852	3.003	2.425
Plasma	9.854	6.519	1.732	6.035	4.083
Blood:plasma ratio	0.57	0.39	0.49	0.48	0.09

*=Results calculated from data less than 30 cpm above background
°=Mean includes results calculated from data less than 30 cpm above background

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Appendix 4 (continued)

Individual Male Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 1 hour Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	046M	047M	048M	Mean	SD
Adipose tissue	0.037	0.073	0.040	0.050	0.020
Adrenal glands	0.293	0.647	0.800	0.580	0.260
Bladder	0.111	0.087	0.088	0.095	0.013
Bone (femur)	0.115	0.085	0.246	0.148	0.085
Bone marrow (femur)	0.561	1.150	1.021	0.910	0.310
Brain	0.033	0.108	0.107	0.083	0.043
Eyes	0.014	0.019	0.049	0.027	0.019
Heart	0.266	0.780	0.847	0.631	0.318
Injection site	503.490	593.230	666.280	587.670	81.536
Kidneys	0.322	0.710	0.857	0.630	0.276
Large intestine	0.026	0.032	0.037	0.031	0.005
Liver	2.667	3.571	5.780	4.006	1.602
Lung	0.428	1.203	0.903	0.845	0.391
Lymph node (Man)	0.151	0.166	0.145	0.154	0.011
Lymph node (Mes)	0.076	0.100	0.109	0.095	0.017
Muscle	0.030	0.036	0.050	0.039	0.010
Pancreas	0.076	0.189	0.193	0.153	0.067
Pituitary gland	0.202	0.502	0.634	0.446	0.221
Prostate	0.063	0.105	0.105	0.091	0.024
Salivary glands	0.084	0.151	0.208	0.148	0.062
Skin	0.020	0.027	0.039	0.028	0.010
Small intestine	0.144	0.214	0.223	0.194	0.043
Spinal cord	0.062	0.070	0.084	0.072	0.011
Spleen	3.314	1.388	1.720	2.140	1.029
Stomach	0.024	0.043	0.049	0.039	0.013
Testes	0.026	0.041	0.057	0.042	0.015
Thymus	0.201	0.133	0.226	0.187	0.048
Thyroid	0.126	0.599	0.448	0.391	0.241
Whole Blood	0.873	4.534	3.018	2.809	1.840
Plasma	2.937	6.047	7.153	5.379	2.186
Blood:plasma ratio	0.30	0.75	0.42	0.49	0.23

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Appendix 4 (continued)

Individual Male Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 2 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	049M	050M	051M	Mean	SD
Adipose tissue	0.084	0.034	0.090	0.070	0.031
Adrenal glands	1.809	0.584	1.226	1.206	0.613
Bladder	0.152	0.080	0.179	0.137	0.051
Bone (femur)	0.250	0.180	0.273	0.235	0.048
Bone marrow (femur)	1.526	0.559	1.323	1.136	0.510
Brain	0.220	0.088	0.121	0.143	0.069
Eyes	0.036	0.023	0.077	0.046	0.028
Heart	1.782	0.682	0.901	1.122	0.582
Injection site	445.930	1052.800	88.843	529.210	487.370
Kidneys	1.467	0.785	1.120	1.124	0.341
Large intestine	0.074	0.056	0.109	0.080	0.027
Liver	12.023	5.816	10.885	9.574	3.304
Lung	2.397	0.968	1.419	1.594	0.730
Lymph node (Man)	0.328	0.112	0.210	0.217	0.108
Lymph node (Mes)	0.312	0.180	0.194	0.229	0.073
Muscle	0.083	0.060	0.057	0.067	0.014
Pancreas	0.296	0.179	0.792	0.423	0.325
Pituitary gland	1.175	0.405	0.764	0.781	0.385
Prostate	0.150	0.095	0.139	0.128	0.029
Salivary glands	0.279	0.113	0.251	0.214	0.089
Skin	0.083	0.032	0.048	0.054	0.026
Small intestine	0.455	0.458	0.500	0.471	0.025
Spinal cord	0.184	0.150	0.163	0.166	0.017
Spleen	6.771	2.590	6.403	5.255	2.315
Stomach	0.121	0.059	0.133	0.104	0.040
Testes	0.120	0.039	0.077	0.079	0.040
Thymus	0.248	0.146	0.265	0.220	0.065
Thyroid	0.749	0.361	0.615	0.575	0.197
Whole Blood	4.913	2.788	4.384	4.028	1.106
Plasma	10.623	6.177	9.341	8.714	2.288
Blood:plasma ratio	0.46	0.45	0.47	0.46	0.01

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Appendix 4 (continued)

Individual Male Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 4 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	052M	053M	054M	Mean	SD
Adipose tissue	0.062	0.092	0.124	0.093	0.031
Adrenal glands	2.252	1.999	3.456	2.569	0.779
Bladder	0.207	0.239	0.234	0.227	0.017
Bone (femur)	0.264	0.234	0.506	0.335	0.149
Bone marrow (femur)	1.318	1.364	1.987	1.557	0.374
Brain	0.136	0.112	0.217	0.155	0.055
Eyes	0.084	0.133	0.067	0.095	0.034
Heart	0.993	0.669	1.484	1.049	0.411
Injection site	445.970	1001.000	412.620	619.850	330.480
Kidneys	0.967	0.737	1.395	1.033	0.334
Large intestine	0.413	0.311	0.327	0.350	0.055
Liver	14.739	16.391	24.445	18.525	5.193
Lung	2.047	1.003	2.265	1.772	0.675
Lymph node (Man)	0.283	0.564	0.426	0.424	0.140
Lymph node (Mes)	0.287	0.258	0.780	0.441	0.293
Muscle	0.064	0.057	0.104	0.075	0.025
Pancreas	0.277	0.413	0.393	0.361	0.073
Pituitary gland	0.933	2.418	0.397	1.249	1.047
Prostate	0.161	0.121	0.190	0.157	0.035
Salivary glands	0.232	0.197	0.380	0.270	0.097
Skin	0.073	0.052	0.131	0.085	0.041
Small intestine	0.822	0.698	1.235	0.919	0.281
Spinal cord	0.193	0.745	0.188	0.375	0.320
Spleen	6.146	11.159	9.529	8.945	2.557
Stomach	0.324	0.058	0.176	0.186	0.134
Testes	0.105	0.098	0.185	0.129	0.049
Thymus	0.210	0.371	0.800	0.461	0.305
Thyroid	1.055	1.301	0.936	1.097	0.186
Whole Blood	3.547	2.519	4.133	3.400	0.817
Plasma	8.820	4.802	12.644	8.755	3.922
Blood:plasma ratio	0.40	0.52	0.33	0.42	0.10

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Appendix 4 (continued)

Individual Male Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 8 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	055M	056M	057M	Mean	SD
Adipose tissue	0.076	0.163	0.109	0.116	0.044
Adrenal glands	4.440	4.886	9.835	6.387	2.995
Bladder	N.S.	0.198	0.224	0.211	N.A.
Bone (femur)	0.510	0.355	0.639	0.502	0.142
Bone marrow (femur)	3.050	1.943	2.199	2.397	0.579
Brain	0.105	0.096	0.103	0.101	0.005
Eyes	N.S.	0.071	0.104	0.088	N.A.
Heart	1.418	1.008	1.142	1.189	0.209
Injection site	181.620	497.270	219.870	299.590	172.260
Kidneys	0.934	0.795	0.783	0.837	0.084
Large intestine	0.735	0.665	0.672	0.690	0.039
Liver	23.158	22.178	38.412	27.916	9.103
Lung	1.679	1.643	1.701	1.674	0.029
Lymph node (Man)	0.432	1.053	0.601	0.695	0.321
Lymph node (Mes)	0.444	0.609	0.892	0.649	0.226
Muscle	0.082	0.096	0.127	0.101	0.023
Pancreas	0.352	0.418	0.276	0.349	0.071
Pituitary gland	0.635	0.477	0.894	0.669	0.211
Prostate	0.184	0.127	0.139	0.150	0.030
Salivary glands	0.170	0.157	0.202	0.176	0.023
Skin	0.138	0.111	0.117	0.122	0.014
Small intestine	1.423	1.518	1.634	1.525	0.106
Spinal cord	0.146	0.119	0.239	0.168	0.063
Spleen	21.122	24.073	28.107	24.434	3.507
Stomach	0.345	0.107	0.777	0.410	0.340
Testes	0.153	0.107	0.179	0.146	0.037
Thymus	0.317	0.278	0.282	0.292	0.021
Thyroid	0.940	0.611	0.792	0.781	0.165
Whole Blood	2.215	1.968	1.817	2.000	0.201
Plasma	3.978	3.465	3.275	3.573	0.364
Blood:plasma ratio	0.56	0.57	0.55	0.56	0.01

N.S. = No sample due to oxidiser failure
N.A. = Not applicable

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Appendix 4 (continued)

Individual Male Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 24 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	058M	059M	060M	Mean	SD
Adipose tissue	0.079	0.116	0.182	0.126	0.053
Adrenal glands	10.795	21.060	27.988	19.948	8.650
Bladder	0.211	0.394	0.365	0.323	0.099
Bone (femur)	0.456	0.408	0.649	0.504	0.127
Bone marrow (femur)	2.286	3.625	4.824	3.579	1.270
Brain	0.049	0.099	0.124	0.090	0.038
Eyes	0.098	0.113	0.178	0.129	0.042
Heart	0.640	0.590	0.520	0.583	0.060
Injection site	178.010	330.550	292.960	267.170	79.471
Kidneys	0.522	0.407	0.584	0.504	0.090
Large intestine	0.592	1.611	3.019	1.741	1.219
Liver	17.750	21.966	30.365	23.360	6.422
Lung	0.942	1.334	1.672	1.316	0.365
Lymph node (Man)	0.577	0.689	0.965	0.744	0.200
Lymph node (Mes)	0.905	1.040	1.373	1.106	0.241
Muscle	0.092	0.068	0.133	0.098	0.033
Pancreas	0.294	0.382	0.513	0.396	0.110
Pituitary gland	0.489	0.768	0.711	0.656	0.147
Prostate	0.150	0.183	0.215	0.183	0.032
Salivary glands	0.168	0.243	0.317	0.243	0.075
Skin	0.134	0.166	0.287	0.195	0.081
Small intestine	0.971	1.994	2.670	1.878	0.855
Spinal cord	0.091	0.144	0.127	0.121	0.027
Spleen	19.140	15.796	33.523	22.819	9.419
Stomach	0.110	0.168	0.386	0.222	0.145
Testes	0.234	0.286	0.392	0.304	0.080
Thymus	0.163	0.235	0.368	0.255	0.104
Thyroid	0.721	0.660	1.081	0.820	0.228
Whole Blood	1.473	1.237	1.112	1.274	0.183
Plasma	2.584	2.935	2.345	2.621	0.297
Blood:plasma ratio	0.57	0.42	0.47	0.49	0.08

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Appendix 4 (continued)

Individual Male Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 48 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	061M	062M	063M	Mean	SD
Adipose tissue	0.104	0.162	0.121	0.129	0.030
Adrenal glands	13.913	35.091	15.424	21.476	11.815
Bladder	0.274	0.447	0.298	0.340	0.094
Bone (femur)	0.344	0.577	0.639	0.520	0.155
Bone marrow (femur)	2.566	5.049	3.455	3.690	1.258
Brain	0.051	0.112	0.087	0.083	0.031
Eyes	0.100	0.121	0.160	0.127	0.031
Heart	0.418	0.955	0.642	0.672	0.270
Injection site	292.370	196.910	317.030	268.770	63.446
Kidneys	0.309	0.673	0.463	0.482	0.182
Large intestine	0.998	1.235	2.045	1.426	0.549
Liver	17.734	20.580	16.177	18.164	2.233
Lung	0.809	1.885	1.170	1.288	0.548
Lymph node (Man)	0.728	1.078	0.656	0.820	0.226
Lymph node (Mes)	0.924	1.620	0.626	1.057	0.510
Muscle	0.078	0.115	0.647	0.280	0.318
Pancreas	0.291	0.506	0.964	0.587	0.344
Pituitary gland	0.431	0.610	0.588	0.543	0.098
Prostate	0.110	0.265	0.135	0.170	0.083
Salivary glands	0.286	0.370	0.234	0.297	0.069
Skin	0.177	0.267	0.183	0.209	0.051
Small intestine	1.178	2.030	1.681	1.630	0.428
Spinal cord	0.089	0.129	0.267	0.162	0.093
Spleen	12.073	25.689	20.887	19.550	6.906
Stomach	0.122	0.315	0.268	0.235	0.101
Testes	0.214	0.471	0.275	0.320	0.134
Thymus	0.226	0.362	0.299	0.296	0.068
Thyroid	0.830	1.797	1.406	1.344	0.486
Whole Blood	0.594	0.473	0.536	0.535	0.060
Plasma	1.021	1.003	1.230	1.085	0.126
Blood:plasma ratio	0.58	0.47	0.44	0.50	0.08

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Appendix 5 Individual Female Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 0.25 min Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	022F	023F[A]	024F	Mean	SD
Adipose tissue	0.203	*0.002	0.015	°0.073	°0.113
Adrenal glands	0.578	*0.000	0.143	°0.240	°0.301
Bladder	0.050	*0.000	0.048	°0.033	°0.029
Bone (femur)	0.146	0.003	0.019	0.056	0.079
Bone marrow (femur)	N.S.	0.264	*0.128	°0.196	N.A.
Brain	0.036	*0.002	0.011	°0.016	°0.018
Eyes	0.015	*0.000	0.004	°0.006	°0.008
Injection site	27.519	77.480	4.697	36.566	37.225
Heart	0.310	*0.001	0.121	°0.144	°0.156
Kidneys	0.544	0.126	0.143	0.271	0.236
Large intestine	0.019	*0.001	0.004	°0.008	°0.010
Liver	0.635	0.018	0.316	0.323	0.309
Lung	0.550	0.012	0.177	0.247	0.275
Lymph node (Man)	0.088	*0.000	0.025	°0.038	°0.045
Lymph node (Mes)	0.127	*0.000	0.018	°0.048	°0.069
Muscle	0.024	0.006	0.007	0.012	0.010
Ovaries	0.206	*0.000	0.106	°0.104	°0.103
Pancreas	0.072	0.008	0.030	0.037	0.033
Pituitary gland	0.310	*0.000	0.113	°0.141	°0.157
Salivary glands	0.133	*0.000	0.028	°0.054	°0.070
Skin	0.018	0.004	0.009	0.010	0.007
Small intestine	0.051	*0.001	0.010	°0.021	°0.026
Spinal cord	0.057	*0.000	0.016	°0.024	°0.029
Spleen	0.366	*0.004	0.570	°0.313	°0.287
Stomach	0.032	*0.001	0.013	°0.015	°0.016
Thymus	0.159	*0.003	0.047	°0.069	°0.080
Thyroid	0.181	*0.000	0.097	°0.093	°0.091
Uterus	0.090	*0.000	0.037	°0.043	°0.045
Whole Blood	2.016	0.013	0.778	0.936	1.011
Plasma	4.189	0.005	1.487	1.894	2.121
Blood:plasma ratio	0.48	2.43	0.52	1.15	1.12

N.S. = No sample due to analysis error (the bone marrow was not able to be removed from the bone since the bone was initially crushed for analysis)
A = Animal 023F appeared to have a slow distribution compared with the other animals
*=Results calculated from data less than 30 cpm above background
°=Mean includes results calculated from data less than 30 cpm above background

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Appendix 5 (continued)

Individual Female Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 1 hour Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	025F	026F	027F	Mean	SD
Adipose tissue	0.145	0.234	0.069	0.149	0.083
Adrenal glands	1.779	2.131	3.254	2.388	0.770
Bladder	0.123	0.206	0.166	0.165	0.042
Bone (femur)	0.216	0.285	0.223	0.241	0.038
Bone marrow (femur)	0.886	1.219	0.926	1.010	0.182
Brain	0.096	0.139	0.115	0.117	0.022
Eyes	0.052	0.052	0.027	0.043	0.015
Heart	1.273	1.884	1.120	1.426	0.404
Injection site	31.021	202.720	366.100	199.950	167.560
Kidneys	1.568	2.396	1.112	1.692	0.651
Large intestine	0.060	0.065	0.070	0.065	0.005
Liver	6.342	4.717	4.674	5.244	0.951
Lung	1.455	1.954	1.313	1.574	0.336
Lymph node (Man)	0.226	0.266	0.176	0.223	0.045
Lymph node (Mes)	0.207	0.226	0.155	0.196	0.037
Muscle	0.080	0.093	0.072	0.082	0.011
Ovaries	1.630	1.650	0.736	1.339	0.522
Pancreas	0.208	0.343	0.234	0.261	0.072
Pituitary gland	0.607	1.114	0.810	0.844	0.255
Salivary glands	0.245	0.327	0.140	0.237	0.094
Skin	0.056	0.956	0.148	0.387	0.495
Small intestine	0.281	0.223	0.235	0.247	0.031
Spinal cord	0.111	0.119	0.137	0.122	0.013
Spleen	2.423	2.626	3.355	2.801	0.490
Stomach	0.085	0.118	0.070	0.091	0.025
Thymus	0.248	0.483	0.164	0.298	0.165
Thyroid	0.510	0.997	0.533	0.680	0.275
Uterus	0.194	0.251	0.164	0.203	0.044
Whole Blood	5.057	8.484	4.243	5.928	2.251
Plasma	9.655	14.318	8.680	10.884	3.014
Blood:plasma ratio	0.52	0.59	0.49	0.54	0.05

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Appendix 5 (continued)

Individual Female Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 2 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	028F	029F	030F	Mean	SD
Adipose tissue	0.110	0.274	0.162	0.182	0.084
Adrenal glands	1.429	8.981	2.285	4.232	4.135
Bladder	0.062	0.289	0.114	0.155	0.119
Bone (femur)	0.132	0.566	0.189	0.296	0.236
Bone marrow (femur)	0.575	1.722	1.714	1.337	0.660
Brain	0.063	0.241	0.095	0.133	0.095
Eyes	0.034	0.117	0.023	0.058	0.051
Heart	0.554	3.221	1.272	1.682	1.380
Injection site	0.092	1.744	277.600	93.144	159.740
Kidneys	0.623	2.870	5.408	2.967	2.394
Large intestine	0.027	0.198	0.092	0.106	0.086
Liver	5.209	21.794	10.108	12.370	8.521
Lung	0.908	4.000	1.313	2.074	1.681
Lymph node (Man)	0.198	0.701	0.188	0.362	0.293
Lymph node (Mes)	1.473	0.640	0.381	0.831	0.571
Muscle	0.045	0.140	0.114	0.100	0.049
Ovaries	0.474	2.683	1.756	1.638	1.109
Pancreas	0.116	0.825	0.270	0.404	0.373
Pituitary gland	0.414	1.853	0.599	0.955	0.783
Salivary glands	0.141	0.562	0.182	0.295	0.232
Skin	0.040	0.263	0.486	0.263	0.223
Small intestine	0.305	0.664	0.473	0.481	0.180
Spinal cord	0.109	0.289	0.118	0.172	0.102
Spleen	2.066	23.785	4.788	10.213	11.832
Stomach	0.088	0.211	0.077	0.126	0.074
Thymus	0.109	1.108	0.160	0.459	0.562
Thyroid	0.371	1.791	1.163	1.109	0.711
Uterus	0.169	0.568	0.178	0.305	0.228
Whole Blood	2.194	14.470	3.655	6.773	6.706
Plasma	4.442	15.480	7.350	9.091	5.721
Blood:plasma ratio	0.49	0.93	0.50	0.64	0.25

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Appendix 5 (continued)

Individual Female Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 4 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	031F	032F	033F	Mean	SD
Adipose tissue	0.134	0.061	0.296	0.163	0.121
Adrenal glands	1.879	3.483	4.255	3.206	1.212
Bladder	0.043	0.101	0.175	0.106	0.066
Bone (femur)	0.136	0.194	0.321	0.217	0.095
Bone marrow (femur)	0.448	0.818	1.480	0.915	0.522
Brain	0.033	0.058	0.133	0.075	0.052
Eyes	0.022	0.046	0.048	0.038	0.015
Heart	0.296	0.746	1.734	0.925	0.735
Injection site	8.920	103.630	56.133	56.227	47.355
Kidneys	0.328	0.627	1.486	0.814	0.601
Large intestine	0.165	0.222	0.283	0.224	0.059
Liver	8.503	14.685	20.519	14.569	6.009
Lung	0.610	1.159	1.898	1.222	0.646
Lymph node (Man)	0.173	0.454	0.546	0.391	0.194
Lymph node (Mes)	0.316	0.598	0.695	0.536	0.197
Muscle	0.033	0.057	0.301	0.130	0.148
Ovaries	0.555	2.916	3.552	2.341	1.579
Pancreas	0.358	0.270	0.568	0.398	0.153
Pituitary gland	0.251	0.317	0.805	0.458	0.303
Salivary glands	0.087	0.156	0.262	0.169	0.088
Skin	0.043	0.371	0.197	0.204	0.164
Small intestine	0.684	0.739	1.089	0.838	0.220
Spinal cord	0.073	0.061	0.236	0.124	0.098
Spleen	9.910	11.442	13.587	11.646	1.847
Stomach	0.050	0.113	0.141	0.101	0.047
Thymus	0.130	0.267	0.231	0.209	0.071
Thyroid	0.225	0.718	0.867	0.604	0.336
Uterus	0.080	0.096	0.246	0.140	0.091
Whole Blood	1.090	1.981	5.022	2.698	2.062
Plasma	2.037	3.442	7.274	4.251	2.711
Blood:plasma ratio	0.53	0.58	0.69	0.60	0.08

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Appendix 5 (continued)

Individual Female Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 8 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	034F	035F	036F	Mean	SD
Adipose tissue	0.095	0.041	0.072	0.069	0.027
Adrenal glands	7.562	6.554	7.538	7.218	0.575
Bladder	0.047	0.080	0.127	0.085	0.040
Bone (femur)	0.243	0.143	0.144	0.177	0.057
Bone marrow (femur)	1.262	1.350	1.210	1.274	0.071
Brain	0.047	0.030	0.058	0.045	0.014
Eyes	0.046	0.013	0.032	0.030	0.016
Heart	0.532	0.193	0.448	0.391	0.177
Injection site	30.227	174.950	172.620	125.930	82.890
Kidneys	0.416	0.239	0.372	0.342	0.092
Large intestine	0.679	0.381	0.764	0.608	0.201
Liver	22.242	25.442	27.834	25.172	2.806
Lung	0.661	0.378	0.846	0.628	0.236
Lymph node (Man)	0.315	0.251	0.551	0.372	0.158
Lymph node (Mes)	0.790	0.481	0.915	0.729	0.223
Muscle	0.040	0.160	0.075	0.091	0.062
Ovaries	2.960	1.276	5.029	3.088	1.880
Pancreas	0.390	0.087	0.241	0.239	0.151
Pituitary gland	0.169	0.099	0.157	0.141	0.037
Salivary glands	0.124	0.074	0.082	0.094	0.027
Skin	0.137	0.057	0.155	0.116	0.052
Small intestine	1.162	0.839	1.098	1.033	0.171
Spinal cord	0.051	0.021	0.060	0.044	0.020
Spleen	19.387	16.090	23.763	19.747	3.849
Stomach	0.243	0.040	0.094	0.126	0.105
Thymus	0.111	0.086	0.102	0.100	0.013
Thyroid	0.395	0.131	0.395	0.307	0.152
Uterus	0.584	0.055	0.223	0.287	0.270
Whole Blood	0.731	0.319	0.833	0.628	0.272
Plasma	1.421	0.574	1.447	1.147	0.496
Blood:plasma ratio	0.51	0.56	0.58	0.55	0.03

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Appendix 5 (continued)

Individual Female Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 24 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	037F	038F	039F	Mean	SD
Adipose tissue	0.031	0.042	0.053	0.042	0.011
Adrenal glands	9.718	3.981	9.084	7.595	3.145
Bladder	0.141	0.135	0.235	0.171	0.056
Bone (femur)	0.158	0.105	0.278	0.180	0.089
Bone marrow (femur)	1.180	1.058	1.978	1.405	0.500
Brain	0.040	0.039	0.063	0.047	0.014
Eyes	0.063	0.037	0.057	0.052	0.014
Heart	0.342	0.259	0.355	0.318	0.052
Injection site	2.568	202.540	162.510	122.540	105.810
Kidneys	0.270	0.412	0.361	0.348	0.072
Large intestine	0.561	0.370	0.465	0.466	0.095
Liver	13.368	10.520	21.469	15.119	5.681
Lung	0.519	0.822	0.945	0.762	0.219
Lymph node (Man)	0.259	0.242	0.589	0.363	0.195
Lymph node (Mes)	0.944	0.550	1.095	0.863	0.281
Muscle	0.028	0.114	0.133	0.092	0.056
Ovaries	4.091	5.266	6.363	5.240	1.136
Pancreas	0.176	0.362	0.422	0.320	0.128
Pituitary gland	0.309	0.213	0.379	0.300	0.083
Salivary glands	0.084	0.083	0.119	0.096	0.021
Skin	0.047	0.156	0.151	0.118	0.062
Small intestine	0.748	0.661	0.769	0.726	0.057
Spinal cord	0.047	0.034	0.064	0.048	0.015
Spleen	15.606	12.977	23.440	17.341	5.443
Stomach	0.094	0.054	0.096	0.081	0.024
Thymus	0.154	0.190	0.135	0.159	0.028
Thyroid	0.302	0.294	0.410	0.335	0.065
Uterus	0.307	0.207	0.354	0.289	0.075
Whole Blood	0.475	0.380	0.779	0.544	0.208
Plasma	0.930	0.681	1.223	0.945	0.271
Blood:plasma ratio	0.51	0.56	0.64	0.57	0.06

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Appendix 5 (continued)

Individual Female Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 48 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	040F	041F	042F	Mean	SD
Adipose tissue	0.081	0.201	0.414	0.232	0.168
Adrenal glands	12.979	15.142	16.707	14.942	1.872
Bladder	0.234	0.640	0.293	0.389	0.219
Bone (femur)	0.299	1.911	0.351	0.854	0.916
Bone marrow (femur)	2.096	1.993	7.463	3.851	3.129
Brain	0.038	0.046	0.072	0.052	0.018
Eyes	0.064	0.105	0.121	0.097	0.029
Heart	0.352	0.369	0.539	0.420	0.103
Injection site	93.643	27.547	62.073	61.088	33.059
Kidneys	0.314	0.378	0.412	0.368	0.050
Large intestine	1.210	1.507	1.031	1.249	0.241
Liver	24.416	20.707	46.111	30.411	13.722
Lung	0.921	0.719	1.053	0.898	0.168
Lymph node (Man)	0.600	0.516	0.784	0.633	0.137
Lymph node (Mes)	1.557	1.669	1.800	1.675	0.122
Muscle	0.126	0.068	0.119	0.104	0.032
Ovaries	9.305	13.544	13.933	12.261	2.567
Pancreas	0.364	0.298	1.170	0.611	0.485
Pituitary gland	0.910	0.816	0.810	0.845	0.056
Salivary glands	0.200	0.204	0.288	0.231	0.049
Skin	0.303	0.173	0.416	0.297	0.122
Small intestine	1.142	1.461	1.339	1.314	0.161
Spinal cord	0.043	0.075	0.069	0.062	0.017
Spleen	19.456	16.775	45.234	27.155	15.714
Stomach	0.154	0.197	0.233	0.195	0.040
Thymus	0.314	0.248	0.536	0.366	0.151
Thyroid	0.584	0.870	0.512	0.655	0.190
Uterus	0.267	0.521	0.581	0.456	0.167
Whole Blood	0.258	0.338	0.320	0.305	0.042
Plasma	0.429	0.598	0.546	0.524	0.087
Blood:plasma ratio	0.60	0.57	0.59	0.58	0.02

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Appendix 6 **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 0.25 min Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	043M	044M	045M	Mean	SD
Adrenal glands	0.002	0.002	0.000	0.001	0.001
Bladder	0.001	0.000	0.000	0.000	0.000
Brain	0.013	0.014	0.005	0.011	0.005
Eyes	0.001	0.000	0.000	0.000	0.000
Heart	0.056	0.024	0.004	0.028	0.026
Injection site	82.460	6.097	10.103	32.887	42.978
Kidneys	0.103	0.087	0.016	0.069	0.046
Large intestine	0.012	0.018	0.002	0.011	0.008
Liver	1.735	1.083	0.167	0.995	0.787
Lung	0.133	0.082	0.031	0.082	0.051
Pancreas	0.004	0.010	0.001	0.005	0.005
Pituitary gland	0.001	0.000	0.000	0.000	0.000
Prostate	0.002	0.002	0.000	0.001	0.001
Salivary glands	0.007	0.005	0.001	0.004	0.003
Small intestine	0.051	0.040	0.005	0.032	0.024
Spinal cord	0.002	0.001	0.000	0.001	0.001
Spleen	0.020	0.019	0.003	0.014	0.009
Stomach	0.008	0.013	0.002	0.008	0.006
Testes	0.012	0.008	0.001	0.007	0.005
Thymus	0.005	0.010	0.001	0.005	0.005
Thyroid	0.000	0.000	0.000	0.000	0.000

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Appendix 6 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 1 hour Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	046M	047M	048M	Mean	SD
Adrenal glands	0.001	0.003	0.002	0.002	0.001
Bladder	0.001	0.001	0.000	0.001	0.000
Brain	0.005	0.014	0.013	0.010	0.005
Eyes	0.000	0.000	0.001	0.000	0.000
Heart	0.015	0.036	0.045	0.032	0.015
Injection site	74.148	46.614	85.725	68.829	20.090
Kidneys	0.047	0.086	0.098	0.077	0.027
Large intestine	0.016	0.017	0.021	0.018	0.002
Liver	2.218	2.607	3.676	2.834	0.755
Lung	0.043	0.131	0.081	0.085	0.044
Pancreas	0.004	0.009	0.006	0.006	0.003
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.001	0.002	0.001	0.001	0.001
Salivary glands	0.003	0.005	0.006	0.005	0.002
Small intestine	0.102	0.133	0.136	0.124	0.019
Spinal cord	0.001	0.000	0.001	0.001	0.000
Spleen	0.115	0.063	0.082	0.087	0.026
Stomach	0.007	0.019	0.023	0.016	0.008
Testes	0.007	0.009	0.013	0.010	0.003
Thymus	0.008	0.004	0.007	0.006	0.002
Thyroid	0.000	0.001	0.000	0.000	0.000

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Appendix 6 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 2 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

		050M	051M		SD
	0.006	0.003	0.005	0.005	0.001
	0.001	0.001	0.001	0.001	0.000
	0.033	0.013	0.016	0.021	0.011
	0.001	0.000	0.002	0.001	0.001
	0.109	0.036	0.051	0.065	0.039
	53.157	53.477	10.525	39.053	24.707
	0.203	0.096	0.148	0.149	0.054
	0.063	0.035	0.063	0.054	0.016
	10.166	4.262	8.460	7.629	3.038
	0.313	0.094	0.160	0.189	0.113
	0.011	0.006	0.028	0.015	0.012
	0.000	0.000	0.000	0.000	0.000
	0.002	0.002	0.003	0.002	0.000
	0.010	0.004	0.008	0.007	0.003
	0.418	0.305	0.336	0.353	0.058
	0.001	0.001	0.002	0.001	0.001
	0.296	0.101	0.299	0.232	0.114
	0.034	0.017	0.047	0.033	0.015
	0.027	0.008	0.017	0.017	0.009
	0.010	0.005	0.008	0.008	0.002
	0.001	0.001	0.000	0.001	0.000

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Appendix 6 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 4 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	052M	053M	054M	Mean	SD
Adrenal glands	0.013	0.009	0.014	0.012	0.002
Bladder	0.001	0.002	0.001	0.001	0.000
Brain	0.019	0.015	0.029	0.021	0.007
Eyes	0.002	0.002	0.001	0.002	0.001
Heart	0.071	0.033	0.096	0.067	0.032
Injection site	61.619	36.450	45.061	47.710	12.792
Kidneys	0.151	0.088	0.169	0.136	0.042
Large intestine	0.271	0.219	0.216	0.236	0.031
Liver	12.655	13.898	18.528	15.027	3.095
Lung	0.356	0.080	0.241	0.226	0.139
Pancreas	0.007	0.020	0.011	0.013	0.007
Pituitary gland	0.001	0.001	0.000	0.001	0.000
Prostate	0.003	0.002	0.003	0.003	0.001
Salivary glands	0.009	0.007	0.012	0.009	0.002
Small intestine	0.632	0.499	0.737	0.623	0.120
Spinal cord	0.002	0.004	0.002	0.003	0.001
Spleen	0.309	0.410	0.334	0.351	0.052
Stomach	0.053	0.027	0.033	0.037	0.013
Testes	0.028	0.021	0.039	0.030	0.009
Thymus	0.010	0.011	0.033	0.018	0.013
Thyroid	0.001	0.001	0.001	0.001	0.000

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Appendix 6 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 8 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	055M	056M	057M	Mean	SD
Adrenal glands	0.013	0.023	0.042	0.026	0.015
Bladder	N.S.	0.001	0.002	0.002	N.A.
Brain	0.014	0.013	0.014	0.014	0.001
Eyes	N.S.	0.001	0.002	0.002	N.A.
Heart	0.071	0.051	0.061	0.061	0.010
Injection site	18.863	19.984	17.346	18.731	1.324
Kidneys	0.114	0.107	0.108	0.109	0.004
Large intestine	0.536	0.424	0.430	0.463	0.063
Liver	17.280	17.862	29.414	21.519	6.844
Lung	0.226	0.146	0.169	0.180	0.042
Pancreas	0.010	0.021	0.012	0.014	0.006
Pituitary gland	0.000	0.000	0.001	0.000	0.000
Prostate	0.004	0.002	0.001	0.003	0.001
Salivary glands	0.008	0.006	0.007	0.007	0.001
Small intestine	0.850	1.034	1.031	0.972	0.106
Spinal cord	0.001	0.001	0.001	0.001	0.000
Spleen	1.037	1.022	1.293	1.118	0.152
Stomach	0.043	0.026	0.097	0.055	0.037
Testes	0.034	0.022	0.045	0.034	0.012
Thymus	0.013	0.010	0.012	0.012	0.001
Thyroid	0.001	0.001	0.001	0.001	0.000

N.S. = No sample due to oxidiser failure
N.A. = Not applicable

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Appendix 6 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 24 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	058M	059M	060M	Mean	SD
Adrenal glands	0.052	0.059	0.137	0.083	0.047
Bladder	0.002	0.002	0.002	0.002	0.000
Brain	0.006	0.013	0.017	0.012	0.006
Eyes	0.002	0.002	0.004	0.002	0.001
Heart	0.051	0.026	0.026	0.035	0.014
Injection site	39.854	26.623	29.394	31.957	6.978
Kidneys	0.075	0.053	0.075	0.068	0.012
Large intestine	0.332	0.895	2.045	1.091	0.873
Liver	14.444	16.303	28.957	19.901	7.897
Lung	0.109	0.118	0.179	0.136	0.038
Pancreas	0.007	0.017	0.015	0.013	0.005
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.003	0.004	0.005	0.004	0.001
Salivary glands	0.005	0.008	0.012	0.008	0.004
Small intestine	0.693	1.198	1.934	1.275	0.624
Spinal cord	0.001	0.002	0.002	0.001	0.001
Spleen	0.977	0.660	1.234	0.957	0.287
Stomach	0.021	0.033	0.107	0.054	0.046
Testes	0.057	0.058	0.105	0.074	0.028
Thymus	0.007	0.010	0.009	0.009	0.002
Thyroid	0.001	0.001	0.001	0.001	0.000

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Appendix 6 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 48 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	061M	062M	063M	Mean	SD
Adrenal glands	0.078	0.157	0.078	0.104	0.046
Bladder	0.001	0.002	0.002	0.002	0.000
Brain	0.006	0.016	0.012	0.011	0.005
Eyes	0.002	0.003	0.003	0.003	0.000
Heart	0.024	0.055	0.037	0.039	0.016
Injection site	49.053	18.355	31.059	32.823	15.425
Kidneys	0.045	0.104	0.063	0.071	0.031
Large intestine	0.541	0.624	1.264	0.810	0.395
Liver	12.962	17.164	11.734	13.953	2.848
Lung	0.088	0.173	0.133	0.131	0.043
Pancreas	0.010	0.013	0.023	0.015	0.007
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.002	0.004	0.004	0.003	0.001
Salivary glands	0.010	0.012	0.008	0.010	0.002
Small intestine	0.635	1.258	1.020	0.971	0.314
Spinal cord	0.001	0.001	0.002	0.001	0.001
Spleen	0.544	1.271	0.926	0.914	0.364
Stomach	0.027	0.065	0.056	0.049	0.019
Testes	0.053	0.109	0.060	0.074	0.030
Thymus	0.004	0.012	0.009	0.008	0.004
Thyroid	0.001	0.002	0.001	0.001	0.001

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Appendix 7 Individual Female Recovery Data

Recovery of Total Radioactivity in Tissues 0.25 min Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	022F	023F	024F	Mean	SD
Adrenal glands	0.003	*0.000	0.001	°0.001	°0.002
Bladder	0.000	*0.000	0.000	°0.000	°0.000
Brain	0.005	*0.000	0.002	°0.002	°0.002
Eyes	0.000	*0.000	0.000	°0.000	°0.000
Heart	0.017	*0.000	0.006	°0.008	°0.008
Injection site	8.145	11.578	0.723	6.815	5.549
Kidneys	0.063	0.012	0.014	0.030	0.028
Large intestine	0.010	*0.000	0.002	°0.004	°0.005
Liver	0.435	0.010	0.180	0.209	0.214
Lung	0.051	0.001	0.013	0.022	0.026
Ovaries	0.002	*0.000	0.001	°0.001	°0.001
Pancreas	0.002	0.000	0.001	0.001	0.001
Pituitary gland	0.000	*0.000	0.000	°0.000	°0.000
Salivary glands	0.004	*0.000	0.001	°0.002	°0.002
Small intestine	0.038	*0.001	0.005	°0.015	°0.020
Spinal cord	0.000	*0.000	0.000	°0.000	°0.000
Spleen	0.014	*0.000	0.017	°0.011	°0.009
Stomach	0.007	*0.000	0.002	°0.003	°0.003
Thymus	0.005	*0.000	0.002	°0.002	°0.002
Thyroid	0.000	*0.000	0.000	°0.000	°0.000
Uterus	0.004	*0.000	0.002	°0.002	°0.002

*=Results calculated from data less than 30 cpm above background
°=Mean includes results calculated from data less than 30 cpm above background

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Appendix 7 (continued) **Individual Female Recovery Data**

Recovery of Total Radioactivity in Tissues 1 hour Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	025F	026F	027F	Mean	SD
Adrenal glands	0.010	0.011	0.015	0.012	0.003
Bladder	0.001	0.001	0.001	0.001	0.000
Brain	0.013	0.019	0.015	0.016	0.003
Eyes	0.001	0.001	0.001	0.001	0.000
Heart	0.066	0.109	0.062	0.079	0.026
Injection site	10.609	47.776	50.847	36.411	22.398
Kidneys	0.162	0.250	0.102	0.171	0.074
Large intestine	0.030	0.035	0.029	0.032	0.003
Liver	3.586	2.713	2.421	2.907	0.606
Lung	0.112	0.131	0.106	0.117	0.013
Ovaries	0.012	0.010	0.004	0.009	0.004
Pancreas	0.009	0.009	0.007	0.008	0.001
Pituitary gland	0.000	0.001	0.001	0.001	0.000
Salivary glands	0.008	0.009	0.006	0.008	0.002
Small intestine	0.153	0.130	0.121	0.135	0.017
Spinal cord	0.002	0.002	0.001	0.002	0.001
Spleen	0.082	0.099	0.112	0.098	0.015
Stomach	0.024	0.021	0.023	0.022	0.002
Thymus	0.007	0.013	0.004	0.008	0.005
Thyroid	0.001	0.001	0.001	0.001	0.000
Uterus	0.008	0.010	0.015	0.011	0.004

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Appendix 7 (continued) **Individual Female Recovery Data**

Recovery of Total Radioactivity in Tissues 2 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	028F	029F	030F	Mean	SD
Adrenal glands	0.010	0.022	0.012	0.015	0.006
Bladder	0.000	0.001	0.001	0.001	0.001
Brain	0.008	0.034	0.014	0.019	0.014
Eyes	0.001	0.003	0.000	0.001	0.001
Heart	0.028	0.201	0.077	0.102	0.089
Injection site	0.018	0.236	72.027	24.094	41.511
Kidneys	0.056	0.264	0.497	0.272	0.221
Large intestine	0.018	0.142	0.065	0.075	0.063
Liver	3.203	12.436	5.452	7.030	4.815
Lung	0.080	0.311	0.110	0.167	0.125
Ovaries	0.003	0.012	0.009	0.008	0.004
Pancreas	0.003	0.022	0.010	0.012	0.010
Pituitary gland	0.000	0.002	0.000	0.001	0.001
Salivary glands	0.005	0.015	0.007	0.009	0.006
Small intestine	0.205	0.367	0.283	0.285	0.081
Spinal cord	0.002	0.004	0.001	0.002	0.002
Spleen	0.063	1.010	0.180	0.418	0.516
Stomach	0.027	0.057	0.022	0.035	0.019
Thymus	0.003	0.028	0.004	0.012	0.014
Thyroid	0.000	0.002	0.001	0.001	0.001
Uterus	0.008	0.025	0.011	0.015	0.009

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Appendix 7 (continued) **Individual Female Recovery Data**

Recovery of Total Radioactivity in Tissues 4 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

					SD
	0.011	0.019	0.023	0.018	0.006
	0.000	0.001	0.001	0.001	0.000
	0.005	0.007	0.020	0.011	0.008
	0.001	0.001	0.001	0.001	0.000
	0.013	0.046	0.097	0.052	0.042
	2.619	19.042	5.508	9.056	8.768
	0.031	0.062	0.154	0.082	0.064
	0.111	0.136	0.198	0.148	0.045
	5.207	8.846	12.045	8.699	3.421
	0.054	0.093	0.188	0.112	0.069
	0.003	0.022	0.022	0.016	0.011
	0.016	0.009	0.027	0.017	0.009
	0.000	0.000	0.001	0.000	0.000
	0.003	0.005	0.011	0.006	0.005
	0.354	0.435	0.596	0.462	0.123
	0.001	0.001	0.003	0.002	0.001
	0.390	0.421	0.447	0.419	0.028
	0.014	0.022	0.029	0.022	0.008
	0.004	0.007	0.006	0.006	0.002
	0.000	0.001	0.001	0.001	0.000
	0.005	0.004	0.016	0.008	0.007

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Appendix 7 (continued) **Individual Female Recovery Data**

Recovery of Total Radioactivity in Tissues 8 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	034F	035F	036F	Mean	SD
Adrenal glands	0.048	0.031	0.051	0.043	0.011
Bladder	0.000	0.000	0.001	0.000	0.000
Brain	0.007	0.004	0.009	0.007	0.002
Eyes	0.001	0.000	0.001	0.001	0.000
Heart	0.029	0.010	0.027	0.022	0.011
Injection site	10.296	26.182	38.500	24.993	14.139
Kidneys	0.056	0.022	0.042	0.040	0.017
Large intestine	0.409	0.233	0.397	0.346	0.098
Liver	13.264	12.033	18.443	14.580	3.402
Lung	0.089	0.028	0.074	0.064	0.031
Ovaries	0.022	0.010	0.042	0.025	0.016
Pancreas	0.034	0.002	0.011	0.016	0.016
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Salivary glands	0.005	0.002	0.003	0.003	0.001
Small intestine	0.718	0.308	0.714	0.580	0.235
Spinal cord	0.001	0.000	0.001	0.001	0.000
Spleen	0.853	0.601	1.082	0.845	0.241
Stomach	0.043	0.005	0.023	0.024	0.019
Thymus	0.004	0.002	0.003	0.003	0.001
Thyroid	0.001	0.000	0.001	0.000	0.000
Uterus	0.030	0.004	0.014	0.016	0.013

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Appendix 7 (continued) **Individual Female Recovery Data**

Recovery of Total Radioactivity in Tissues 24 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	037F	038F	039F	Mean	SD
Adrenal glands	0.064	0.032	0.050	0.049	0.016
Bladder	0.001	0.001	0.001	0.001	0.000
Brain	0.005	0.006	0.009	0.007	0.002
Eyes	0.001	0.001	0.001	0.001	0.000
Heart	0.019	0.014	0.020	0.018	0.003
Injection site	0.444	39.677	38.765	26.295	22.392
Kidneys	0.029	0.053	0.035	0.039	0.013
Large intestine	0.334	0.283	0.263	0.293	0.037
Liver	9.112	9.776	14.042	10.977	2.675
Lung	0.053	0.071	0.072	0.065	0.010
Ovaries	0.031	0.038	0.043	0.037	0.006
Pancreas	0.005	0.007	0.014	0.009	0.004
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Salivary glands	0.003	0.003	0.004	0.003	0.001
Small intestine	0.575	0.601	0.432	0.536	0.091
Spinal cord	0.001	0.001	0.001	0.001	0.000
Spleen	0.591	0.508	0.955	0.685	0.237
Stomach	0.019	0.011	0.029	0.020	0.009
Thymus	0.003	0.005	0.003	0.004	0.001
Thyroid	0.000	0.000	0.001	0.000	0.000
Uterus	0.027	0.009	0.017	0.018	0.009

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Appendix 7 (continued) **Individual Female Recovery Data**

Recovery of Total Radioactivity in Tissues 48 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	040F	041F	042F	Mean	SD
Adrenal glands	0.085	0.126	0.114	0.108	0.021
Bladder	0.001	0.004	0.002	0.002	0.001
Brain	0.005	0.006	0.010	0.007	0.002
Eyes	0.001	0.003	0.003	0.002	0.001
Heart	0.018	0.017	0.024	0.020	0.004
Injection site	20.139	5.852	23.287	16.426	9.292
Kidneys	0.036	0.045	0.044	0.042	0.005
Large intestine	0.570	0.928	0.644	0.714	0.189
Liver	15.122	13.811	26.137	18.357	6.770
Lung	0.066	0.066	0.076	0.070	0.006
Ovaries	0.075	0.113	0.097	0.095	0.019
Pancreas	0.011	0.007	0.050	0.023	0.024
Pituitary gland	0.001	0.001	0.000	0.001	0.000
Salivary glands	0.007	0.005	0.009	0.007	0.002
Small intestine	0.540	0.825	0.729	0.698	0.145
Spinal cord	0.001	0.002	0.001	0.001	0.000
Spleen	0.772	0.848	1.818	1.146	0.583
Stomach	0.023	0.028	0.035	0.029	0.006
Thymus	0.007	0.005	0.009	0.007	0.002
Thyroid	0.001	0.001	0.001	0.001	0.000
Uterus	0.010	0.031	0.025	0.022	0.010

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Appendix 8 **Individual Male 100 µg mRNA data**

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 0.25 min Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	001M	002M	003M	Mean	SD
Adipose tissue	0.075	0.108	0.018	0.067	0.046
Adrenal glands	0.193	0.192	0.184	0.190	0.005
Bladder	0.035	0.079	0.026	0.047	0.028
Bone (femur)	0.195	0.054	0.044	0.098	0.085
Bone marrow (femur)	0.312	0.163	0.229	0.234	0.075
Brain	0.050	0.047	0.046	0.048	0.002
Eyes	0.015	0.021	0.007	0.014	0.007
Heart	0.394	0.365	0.460	0.406	0.048
Injection site	16.832	24.313	179.840	73.662	92.030
Kidneys	0.576	0.552	0.273	0.467	0.169
Large intestine	0.016	0.012	0.051	0.026	0.022
Liver	0.963	0.503	0.670	0.712	0.233
Lung	0.689	0.497	0.410	0.532	0.143
Lymph node (Man)	0.043	0.046	0.042	0.044	0.002
Lymph node (Mes)	0.045	0.020	0.018	0.028	0.015
Muscle	0.035	0.040	0.285	0.120	0.143
Pancreas	0.088	0.068	0.068	0.075	0.012
Pituitary gland	0.787	0.796	0.225	0.603	0.327
Prostate	0.035	0.045	0.047	0.042	0.006
Salivary glands	0.087	0.087	0.049	0.074	0.022
Skin	2.094	3.233	12.691	6.499	6.668
Small intestine	0.046	0.030	0.016	0.031	0.015
Spinal cord	0.091	0.064	0.068	0.074	0.015
Spleen	0.426	1.463	0.221	0.704	0.666
Stomach	0.032	0.026	*0.007	°0.022	°0.013
Testes	0.033	0.030	0.020	0.028	0.007
Thymus	0.121	0.161	0.216	0.166	0.048
Thyroid	0.175	0.498	0.105	0.259	0.209
Whole Blood	2.291	2.426	1.678	2.132	0.398
Plasma	5.640	5.530	3.924	5.031	0.960
Blood:plasma ratio	0.41	0.44	0.43	0.42	0.02

*=Results calculated from data less than 30 cpm above background
°=Mean includes results calculated from data less than 30 cpm above background

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Appendix 8 (continued)

Individual Male 100 µg mRNA Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 1 hour Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	004M	005M	006M	Mean	SD
Adipose tissue	0.193	0.307	0.350	0.283	0.081
Adrenal glands	1.775	1.877	2.208	1.953	0.227
Bladder	0.224	0.098	0.264	0.195	0.086
Bone (femur)	1.102	0.530	0.566	0.733	0.320
Bone marrow (femur)	2.111	4.732	2.456	3.100	1.424
Brain	0.253	0.297	0.296	0.282	0.025
Eyes	0.229	0.070	0.093	0.131	0.086
Heart	1.948	3.461	2.496	2.635	0.766
Injection site	152.370	78.654	150.890	127.300	42.139
Kidneys	3.017	3.096	3.170	3.094	0.077
Large intestine	0.090	0.091	0.152	0.111	0.035
Liver	13.805	10.906	16.323	13.678	2.711
Lung	3.523	3.532	2.901	3.319	0.362
Lymph node (Man)	0.366	0.379	0.437	0.394	0.038
Lymph node (Mes)	0.268	0.412	0.389	0.356	0.077
Muscle	0.184	0.213	0.195	0.198	0.015
Pancreas	0.335	0.375	0.469	0.393	0.069
Pituitary gland	1.389	1.810	1.717	1.639	0.221
Prostate	0.328	0.363	0.380	0.357	0.027
Salivary glands	0.471	0.613	0.493	0.526	0.076
Skin	3.043	0.407	1.179	1.543	1.355
Small intestine	0.393	3.191	3.563	2.382	1.733
Spinal cord	0.216	0.356	0.303	0.292	0.071
Spleen	4.066	4.402	4.868	4.445	0.402
Stomach	0.332	2.377	8.099	3.603	4.026
Testes	0.185	0.196	0.486	0.289	0.171
Thymus	0.332	0.343	0.596	0.424	0.149
Thyroid	1.219	1.909	1.266	1.465	0.385
Whole Blood	7.985	11.835	10.357	10.059	1.942
Plasma	23.703	26.782	26.070	25.518	1.612
Blood:plasma ratio	0.34	0.44	0.40	0.39	0.05

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Appendix 8 (continued)

Individual Male 100 µg mRNA Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 2 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	007M	008M	009M	Mean	SD
Adipose tissue	0.311	0.211	0.486	0.336	0.140
Adrenal glands	3.152	3.337	2.559	3.016	0.406
Bladder	0.310	0.241	0.479	0.343	0.122
Bone (femur)	0.835	0.462	0.385	0.561	0.241
Bone marrow (femur)	3.322	2.694	2.057	2.691	0.632
Brain	0.348	0.310	0.250	0.302	0.049
Eyes	0.126	0.104	0.064	0.098	0.031
Heart	2.866	3.359	3.481	3.235	0.326
Injection site	6.971	61.485	30.751	33.069	27.331
Kidneys	2.887	2.858	2.679	2.808	0.113
Large intestine	0.283	0.125	0.148	0.185	0.085
Liver	33.320	24.542	22.034	26.632	5.926
Lung	3.839	2.982	3.769	3.530	0.476
Lymph node (Man)	0.784	0.413	0.474	0.557	0.199
Lymph node (Mes)	0.859	0.503	0.333	0.565	0.268
Muscle	0.220	0.182	0.189	0.197	0.020
Pancreas	0.595	0.512	0.557	0.554	0.041
Pituitary gland	1.998	1.921	1.729	1.883	0.139
Prostate	0.458	0.354	0.461	0.424	0.061
Salivary glands	0.740	0.597	0.539	0.625	0.104
Skin	0.524	0.353	0.454	0.444	0.086
Small intestine	1.147	0.887	0.755	0.930	0.199
Spinal cord	0.396	0.373	0.360	0.377	0.018
Spleen	14.103	8.227	7.803	10.044	3.521
Stomach	0.234	0.142	0.143	0.173	0.053
Testes	0.239	0.402	0.317	0.320	0.081
Thymus	0.447	0.424	0.371	0.414	0.039
Thyroid	1.906	1.397	1.481	1.595	0.273
Whole Blood	11.413	10.005	10.736	10.718	0.704
Plasma	25.479	22.927	22.340	23.582	1.669
Blood:plasma ratio	0.45	0.44	0.48	0.45	0.02

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Appendix 8 (continued) **Individual Male 100 µg mRNA Data**

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 4 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	010M	011M	012M	Mean	SD
Adipose tissue	0.222	0.262	0.105	0.196	0.082
Adrenal glands	5.481	2.469	2.491	3.480	1.732
Bladder	0.237	0.151	0.156	0.181	0.048
Bone (femur)	1.452	1.249	0.348	1.016	0.588
Bone marrow (femur)	1.880	3.875	1.459	2.405	1.291
Brain	0.373	0.123	0.090	0.195	0.155
Eyes	0.095	0.056	0.042	0.065	0.027
Heart	1.233	1.095	1.064	1.131	0.090
Injection site	55.286	464.630	257.860	259.260	204.680
Kidneys	2.190	1.607	1.007	1.601	0.591
Large intestine	0.180	0.713	0.338	0.410	0.274
Liver	38.606	14.955	19.426	24.329	12.565
Lung	1.255	3.060	1.398	1.904	1.003
Lymph node (Man)	0.694	0.271	0.242	0.402	0.253
Lymph node (Mes)	0.970	0.427	0.502	0.633	0.294
Muscle	0.129	0.076	0.085	0.097	0.029
Pancreas	0.189	0.419	0.299	0.302	0.115
Pituitary gland	0.870	0.599	0.480	0.649	0.200
Prostate	0.244	0.133	0.133	0.170	0.064
Salivary glands	0.334	0.192	0.170	0.232	0.089
Skin	0.931	0.178	2.172	1.094	1.007
Small intestine	0.758	1.381	1.189	1.110	0.319
Spinal cord	0.154	0.094	0.111	0.120	0.031
Spleen	9.286	27.731	9.780	15.599	10.510
Stomach	0.057	0.131	0.302	0.163	0.125
Testes	0.397	0.134	0.110	0.214	0.159
Thymus	0.164	0.229	0.185	0.193	0.033
Thyroid	1.256	0.565	0.742	0.854	0.359
Whole Blood	4.741	2.416	2.502	3.220	1.318
Plasma	11.200	5.253	5.862	7.438	3.272
Blood:plasma ratio	0.42	0.46	0.43	0.44	0.02

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Appendix 8 (continued)

Individual Male 100 µg mRNA Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 8 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	013M	014M	015M	Mean	SD
Adipose tissue	0.134	0.147	0.269	0.184	0.075
Adrenal glands	6.445	9.564	32.615	16.208	14.294
Bladder	0.741	0.264	0.499	0.501	0.238
Bone (femur)	0.835	0.274	0.855	0.655	0.330
Bone marrow (femur)	1.920	1.495	2.225	1.880	0.367
Brain	0.165	0.120	0.214	0.166	0.047
Eyes	0.188	0.146	0.229	0.188	0.041
Heart	2.084	1.104	2.398	1.862	0.675
Injection site	126.340	106.800	2.416	78.521	66.629
Kidneys	2.145	1.122	1.472	1.580	0.520
Large intestine	1.713	1.199	1.781	1.564	0.318
Liver	34.463	41.789	61.002	45.751	13.706
Lung	2.999	1.707	3.360	2.689	0.869
Lymph node (Man)	1.158	0.644	1.099	0.967	0.282
Lymph node (Mes)	1.076	1.409	1.701	1.395	0.313
Muscle	0.158	0.096	0.196	0.150	0.051
Pancreas	0.433	0.326	0.579	0.446	0.127
Pituitary gland	0.858	0.517	0.994	0.790	0.246
Prostate	0.314	0.176	0.386	0.292	0.107
Salivary glands	0.242	0.168	0.386	0.265	0.111
Skin	0.295	0.285	0.547	0.376	0.148
Small intestine	2.012	1.963	1.865	1.946	0.075
Spinal cord	0.185	0.148	0.252	0.195	0.053
Spleen	24.956	16.693	35.344	25.664	9.345
Stomach	0.113	0.187	2.187	0.829	1.177
Testes	0.269	0.328	0.361	0.319	0.047
Thymus	0.110	0.295	0.481	0.295	0.185
Thyroid	1.544	0.885	2.170	1.533	0.642
Whole Blood	3.450	2.106	4.202	3.253	1.062
Plasma	7.541	4.597	8.168	6.768	1.907
Blood:plasma ratio	0.46	0.46	0.51	0.48	0.03

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Appendix 8 (continued) **Individual Male 100 µg mRNA Data**

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 24 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	016M	017M	018M	Mean	SD
Adipose tissue	0.268	0.219	0.261	0.249	0.027
Adrenal glands	63.795	42.538	52.924	53.085	10.629
Bladder	0.609	0.643	0.373	0.542	0.147
Bone (femur)	1.254	2.075	0.950	1.426	0.582
Bone marrow (femur)	5.002	4.711	7.513	5.742	1.541
Brain	0.186	0.221	0.255	0.221	0.034
Eyes	0.342	0.247	0.360	0.316	0.061
Heart	1.613	1.877	1.760	1.750	0.132
Injection site	50.606	70.405	268.240	129.750	120.340
Kidneys	1.971	1.774	2.460	2.068	0.353
Large intestine	5.083	2.282	3.210	3.525	1.427
Liver	51.485	71.224	45.827	56.179	13.334
Lung	3.831	3.615	3.360	3.602	0.236
Lymph node (Man)	3.227	1.555	1.570	2.117	0.961
Lymph node (Mes)	5.835	3.496	3.765	4.366	1.279
Muscle	0.208	0.263	0.247	0.239	0.028
Pancreas	0.767	0.966	0.781	0.838	0.111
Pituitary gland	1.320	1.362	1.603	1.428	0.152
Prostate	0.407	0.446	0.481	0.445	0.037
Salivary glands	0.617	0.561	0.701	0.626	0.071
Skin	0.833	0.937	0.645	0.805	0.148
Small intestine	3.736	3.157	3.433	3.442	0.289
Spinal cord	0.229	0.200	0.326	0.252	0.066
Spleen	47.746	74.940	44.431	55.706	16.739
Stomach	0.572	0.802	0.489	0.621	0.162
Testes	0.638	0.502	0.616	0.585	0.073
Thymus	0.473	0.568	0.506	0.516	0.048
Thyroid	1.845	1.890	2.651	2.129	0.453
Whole Blood	2.448	1.756	3.404	2.536	0.827
Plasma	5.639	5.297	8.191	6.376	1.581
Blood:plasma ratio	0.43	0.33	0.42	0.39	0.05

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Appendix 8 (continued)

Individual Male 100 µg mRNA Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 48 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	019M	020M	Mean
Adipose tissue	0.276	0.234	0.255
Adrenal glands	52.496	45.684	49.090
Bladder	0.779	0.849	0.814
Bone (femur)	0.639	0.867	0.753
Bone marrow (femur)	3.233	2.890	3.062
Brain	0.477	0.173	0.325
Eyes	0.239	0.260	0.249
Heart	1.132	1.158	1.145
Injection site	48.800	59.876	54.338
Kidneys	0.971	1.131	1.051
Large intestine	4.144	2.190	3.167
Liver	48.512	36.690	42.601
Lung	1.853	2.477	2.165
Lymph node (Man)	2.418	1.157	1.788
Lymph node (Mes)	5.067	3.297	4.182
Muscle	0.166	0.926	0.546
Pancreas	0.540	0.701	0.620
Pituitary gland	0.987	0.884	0.936
Prostate	0.308	0.285	0.296
Salivary glands	0.488	0.588	0.538
Skin	0.640	0.699	0.670
Small intestine	3.644	3.750	3.697
Spinal cord	0.212	0.237	0.224
Spleen	35.545	33.899	34.722
Stomach	0.794	1.011	0.903
Testes	0.523	0.555	0.539
Thymus	0.514	0.655	0.584
Thyroid	1.604	1.523	1.564
Whole Blood	0.967	1.011	0.989
Plasma	1.451	1.493	1.472
Blood:plasma ratio	0.67	0.68	0.67

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Appendix 8 (continued)

Individual Male 100 µg mRNA Data

Recovery of Total Radioactivity in Tissues 0.25 min Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	001M	002M	003M	Mean	SD
Adrenal glands	0.000	0.000	0.000	0.000	0.000
Bladder	0.000	0.000	0.000	0.000	0.000
Brain	0.003	0.003	0.003	0.003	0.000
Eyes	0.000	0.000	0.000	0.000	0.000
Heart	0.011	0.009	0.017	0.013	0.004
Injection site	1.865	3.345	18.252	7.821	9.064
Kidneys	0.037	0.033	0.019	0.030	0.010
Large intestine	0.006	0.004	0.018	0.009	0.008
Liver	0.368	0.185	0.278	0.277	0.091
Lung	0.028	0.017	0.023	0.023	0.005
Pancreas	0.001	0.001	0.002	0.001	0.000
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.000	0.000	0.000	0.000	0.000
Salivary glands	0.001	0.002	0.001	0.001	0.000
Small intestine	0.016	0.009	0.006	0.010	0.005
Spinal cord	0.001	0.001	0.000	0.001	0.000
Spleen	0.010	0.026	0.006	0.014	0.011
Stomach	0.005	0.004	*0.002	°0.003	°0.002
Testes	0.004	0.003	0.003	0.003	0.001
Thymus	0.003	0.003	0.004	0.003	0.001
Thyroid	0.000	0.000	0.000	0.000	0.000

*=Results calculated from data less than 30 cpm above background
°=Mean includes results calculated from data less than 30 cpm above background

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Appendix 8 (continued)

Individual Male 100 µg mRNA Data

Recovery of Total Radioactivity in Tissues 1 hour Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	004M	005M	006M	Mean	SD
Adrenal glands	0.005	0.003	0.004	0.004	0.001
Bladder	0.001	0.000	0.001	0.001	0.000
Brain	0.019	0.020	0.020	0.019	0.001
Eyes	0.002	0.001	0.001	0.001	0.001
Heart	0.049	0.103	0.074	0.075	0.027
Injection site	15.619	13.609	16.094	15.107	1.319
Kidneys	0.191	0.176	0.188	0.185	0.008
Large intestine	0.024	0.027	0.050	0.034	0.014
Liver	5.198	3.856	5.564	4.873	0.899
Lung	0.148	0.159	0.103	0.137	0.030
Pancreas	0.004	0.006	0.007	0.006	0.002
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.003	0.003	0.003	0.003	0.000
Salivary glands	0.007	0.009	0.011	0.009	0.002
Small intestine	0.132	1.003	1.062	0.732	0.521
Spinal cord	0.001	0.003	0.001	0.002	0.001
Spleen	0.090	0.087	0.089	0.089	0.001
Stomach	0.075	0.362	1.259	0.565	0.618
Testes	0.020	0.021	0.057	0.033	0.021
Thymus	0.007	0.005	0.006	0.006	0.001
Thyroid	0.001	0.001	0.001	0.001	0.000

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Appendix 8 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 2 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	007M	008M	009M	Mean	SD
Adrenal glands	0.008	0.006	0.007	0.007	0.001
Bladder	0.001	0.001	0.001	0.001	0.000
Brain	0.024	0.021	0.018	0.021	0.003
Eyes	0.001	0.001	0.001	0.001	0.000
Heart	0.078	0.095	0.115	0.096	0.019
Injection site	0.598	9.070	3.532	4.400	4.302
Kidneys	0.180	0.148	0.160	0.163	0.016
Large intestine	0.088	0.038	0.055	0.061	0.025
Liver	11.802	8.114	8.654	9.523	1.992
Lung	0.147	0.112	0.153	0.137	0.022
Pancreas	0.008	0.007	0.011	0.009	0.002
Pituitary gland	0.001	0.000	0.000	0.000	0.000
Prostate	0.003	0.004	0.004	0.004	0.001
Salivary glands	0.012	0.010	0.013	0.011	0.002
Small intestine	0.434	0.294	0.281	0.336	0.085
Spinal cord	0.003	0.004	0.002	0.003	0.001
Spleen	0.271	0.155	0.192	0.206	0.059
Stomach	0.036	0.023	0.026	0.028	0.007
Testes	0.025	0.045	0.036	0.035	0.010
Thymus	0.010	0.008	0.007	0.008	0.001
Thyroid	0.001	0.001	0.001	0.001	0.000

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Appendix 8 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 4 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	010M	011M	012M	Mean	SD
Adrenal glands	0.010	0.005	0.005	0.007	0.003
Bladder	0.001	0.000	0.000	0.001	0.000
Brain	0.027	0.009	0.006	0.014	0.011
Eyes	0.001	0.001	0.000	0.001	0.000
Heart	0.031	0.043	0.033	0.036	0.007
Injection site	5.231	59.191	24.168	29.530	27.377
Kidneys	0.141	0.101	0.058	0.100	0.041
Large intestine	0.062	0.258	0.123	0.147	0.100
Liver	13.675	6.428	7.436	9.180	3.926
Lung	0.079	0.141	0.069	0.096	0.039
Pancreas	0.003	0.008	0.006	0.006	0.003
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.002	0.001	0.001	0.001	0.001
Salivary glands	0.005	0.003	0.003	0.004	0.001
Small intestine	0.234	0.614	0.356	0.401	0.194
Spinal cord	0.001	0.001	0.001	0.001	0.000
Spleen	0.177	0.530	0.167	0.291	0.207
Stomach	0.007	0.035	0.043	0.028	0.019
Testes	0.048	0.017	0.012	0.026	0.019
Thymus	0.003	0.005	0.003	0.003	0.001
Thyroid	0.001	0.000	0.001	0.001	0.000

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Appendix 8 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 8 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	013M	014M	015M	Mean	SD
Adrenal glands	0.025	0.021	0.080	0.042	0.033
Bladder	0.002	0.001	0.001	0.001	0.001
Brain	0.012	0.009	0.014	0.012	0.003
Eyes	0.002	0.001	0.002	0.002	0.001
Heart	0.058	0.035	0.081	0.058	0.023
Injection site	8.806	17.803	0.313	8.974	8.746
Kidneys	0.134	0.073	0.091	0.099	0.031
Large intestine	0.511	0.398	0.634	0.514	0.118
Liver	11.864	16.293	24.504	17.553	6.414
Lung	0.192	0.129	0.197	0.172	0.038
Pancreas	0.005	0.006	0.012	0.007	0.004
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.002	0.001	0.003	0.002	0.001
Salivary glands	0.004	0.003	0.008	0.005	0.003
Small intestine	0.585	0.529	0.633	0.582	0.052
Spinal cord	0.002	0.001	0.002	0.002	0.000
Spleen	0.560	0.369	0.848	0.592	0.241
Stomach	0.021	0.019	0.288	0.109	0.155
Testes	0.031	0.036	0.038	0.035	0.004
Thymus	0.002	0.004	0.007	0.004	0.002
Thyroid	0.001	0.001	0.001	0.001	0.000

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Appendix 8 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 24 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

	016M	017M			
	0.137	0.095	0.106	0.113	0.022
	0.003	0.002	0.001	0.002	0.001
	0.012	0.015	0.019	0.015	0.003
	0.004	0.002	0.004	0.003	0.001
	0.038	0.052	0.051	0.047	0.008
	3.590	15.406	29.435	16.144	12.938
	0.107	0.104	0.165	0.125	0.034
	1.668	0.752	0.996	1.139	0.475
	22.736	26.544	20.865	23.382	2.894
	0.170	0.160	0.226	0.185	0.036
	0.010	0.016	0.012	0.013	0.003
	0.000	0.000	0.000	0.000	0.000
	0.003	0.004	0.004	0.004	0.000
	0.011	0.010	0.011	0.010	0.001
	1.194	0.896	1.321	1.137	0.218
	0.002	0.001	0.002	0.002	0.001
	1.003	1.590	1.111	1.234	0.312
	0.066	0.099	0.065	0.077	0.019
	0.070	0.056	0.075	0.067	0.010
	0.007	0.009	0.007	0.008	0.002
	0.001	0.001	0.001	0.001	0.000

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Appendix 8 (continued) **Individual Male Recovery Data**

Recovery of Total Radioactivity in Tissues 48 hours Following Single Intramuscular Administration of [^{3}H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	019M	020M	Mean
Adrenal glands	0.155	0.112	0.134
Bladder	0.002	0.002	0.002
Brain	0.034	0.012	0.023
Eyes	0.002	0.003	0.002
Heart	0.030	0.031	0.030
Injection site	2.978	10.414	6.696
Kidneys	0.063	0.076	0.070
Large intestine	1.070	0.719	0.894
Liver	17.436	16.159	16.797
Lung	0.071	0.132	0.102
Pancreas	0.007	0.006	0.006
Pituitary gland	0.000	0.000	0.000
Prostate	0.003	0.002	0.003
Salivary glands	0.008	0.009	0.008
Small intestine	0.790	1.021	0.905
Spinal cord	0.002	0.002	0.002
Spleen	0.886	0.649	0.768
Stomach	0.044	0.047	0.046
Testes	0.064	0.054	0.059
Thymus	0.006	0.005	0.006
Thyroid	0.001	0.001	0.001

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This is Exhibit "H" to the Affidavit

of Bonnie Mallard, sworn before me

on this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

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本項で使用する用語・略語

用語・略号	省略していない表現または定義
ALC-0159	本剤に添加される PEG 脂質
ALC-0315	本剤に添加されるアミノ脂質
[^{3}H]-CHE	Radiolabeled [Cholesteryl-1,2-^{3}H(N)]-Cholesteryl Hexadecyl Ether：放射性標識 ［コレステリル-1, 2-^{3}H(N)］ヘキサデシルエーテル
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine：1,2-ジステアロイル-sn-グリセロ-3-ホスホコリン
GLP	Good Laboratory Practice：医薬品の安全性に関する非臨床試験の実施の基準
LNP	Lipid-nanoparticle：脂質ナノ粒子
modRNA	Nucleoside-modified mRNA：修飾ヌクレオシド mRNA
mRNA	Messenger RNA：メッセンジャーRNA
m/z	m/z（m・オーバー・z）：イオンの質量を統一原子質量単位（＝ダルトン）で割って得られた無次元量をさらにイオンの電荷数の絶対値で割って得られる無次元量
PEG	Polyethylene glycol：ポリエチレングリコール
PK	Pharmacokinetics：薬物動態
RNA	Ribonucleic acid：リボ核酸
S9	Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g：肝ホモジネートを 9000 g で遠心分離した上清画分
WHO	World Health Organization：世界保健機関

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1. まとめ

BNT162b2（BioNTech コード番号：BNT162，Pfizer コード番号：PF-07302048）は，重症急性呼吸器症候群コロナウイルス 2（SARS-CoV-2）のスパイク糖タンパク質（S タンパク質）全長体をコードする修飾ヌクレオシド mRNA（modRNA）であり，SARS-CoV-2 による感染症に対する mRNA ワクチンの本質として開発が進められている。BNT162b2 の製剤化にあたっては，2 つの機能脂質である ALC-0315（アミノ脂質）および ALC-0159（PEG 脂質）ならびに 2 つの構造脂質として DSPC（1,2-distearoyl-sn-glycero-3-phosphocholine）およびコレステロールと混合することで BNT162b2 を封入する脂質ナノ粒子（LNP）が形成される（以降，「BNT162b2 封入 LNP」）。

BNT162b2 封入 LNP の非臨床薬物動態を評価するために，LNP に含まれる ALC-0315 および ALC-0159 の吸収（PK），代謝および排泄を評価する in vivo および in vitro 試験ならびに BNT162b2 の代替レポーターとしてルシフェラーゼまたは放射能標識した脂質を利用した生体内分布試験を実施した。

感染症予防を目的としたワクチンの開発では全身曝露量の評価を必要としないことを踏まえ（WHO, 2005；感染症予防ワクチンの非臨床試験ガイドライン）[1,2]，BNT162b2 封入 LNP の筋肉内投与による PK 試験は実施しなかった。また，本剤に含有される他の 2 種類の脂質（コレステロールおよび DSPC）は天然に存在する脂質であり，内在性脂質と同様に代謝，排泄されると考えられる。加えて，BNT162b2 は取り込んだ細胞中のリボヌクレアーゼにより分解されて核酸代謝され，BNT162b2 由来の S タンパク質はタンパク分解を受けると予想される。以上のことから，あらためてこれらの成分の代謝および排泄を評価する必要はないと考えられた。

BNT162b2 の代替レポーターとしてルシフェラーゼをコードする RNA を封入した LNP（ルシフェラーゼ RNA を BNT162b2 封入 LNP と同一の脂質構成を持つ LNP に封入：以降，「ルシフェラーゼ RNA 封入 LNP」）を Wistar Han ラットに静脈内投与した PK 試験では，血漿，尿，糞および肝臓試料を経時的に採取して，各試料中の ALC-0315 および ALC-0159 濃度を測定した。その結果，ALC-0315 および ALC-0159 は血中から肝臓にすみやかに分布することが示された。また，ALC-0315 および ALC-0159 はそれぞれ投与量の約 1%および約 50%が未変化体として糞中に排泄され，尿中においてはいずれも検出限界未満であった。

生体内分布試験では，ルシフェラーゼ RNA 封入 LNP を BALB/c マウスに筋肉内投与した。その結果，ルシフェラーゼの発現が投与部位でみられ，それより発現量は低値であったものの肝臓でも認められた。ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現も投与後 6 時間に認められ，投与後 48 時間までに消失した。また，ルシフェラーゼ RNA 封入 LNP の放射能標識体をラットに筋肉内投与して生体内分布を定量的に評価したところ，放射能濃度は投与部位で最も高値であった。投与部位以外では肝臓が最も高かった（投与量の最大 18%）。

ALC-0315 および ALC-0159 の代謝を CD-1/ICR マウス，Wistar Han または Sprague Dawley ラット，カニクイザルもしくはヒトの血液，肝ミクロソーム，肝 S9 画分および肝細胞を用いて in vitro で評価した。また，上記のラット静脈内投与 PK 試験で採取した血漿，尿，糞および肝臓試料を用いて in vivo 代謝についても検討した。これら in vitro および in vivo 試験から，ALC-0315 および ALC-0159 は，試験したいずれの動物種でも，それぞれエステル結合およびアミド結合の加水分解により緩徐に代謝されることが示された。

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以上の非臨床薬物動態評価より，循環血中に到達した LNP は肝臓に分布することが示された。また，ALC-0315 および ALC-0159 の消失には，それぞれ代謝および糞中排泄が関与することが示唆された。

2. 分析法

報告書番号：PF-07302048_06[redacted]_072424

GLP 非適用のラット静脈内投与 PK 試験（M2.6.4.3 項）で LNP の構成脂質である ALC-0315 および ALC-0159 濃度を定量するために適切な性能を有する LC/MS 法を開発した。すなわち，20 µL の血漿，肝ホモジネート（肝臓の 3 箇所から採取した切片を用いてホモジネートを調製し，それらをプールしたものを適宜，ブランクマトリクスで希釈），尿および糞ホモジネート（適宜，ブランクマトリクスで希釈）試料をそれぞれ内部標準物質（PEG-2000）を含有するアセトニトリルで除タンパクした後，遠心分離し，その上清を LC-MS/MS 測定に供した。

3. 吸収

報告書番号：PF-07302048_06[redacted]_072424，概要表：2.6.5.3

ALC-0315 および ALC-0159 の体内動態を検討するため，ルシフェラーゼ RNA 封入 LNP を雄性 Wistar Han ラットに 1 mg RNA/kg の用量で単回静脈内投与し，経時的（投与前，投与後 0.1，0.25，0.5，1，3，6 および 24 時間ならびに投与後 2，4，8 および 14 日）に血漿および肝臓をスパースサンプリングにより採取（3 匹/時点）した。血漿中および肝臓中の ALC-0315 および ALC-0159 濃度を測定し，PK パラメータを算出した（Table 1）。血中の ALC-0315 および ALC-0159 は，投与後 24 時間までにすみやかに肝臓へ分布した。また，投与後 24 時間の血漿中濃度は最高血漿中濃度の 1%未満であった（Figure 1）。見かけの終末相消失半減期（t½）は血漿中および肝臓中で同程度で，ALC-0315 は 6～8 日，ALC-0159 は 2～3 日であった。本試験の結果から，肝臓が血中からの ALC-0315 および ALC-0159 を取り込む主要組織の 1 つであることが示唆された。

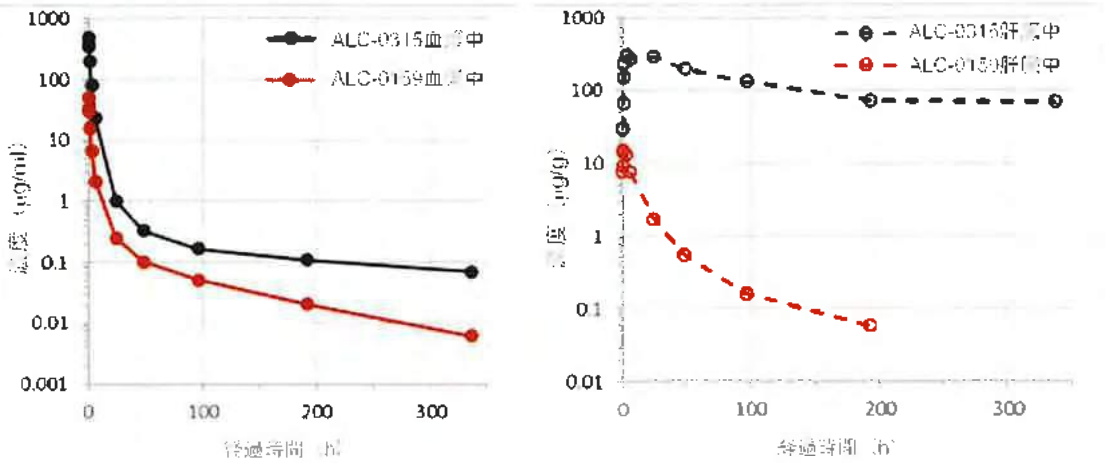
本試験において実施した ALC-0315 および ALC-0159 の尿中および糞中濃度の検討結果については M2.6.4.6 項で述べる。

Table 1 ルシフェラーゼ RNA 封入 LNP を Wistar Han ラットに 1 mg RNA/kg の用量で静脈内投与したときの ALC-0315 および ALC-0159 の薬物動態

分析物	分析物の投与量 (mg/kg)	性/N	t½ (h)	AUC_{inf} (µg•h/mL)	AUC_{last} (µg•h/mL)	肝臓への分布割合 (%)[a]
ALC-0315	15.3	雄/3[b]	139	1030	1020	60
ALC-0159	1.96	雄/3[b]	72.7	99.2	98.6	20

a. ［最高肝臓分布量 (µg)］/［投与量 (µg)］として算出。
b. 各時点 3 匹。スパースサンプリング。

Figure 1 ルシフェラーゼ RNA 封入 LNP を Wistar Han ラットに 1 mg RNA/kg の用量で静脈内投与したときの ALC-0315 および ALC-0159 の血漿および肝臓中濃度

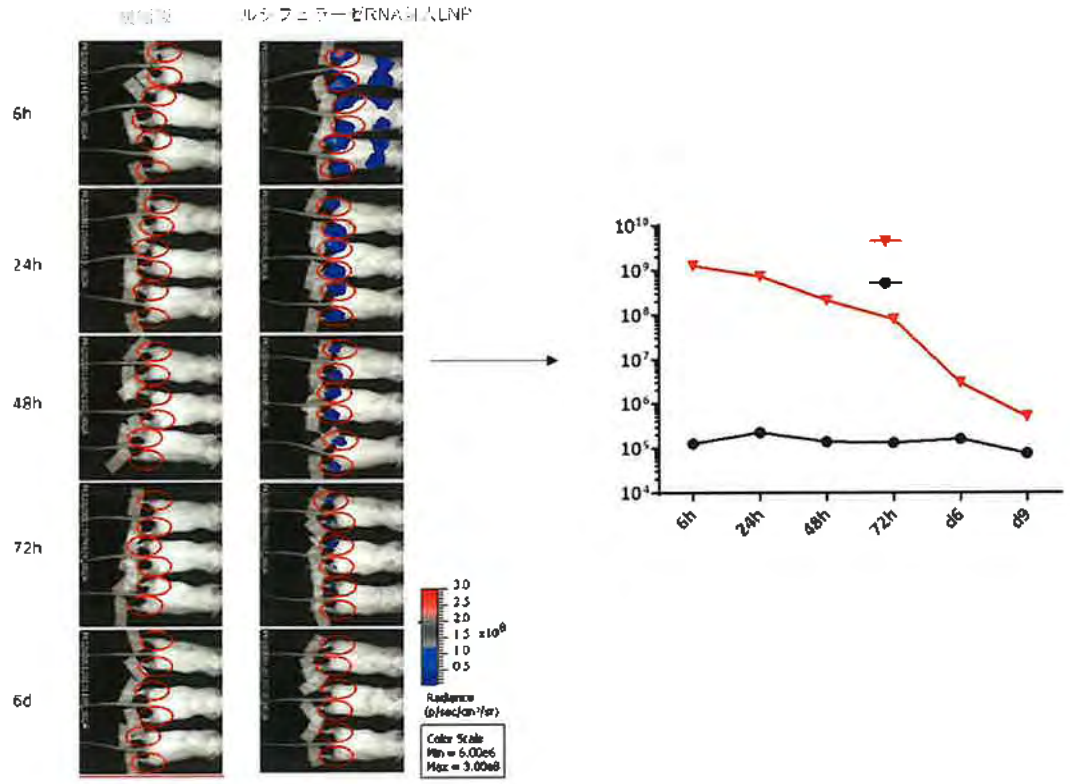


4. 分布

報告書番号：R-[redacted]-0072，185350，概要表：2.6.5.5A，2.6.5.5B

雌性 BALB/c マウス（3 匹）にルシフェラーゼ RNA 封入 LNP を投与し，ルシフェラーゼ発光を代替マーカーとして BNT162b2 の生体内分布を検討した。すなわち，ルシフェラーゼ RNA 封入 LNP をマウスの左右の後肢に各 1 µg RNA（計 2 µg RNA）の用量で筋肉内投与した。その後，ルシフェラーゼ発光検出の 5 分前に発光基質であるルシフェリンを腹腔内投与し，イソフルラン麻酔下，in vivo における発光を Xenogen IVIS Spectrum を用いて投与後 6 および 24 時間ならびに 2，3，6 および 9 日に測定することにより，ルシフェラーゼタンパクの同一個体での経時的な発現推移を評価した。その結果，ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現も投与後 6 時間からみられ，投与後 48 時間までに消失した。肝臓への分布は局所投与したルシフェラーゼ RNA 封入 LNP の一部が循環血中に到達し，肝臓で取り込まれたことを示すものと考えられた。M2.6.4.3 項で詳述したように，ラットにルシフェラーゼ RNA 封入 LNP を静脈内投与した場合には，肝臓が ALC-0315 および ALC-0159 の主要な分布臓器であることが示唆されており，このことはマウスに筋肉内投与した本試験結果の所見と符合するものであった。なお，ラット反復投与毒性試験で肝障害を示す毒性所見は認められていない（M2.6.6.3 項）。

Figure 2 ルシフェラーゼ RNA 封入 LNP を筋肉内投与した BALB/c マウスにおける生体内発光



雌雄 Wistar Han ラットに，[^{3}H]-コレステリルヘキサデシルエーテル（[^{3}H]- CHE）で標識した LNP を用いたルシフェラーゼ RNA 封入 LNP を 50 μg RNA の用量で筋肉内投与し，投与後 15 分ならびに 1，2，4，8，24 および 48 時間の各時点において雌雄各 3 匹から血液，血漿および組織を採取し，液体シンチレーション計数法により放射能濃度を測定することで LNP の生体内分布を評価した。雌雄ともに，放射能濃度はいずれの測定時点においても投与部位が最も高値であった。血漿中の放射能濃度は投与後 1～4 時間で最も高値を示した。また，主に肝臓，脾臓，副腎および卵巣への分布がみられ，これらの組織において放射能濃度が最も高くなったのは投与後 8～48 時間であった。投与部位以外での投与量に対する総放射能回収率は肝臓で最も高く（最大 18%），脾臓（1.0%以下），副腎（0.11%以下）および卵巣（0.095%以下）では肝臓と比較して著しく低かった。また，放射能の平均濃度および組織分布パターンは雌雄でおおむね類似していた。

BNT162b2 がコードする抗原の生体内発現分布は LNP 分布に依存すると考えられる。本試験で用いたルシフェラーゼ RNA 封入 LNP の脂質の構成は，BNT162b2 の申請製剤と同一であることから，本試験結果は BNT162b2 封入 LNP の分布を示すと考えられる。

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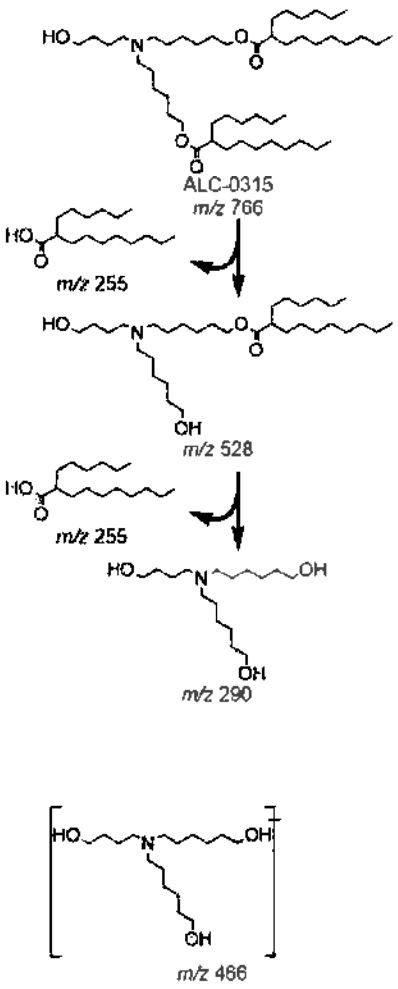
5. 代謝

報告書番号：01049-[redacted]008，01049-[redacted]009，01049-[redacted]010，01049-[redacted]020，01049-[redacted]021，01049-[redacted]022，PF-07302048_05[redacted]_043725，概要表：2.6.5.10A，2.6.5.10B，2.6.5.10C，2.6.5.10D

CD-1/ICR マウス，Wistar Han または Sprague Dawley ラット，カニクイザルならびにヒトの肝ミクロソーム，肝 S9 画分および肝細胞を用いて，ALC-0315 および ALC-0159 の in vitro 代謝安定性を評価した。ALC-0315 または ALC-0159 を各動物種の肝ミクロソームまたは肝 S9 画分（120 分間インキュベーション）もしくは肝細胞（240 分間インキュベーション）に添加して，インキュベーション後の未変化体の割合を測定した。その結果，ALC-0315 および ALC-0159 はいずれの動物種・試験系でも代謝的に安定であり，未変化体の最終的な割合は 82%超であった。

さらに ALC-0315 および ALC-0159 の代謝経路について in vitro および in vivo で評価した。これらの試験では，CD-1 マウス，Wistar Han ラット，カニクイザルおよびヒトの血液，肝 S9 画分および肝細胞を用いて in vitro での代謝を評価した。また，ラット PK 試験で採取した血漿，尿，糞および肝臓試料を用い，in vivo での代謝を評価した（M2.6.4.3 項）。試験結果から，ALC-0315 と ALC-0159 の代謝はいずれも緩徐であり，それぞれエステル結合およびアミド結合の加水分解により代謝されることが明らかになった。Figure 3 および Figure 4 に示した加水分解による代謝は，評価したすべての動物種でみられた。

種　　謝経



H：ヒト，Mk: サル，Mo：マウス，R：ラット

ALC-0315 はエステル加水分解を 2 回連続で受けることにより代謝される。この 2 回の加水分解により，最初，モノエステル代謝物（*m/z* 528），次に二重脱エステル化代謝物（*m/z* 290）が生成される。この二重脱エステル化代謝物はさらに代謝され，グルクロン酸抱合体（*m/z* 466）となるが，このグルクロン酸抱合体はラット PK 試験で尿中にのみ検出された。また，2 回の加水分解の酸性生成物がいずれも 6-ヘキシルデカン酸（*m/z* 255）であることも確認された。

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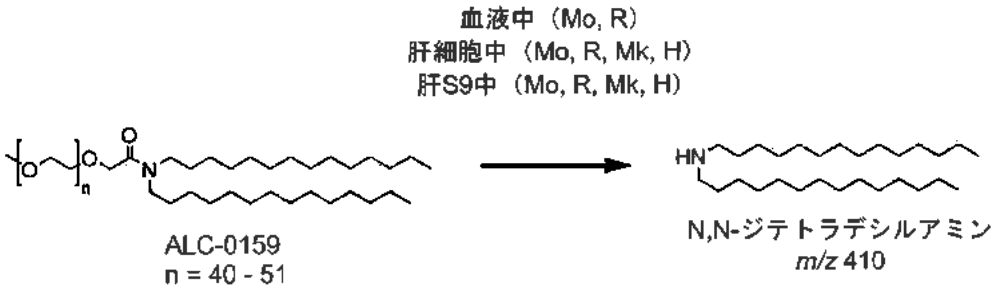
Figure 4 種々の動物種での ALC-0159 の推定生体内代謝経路



H：ヒト，Mk: サル，Mo：マウス，R：ラット

ALC-0159 は，アミド結合の加水分解により *N,N*-ジテトラデシルアミン（*m/z* 410）が生成される経路が主要な代謝経路であった。この代謝物は，マウス・ラットの血液ならびにマウス・ラット・サル・ヒトの肝細胞および肝 S9 画分中に検出された。In vivo 試料からは ALC-0159 の代謝物は確認されなかった。

6. 排泄

ルシフェラーゼ RNA 封入 LNP を 1 mg RNA/kg の用量でラットに静脈内投与した PK 試験（M2.6.4.3 項）で経時的に採取した尿および糞中の ALC-0315 および ALC-0159 濃度を測定した。ALC-0315 および ALC-0159 の未変化体はいずれも尿中に検出されなかった。一方，糞中には ALC-0315 および ALC-0159 の未変化体が検出され，投与量当たりの割合はそれぞれ約 1%および約 50%であった。また，Figure 3 に示したように，ALC-0315 の代謝物が尿中で検出された。

7. 薬物動態学的薬物相互作用

本ワクチンの薬物動態学的薬物相互作用試験は実施していない。

8. その他の薬物動態試験

本ワクチンのその他の薬物動態試験は実施していない。

9. 考察および結論

ラット PK 試験において，血漿および肝臓中 ALC-0315 濃度は，投与後 2 週間までに最高濃度のそれぞれ約 7000 分の 1 および約 4 分の 1 に減少し，ALC-0159 濃度はそれぞれ約 8000 分の 1 および約 250 分の 1 に減少した。t½は血漿中および肝臓中で同程度で，ALC-0315 は 6～8 日，ALC-0159 は 2～3 日であった。血漿中 t½値は，それぞれの脂質が LNP として組織中に分布し，その後，消失過程で血漿中に再分布したことを表すと考えられる。

ALC-0315 の未変化体は尿中と糞中のいずれにもほとんど検出されなかったが，ラット PK 試験で採取した糞および血漿試料からモノエステル代謝物，二重脱エステル化代謝物および 6-ヘキシルデカン酸が，尿からは二重脱エステル化代謝物のグルクロン酸抱合体が検出された。この代謝過程が ALC-0315 の主要消失機序と考えられるが，この仮説を検証する定量データは得られていない。一方，ALC-0159 は投与量の約 50%が未変化体として糞中に排泄された。In vitro 代謝実験において，アミド結合の加水分解により緩徐に代謝された。

BNT162b2 がコードする抗原の生体内発現分布は LNP 分布に依存すると考えられることから，BALB/c マウスにルシフェラーゼ RNA 封入 LNP を筋肉内投与し，代替レポータータンパク質の生体内分布を検討した。その結果，ルシフェラーゼの発現が投与部位においてみられ，それより発現量は低値であったものの肝臓でも認められた。ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ，投与後 9 日には消失した。肝臓での発現は投与後 6 時間から認められ，投与後 48 時間までに消失した。肝臓への分布は局所投与したルシフェラーゼ RNA 封入 LNP が循環血中に到達し，肝臓で取り込まれたことを示すものと考えられた。また，ラットにルシフェラーゼ RNA 封入 LNP の放射能標識体を筋肉内投与したところ，放射能濃度は投与部位で最も高値を示した。投与部位以外では，肝臓で最も高く，次いで脾臓，副腎および卵巣でも検出されたが，これらの組織における投与量に対する総放射能回収率は肝臓より著しく低かった。この結果は，マウス生体内分布試験において肝臓でルシフェラーゼ発現がみられたことと符合した。なお，ラット反復投与毒性試験で肝障害を示す毒性所見は認められなかった（M2.6.6.3 項）。

以上の非臨床薬物動態評価より，循環血中に到達した LNP は肝臓に分布することが示された。また，ALC-0315 および ALC-0159 の消失には，それぞれ代謝および糞中排泄が関与することが示唆された。

10. 図表

図表は本文中および概要表に示した。

参考文献

1 World Health Organization. Annex 1. Guidelines on the nonclinical evaluation of vaccines. In: WHO Technical Report Series No. 927, Geneva, Switzerland. World Health Organization; 2005:31-63.

2 感染症予防ワクチンの非臨床試験ガイドラインについて（薬食審査発 0527 第 1 号，平成 22 年 5 月 27 日）

2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test item	Method of Administration	Testing Facility	Report Number
Single Dose Pharmacokinetics					
Single Dose Pharmacokinetics and Excretion in Urine and Feces of ALC-0159 and ALC-0315	Rat (Wistar Han)	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	IV bolus	Pfizer Inc[a]	PF-07302048_06[redacted]_072424
Distribution					
In Vivo Distribution	Mice BALB/c	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	IM Injection	[redacted][b]	R-[redacted]-0072
In Vivo Distribution	Rat (Wistar Han)	modRNA encoding luciferase formulated in LNP comparable to BNT162b2 with trace amounts of [^{3}H]-CHE as non-diffusible label	IM Injection	[redacted][c]	185350
Metabolism					
In Vitro and In Vivo Metabolism					
In Vitro Metabolic Stability of ALC-0315 in Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	ALC-0315	In vitro	[redacted][d]	01049-[redacted]008
In Vitro Metabolic Stability of ALC-0315 in Liver S9	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 liver fractions	ALC-0315	In vitro	[redacted][d]	01049-[redacted]009

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2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test item	Method of Administration	Testing Facility	Report Number
In Vitro Metabolic Stability of ALC-0315 in Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	ALC-0315	In vitro	[redacted][d]	049-[redacted]0
In Vitro Metabolic Stability of ALC-0159 in Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	ALC-0159	In vitro	[redacted][d]	[redacted]
In Vitro Metabolic Stability of ALC-0159 in Liver S9	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 fractions	ALC-0159	In vitro	[redacted][d]	[redacted]
In Vitro Metabolic Stability of ALC-0159 in Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	ALC-0159	In vitro	[redacted][d]	[redacted]
Biotransformation of ALC-0159 and ALC-0315 In Vitro and In Vivo in Rats	In vitro: CD-1 mouse, Wistar Han rat, cynomolgus monkey, and human blood, liver S9 fractions and hepatocytes In vivo: male Wistar Han rats	ALC-0315 and ALC-0159	In vitro or IV (in vivo in rats)	Pfizer Inc[e]	5[redacted]

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2.6.5.1. PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test Item	Method of Administration	Testing Facility	Report Number

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; IM = Intramuscular; IV = Intravenous; LNP = lipid nanoparticles; S9 = Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g.

a. La Jolla, California.
b. [redacted], Germany.
c. [redacted], UK.
d. [redacted], China.
e. Groton, Connecticut.

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2.6.5.3. PHARMACOKINETICS: PHARMACOKINETICS AFTER A SINGLE DOSE

Test Article: modRNA encoding luciferase in LNP
Report Number: PF-07302048_06[redacted]_072424

Species (Strain)	Rat (Wistar Han)	
Sex/Number of Animals	Male/ 3 animals per timepoint[a]	
Feeding Condition	Fasted	
Method of Administration	IV	
Dose modRNA (mg/kg)	1	
Dose ALC-0159 (mg/kg)	1.96	
Dose ALC-0315 (mg/kg)	15.3	
Sample Matrix	Plasma, liver, urine and feces	
Sampling Time Points (h post dose):	Predose, 0.1, 0.25, 0.5, 1, 3, 6, 24, 48, 96, 192, 336	
Analyte	ALC-0315	ALC-0159
PK Parameters:	Mean[b]	Mean[b]
AUC_{inf} (µg•h/mL)[c]	1030	99.2
AUC_{last} (µg•h/mL)	1020	98.6
Initial $t_{½}$ (h)[d]	1.62	1.74
Terminal elimination $t_{½}$ (h)[e]	139	72.7
Estimated fraction of dose distributed to liver (%)[f]	59.5	20.3
Dose in Urine (%)	NC[g]	NC[g]
Dose in Feces (%)[h]	1.05	47.2

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; AUC_{inf} = Area under the plasma drug concentration-time curve from 0 to infinite time; AUC_{last} = Area under the plasma drug concentration-time curve from 0 to the last quantifiable time point; BLQ = Below the limit of quantitation; LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA; PK = Pharmacokinetics; $t_{½}$ = Half-life.

a. Non-serial sampling, 36 animals total.
b. Only mean PK parameters are reported due to non-serial sampling.
c. Calculated using the terminal log-linear phase (determined using 48, 96, 192, and 336 h for regression calculation).
d. ln(2)/initial elimination rate constant (determined using 1, 3, and 6 h for regression calculation).
e. ln(2)/terminal elimination rate constant (determined using 48, 96, 192, and 336 h for regression calculation).
f. Calculated as follows: highest mean amount in the liver (µg)/total mean dose (µg) of ALC-0315 or ALC-0159.
g. Not calculated due to BLQ data.
h. Fecal excretion, calculated as: (mean µg of analyte in feces/ mean µg of analyte administered) × 100

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2.6.5.5A. PHARMACOKINETICS: ORGAN DISTRIBUTION

Test Article: modRNA encoding luciferase in LNP
Report Number: R-[redacted]-0072

Species (Strain):	Mice (BALB/c)
Sex/Number of Animals:	Female/3 per group
Feeding Condition:	Fed ad libitum
Vehicle/Formulation:	Phosphate-buffered saline
Method of Administration:	Intramuscular injection
Dose (mg/kg):	1 µg/hind leg in gastrocnemius muscle (2 µg total)
Number of Doses:	1
Detection:	Bioluminescence measurement
Sampling Time (hour):	6, 24, 48, 72 hours; 6 and 9 days post-injection

Time point	Total Mean Bioluminescence signal (photons/second)		Mean Bioluminescence signal in the liver (photons/second)
	Buffer control	modRNALuciferase in LNP	modRNALuciferase in LNP
6 hours	1.28×10^{5}	1.26×10^{9}	4.94×10^{7}
24 hours	2.28×10^{5}	7.31×10^{8}	2.4×10^{6}
48 hours	1.40×10^{5}	2.10×10^{8}	Below detection[a]
72 hours	1.33×10^{5}	7.87×10^{7}	Below detection[a]
6 days	1.62×10^{5}	2.92×10^{6}	Below detection[a]
9 days	7.66×10^{4}	5.09×10^{5}	Below detection[a]

LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA.
a. At or below the background level of the buffer control.

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Species (Strain):	Rat (Wistar Han)
Sex/Number of Animals:	Male and female/3 animals/sex/timepoint (21 animals/sex total for the 50 µg dose)
Feeding Condition:	Fed ad libitum
Method of Administration:	Intramuscular injection
Dose:	50 µg [^{3}H]-08-A01-C0 (lot # NC-0552-1)
Number of Doses:	1
Detection:	Radioactivity quantitation using liquid scintillation counting
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, and 48 hours post-injection

Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL) (males and females combined)							% of administered dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	--	--	--	--	--	--	--
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2	0.001	0.007	0.010	0.015	0.035	0.066	0.106
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	--	--	--	--	--	--	--
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77	--	--	--	--	--	--	--
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030
Injection site	128	394	311	338	213	195	165	19.9	52.6	31.6	28.4	21.9	29.1	24.6
Kidneys	0.391	1.16	2.05	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34	0.008	0.025	0.065	0.192	0.405	0.692	0.762
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3	0.602	2.87	7.33	11.9	18.1	15.4	16.2
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09	0.052	0.101	0.178	0.169	0.122	0.101	0.101

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Sample	Total Lipid concentration (µg lipid equivalent/g [or mL]) (males and females combined)							% of Administered Dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	--	--	--	--	--	--	--
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37	--	--	--	--	--	--	--
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	--	--	--	--	--	--	--
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	--	--	--	--	--	--	--
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4	0.013	0.093	0.325	0.385	0.982	0.821	1.03
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420	--	--	--	--	--	--	--
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805	--	--	--	--	--	--	--
Blood:Plasma ratio[a]	0.815	0.515	0.550	0.510	0.555	0.530	0.540	--	--	--	--	--	--	--

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2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

-- = Not applicable, partial tissue taken; [^{3}H]-08-A01-C0 = An aqueous dispersion of LNPs, including ALC-0315, ALC-0159, distearoylphosphatidylcholine, cholesterol, mRNA encoding luciferase and trace amounts of radiolabeled [Cholesteryl-1,2-3H(N)]-Cholesteryl Hexadecyl Ether, a nonexchangeable, non-metabolizable lipid marker used to monitor the disposition of the LNPs; ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N--ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4--hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; LNP = Lipid nanoparticle; mRNA = messenger RNA.

a. The mean male and female blood:plasma values were first calculated separately and this value represents the mean of the two values.

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2.6.5.9. PHARMACOKINETICS: METABOLISM IN VIVO, RAT

Test Article: modRNA encoding luciferase in LNP
Report Number: PF-07302048_05[redacted]_043725

Species (Strain):	Rat (Wistar Han)
Sex/ Number of animals	Male/ 36 animals total for plasma and liver, 3 animals for urine and feces
Method of Administration:	Intravenous
Dose (mg/kg):	1
Test System:	Plasma, Urine, Feces, Liver
Analysis Method:	Ultrahigh performance liquid chromatography/ mass spectrometry

Biotransformation	m/z	Metabolites of ALC-0315 Detected			
		Plasma	Urine	Feces	Liver
N-dealkylation, oxidation	102.0561[a]	ND	ND	ND	ND
N-Dealkylation, oxidation	104.0706[b]	ND	ND	ND	ND
N-dealkylation, oxidation	130.0874[a]	ND	ND	ND	ND
N-Dealkylation, oxidation	132.1019[b]	ND	ND	ND	ND
N-dealkylation, hydrolysis, oxidation	145.0506[a]	ND	ND	ND	ND
Hydrolysis (acid)	255.2330[a]	+	ND	ND	ND
Hydrolysis, hydroxylation	271.2279[a]	ND	ND	ND	ND
Bis-hydrolysis (amine)	290.2690[b]	+	+	+	+
Hydrolysis, glucuronidation	431.2650[a]	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	464.2865[a]	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	466.3011[b]	ND	+	ND	ND
Hydrolysis (amine)	528.4986[b]	+	ND	ND	+
Hydrolysis (amine), Glucuronidation	704.5307[b]	ND	ND	ND	ND
Oxidation to acid	778.6930[a]	ND	ND	ND	ND
Oxidation to acid	780.7076[b]	ND	ND	ND	ND
Hydroxylation	782.7232[b]	ND	ND	ND	ND
Sulfation	844.6706[a]	ND	ND	ND	ND
Sulfation	846.6851[b]	ND	ND	ND	ND
Glucuronidation	940.7458[a]	ND	ND	ND	ND
Glucuronidation	942.7604[b]	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = minor metabolite as assessed by ultraviolet detection.
a. Negative ion mode.
b. Positive ion mode.

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2.6.5.10A. PHARMACOKINETICS: METABOLISM IN VITRO

Test Article: ALC-0315
Report Numbers: 01049-[redacted]008
01049-[redacted]009
01049-[redacted]010

Type of Study:	Stability of ALC-0315 In Vitro		
Study System:	Liver Microsomes + NADPH	S9 Fraction + NADPH, UDPGA, and alamethicin	Hepatocytes
ALC-0315 Concentration:	1 µM	1 µM	1 µM
Duration of Incubation (min):	120 min	120 min	240 min
Analysis Method:	Ultra-high performance liquid chromatography-tandem mass spectrometry		

Incubation time (min)	Percent ALC-0315 remaining													
	Liver Microsomes					Liver S9 Fraction				Hepatocytes				
	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
15	98.77	94.39	96.34	97.96	100.24	97.69	98.85	99.57	95.99	--	--	--	--	--
30	97.78	96.26	97.32	96.18	99.76	97.22	99.62	96.96	97.32	101.15	97.75	102.70	96.36	100.72
60	100.49	99.73	98.54	100.00	101.45	98.61	99.62	99.13	94.98	100.77	98.50	102.32	97.82	101.44
90	97.78	98.66	94.15	97.96	100.48	98.15	98.85	98.70	98.33	101.92	99.25	103.09	100.0	100.36
120	96.54	95.99	93.66	97.71	98.31	96.76	98.46	99.57	99.33	98.85	97.38	99.61	96.36	100.72
180	--	--	--	--	--	--	--	--	--	101.15	98.88	103.47	95.64	98.92
240	--	--	--	--	--	--	--	--	--	99.62	101.12	100.00	93.82	99.64
$t_{½}$ (min)	>120	>120	>120	>120	>120	>120	>120	>120	>120	>240	>240	>240	>240	>240

-- = Data not available; ALC-0315 = (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the lipid nanoparticle formulation used in BNT162b2; Cyno = Cynomolgus; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; NC = not calculated; SD = Sprague Dawley; $t_{½}$ = half-life; WH = Wistar-Han; UDPGA= uridine-diphosphate-glucuronic acid trisodium salt.

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2.6.5.10B. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0159
Report Numbers: 01049-[redacted]020
01049-[redacted]021
01049-[redacted]022

Type of Study:	Stability of ALC-0159 In Vitro		
Study System:	Liver Microsomes + NADPH	S9 Fraction + NADPH, UDPGA, and alamethicin	Hepatocytes
ALC-0159 Concentration:	1 µM	1 µM	1 µM
Duration of Incubation (min):	120 min	120 min	240 min
Analysis Method:	Ultra-high performance liquid chromatography-tandem mass spectrometry		

Incubation time (min)	Percent ALC-0159 remaining													
	Liver Microsomes					Liver S9 Fraction				Hepatocytes				
	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
15	82.27	101.24	112.11	100.83	99.59	98.93	84.38	91.30	106.73	--	--	--	--	--
30	86.40	93.78	102.69	85.12	92.28	91.10	90.87	97.96	107.60	100.85	93.37	113.04	90.23	106.34
60	85.54	98.34	105.38	86.36	95.53	102.85	97.97	105.56	104.97	94.92	91.81	105.07	92.93	101.58
90	85.41	95.44	100.90	94.63	97.97	90.75	93.51	108.33	109.36	94.28	90.25	112.80	94.59	92.67
120	95.87	97.10	108.97	93.39	93.09	106.76	92.70	105.74	119.59	87.08	89.47	104.11	97.51	96.04
180	--	--	--	--	--	--	--	--	--	94.92	93.96	102.90	89.81	93.66
240	--	--	--	--	--	--	--	--	--	102.75	94.93	98.79	92.93	102.57
$t_{1/2}$ (min)	>120	>120	>120	>120	>120	>120	>120	>120	>120	>240	>240	>240	>240	>240

-- = Data not available; ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the lipid nanoparticle formulation used in BNT162b2; Cyno = Cynomolgus; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; NC = not calculated; SD = Sprague Dawley; WH = Wistar-Han; UDPGA= uridine-diphosphate-glucuronic acid trisodium salt.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

2.6.5.10C. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0315

Report Number: PF-07302048_05[redacted]_043725

Type of study	Metabolism of ALC-0315 In Vitro		
Study system	Blood	Hepatocytes	Liver S9 Fraction
ALC-0315 concentration	10 µM	10 µM	10 µM
Duration of incubation	24 h	4 h	24 h
Analysis Method:	Ultrahigh performance liquid chromatography/ mass spectrometry		

Biotransformation	m/z	Blood				Hepatocytes				Liver S9 Fraction			
		Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human
N-dealkylation, oxidation	102.0561[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	104.0706[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-dealkylation, oxidation	130.0874[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	132.1019[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-dealkylation, hydrolysis, oxidation	145.0506[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (acid)	255.2330[a]	+	+	ND	ND	+	+	+	+	+	+	ND	+
Hydrolysis, hydroxylation	271.2279[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine)	290.2690[b]	+	+	ND	ND	ND	ND	ND	ND	ND	ND	+	ND
Hydrolysis, glucuronidation	431.2650[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	464.2865[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	466.3011[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (amine)	528.4986[b]	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	+	ND
Hydrolysis (amine), glucuronidation	704.5307[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Oxidation to acid	778.6930[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Oxidation to acid	780.7076[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydroxylation	782.7232[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sulfation	844.6706[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sulfation	846.6851[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Glucuronidation	940.7458[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Glucuronidation	942.7604[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = metabolite present.
a. Negative ion mode.
b. Positive ion mode.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
Court File No./N° du dossier du greffe : CV-22-00691880-0000

2.6.5.10D. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0159

Report Number: PF-07302048_05[redacted]_043725

Type of study	Metabolism of ALC-0159 In Vitro		
Study system	Blood	Hepatocytes	Liver S9 Fraction
ALC-0159 concentration	10 µM	10 µM	10 µM
Duration of incubation	24 h	4 h	24 h
Analysis Method:	Ultrahigh performance liquid chromatography/ mass spectrometry		

Biotransformation	m/z	Blood				Hepatocytes				Liver S9 Fraction			
		Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human
O-Demethylation, *O*-dealkylation	107.0703[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, *O*-dealkylation	151.0965[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, *O*-dealkylation	195.1227[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis, *N*-Dealkylation	214.2529[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation, oxidation	227.2017[a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (amine)	410.4720[b]	+	+	ND	ND	+	+	+	+	+	+	+	+
N,*N*-Didealkylation	531.5849[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
N-Dealkylation	580.6396[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
O-Demethylation, oxidation	629.6853[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydroxylation	633.6931[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
ω-Hydroxylation, Oxidation	637.1880[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hydrolysis (acid)	708.7721[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = metabolite present.
a. Negative ion mode.
b. Positive ion mode.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice
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This is Exhibit "I" to the Affidavit of

Bonnie Mallard, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

Court File No./N° du dossier du greffe : CV-22-00691880-0000

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

[redacted] shared "June 23, 2021 - J Scott Weese Post and Retweet" with you.

[redacted]

Wed 8/23/2021 11:18 AM

To:Bonnie Mallard <bmallard@ovc.uoguelph.ca>

[redacted] shared a file with you

Check out the latest tweet from today - The WHO updated their advice....but Scott Weese twisted it

"WHO's Strategic Advisory Group of Experts (SAGE) has concluded that the Pfizer/BionTech vaccine is suitable for use by people aged 12 years and above. Children aged between 12 and 15 who are at high risk may be offered this vaccine alongside other priority groups for vaccination."

June 23, 2021 - J Scott Weese Post and Retweet

This link only works for the direct recipients of this message.

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Name	Modified	Modified...	File size	Sharing	Activity
June 23, 2021 - J Scott Weese Post and Retweet.png	June 23, 2021	[redacted]	356 KB	Shared	
June 21, 2021 - part 2 - Jean Marc Benoit - Rachel Green - JMB- Diana C - J Scott Weese - Patti Tweet Reply .png	June 21, 2021	[redacted]	146 KB	Shared	
June 21, 2021 - part 3 - Jean Marc Benoit - Rachel Green - JMB- Diana C - J Scott Weese - Patti Tweet Reply .png	June 21, 2021	[redacted]	76.3 KB	Shared	
June 21, 2021 - part 1 - Jean Marc Benoit - Rachel Green - JMB- Diana C - J Scott Weese - Patti Tweet Reply.png	June 21, 2021	[redacted]	159 KB	Shared	
June 14, 2021 - part 1 - Meanka Pai - WonderingGirl10 - J Scott Weese Reply Tweet .png	June 21, 2021	[redacted]	155 KB	Shared	
June 14, 2021 - part 2 - Meneka Pai - Wandering Girl10- J Scott Weese Reply Tweet.png	June 21, 2021	[redacted]	76.3 KB	Shared	
June 15, 2021 - fly - J Scott Weese Reply Tweet .png	June 21, 2021	[redacted]	306 KB	Shared	
June 21, 2021 - J Scott Weese Toronto Star Article Tweet.png	June 21, 2021	[redacted]	366 KB	Shared	
June 21, 2021 - Glen Pyle Reply Tweet to CT Cynic re Scott Weese, David Fisman and the Toronto Star.png	June 21, 2021	[redacted]	186 KB	Shared	
June 17, 2021 - J Scott Weese Tweet - Joke about Derek Sloan's Press Conference.png	June 21, 2021	[redacted]	48.7 KB	Shared	

[redacted]

← **Tweet**

Menaka Pai, MSc MD FRCPC @MPaiMD · Jun 14

The vaccine rollout is spreading - and so is the delta variant. Lots of folks are concerned about the risk of myocarditis in young people who receive mRNA. My advice: make sure your sources include true experts - in this case, doctors who look after heart disease in kids. 1/n

37 128 651

WanderingGirl10 @WanderingGirl10 · Jun 14

My parents need to learn this - last I checked, they were using advice from a VETERINARIAN to argue against getting the mRNA vaccines. 🤦

2 20

J Scott Weese @weese_scott · Jun 14

He's not a vet. He has a PhD, not any medical degree (human or animal).

3 11

WanderingGirl10
@WanderingGirl10

Replying to @weese_scott and @MPaiMD

J Scott, if they're not a veterinarian, then you and I are clearly NOT talking about the same individual. The person I'm talking about is indeed a veterinarian and there are anti-vaxxers listening to this clown.

8:19 PM · Jun 14, 2021 Twitter Web App

2 Likes

J Scott Weese @weese_scott · Jun 14

Replying to @WanderingGirl10 and @MPaiMD

Bridle?

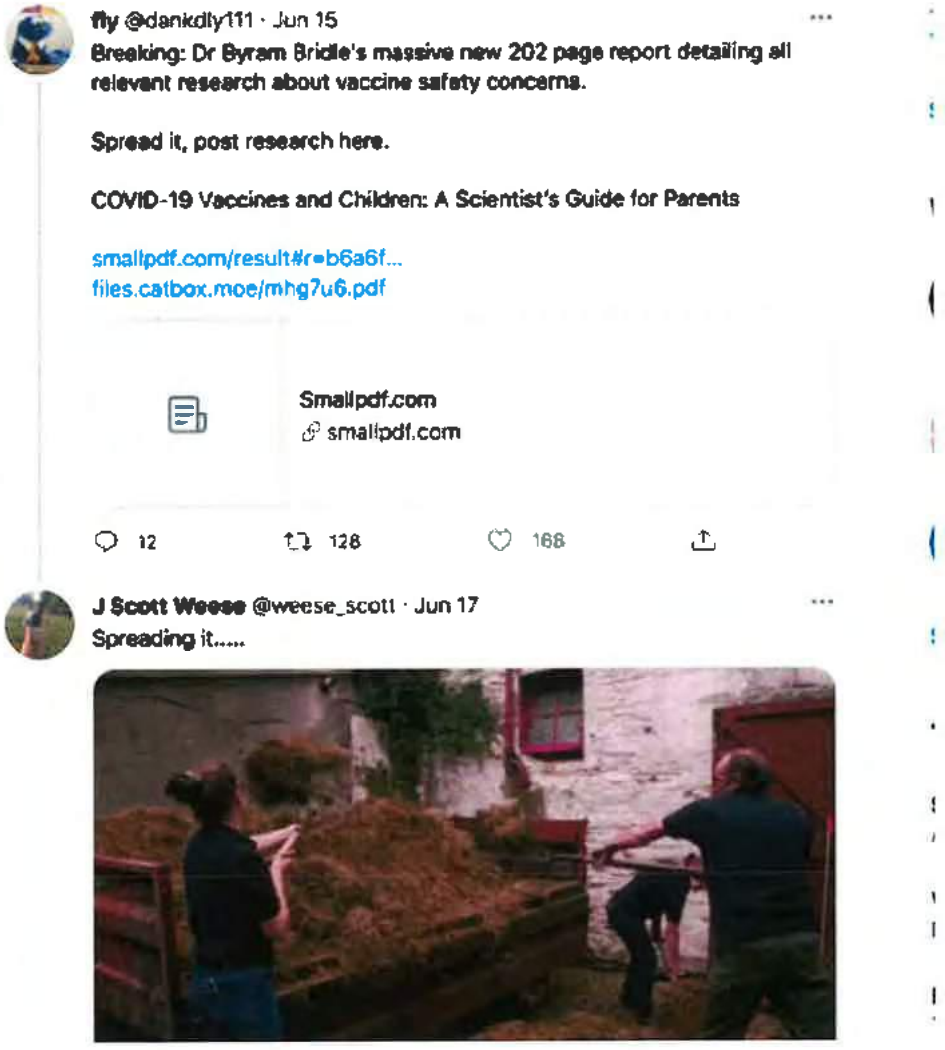
If so, not a vet.

If not, it would be good to know who else we need to worry about.

4 2

WanderingGirl10 @WanderingGirl10 · Jun 15

I'll have to see if it's still on their Facebook page and check the name. I keep reporting the stuff they share to Facebook as false information - Facebook leaves most of it up, but occasionally flags it - my parent often deletes it when that happens. Saving face maybe??? Sigh.



fly @dankdly111 · Jun 15

Breaking: Dr Byram Bridle's massive new 202 page report detailing all relevant research about vaccine safety concerns.

Spread it, post research here.

COVID-19 Vaccines and Children: A Scientist's Guide for Parents

smallpdf.com/result#r=b6a6f...
files.catbox.moe/mhg7u6.pdf

Smallpdf.com
smallpdf.com

12 128 168

J Scott Weese @weese_scott · Jun 17

Spreading it.....

J Scott Weese @weese_scott · Jun 17

An far right politician, anti-vaxxer and guy who compared public health measures to the Holocaust walk into a press room...

I wish there was an actual joke in there. The real story's too sad/frustrating/maddening.

Misinformation kills. We need to address and remember that.

1 6

Show this thread

J Scott Weese @weese_scott · 13h

Immunologists raise concerns on U of Guelph prof's views on COVID-19 vaccine safety thestar.com/local-guelph/n... via @torontostar

Immunologists raise concerns on U of Guelph prof's views on COVID...
A professor at the University of Guelph is calling on the federal government to stop vaccinating children against COVID-19 due to ...
thestar.com

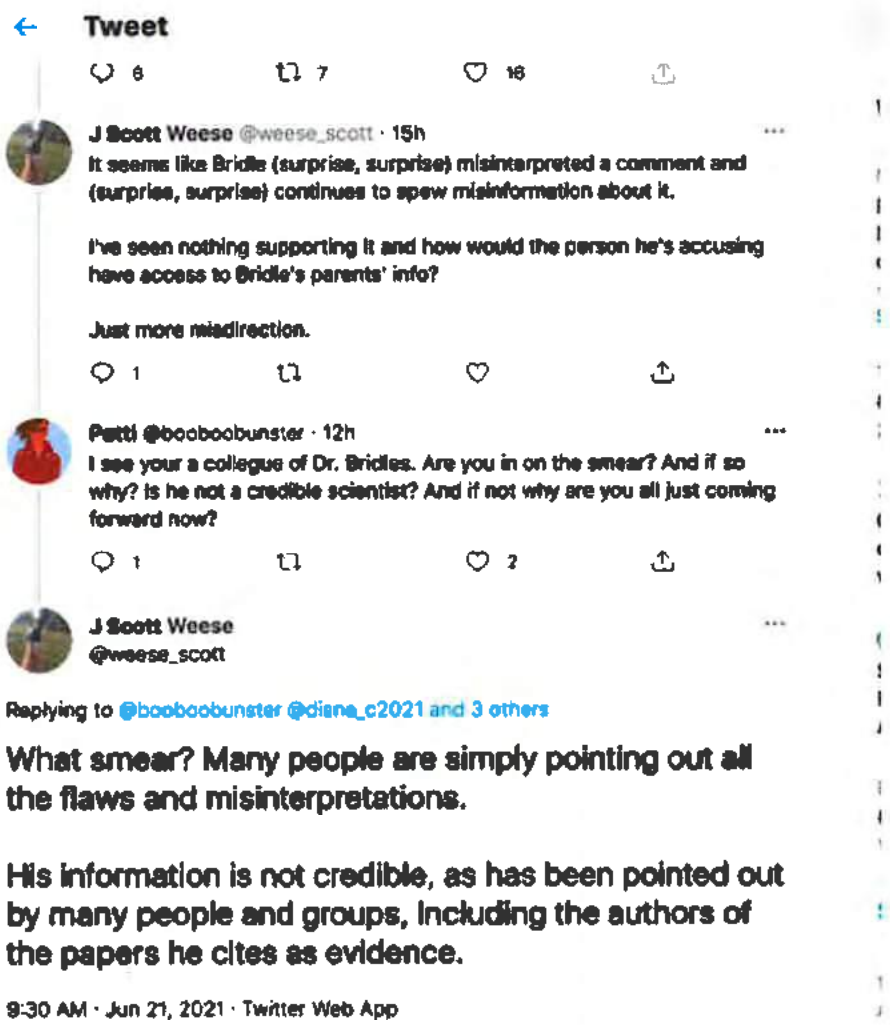
15 48 79

J Scott Weese @weese_scott · Jun 14

We need to continue to challenge misinformation.

Unnecessary deaths are going to occur because of these irresponsible people. The number of people that have mentioned they cancelled or are rethinking vax is scary.

We need everyone on board with vax bc of delta.



Tweet

6 7 16

J Scott Weese @weese_scott · 15h

It seems like Bridle (surprise, surprise) misinterpreted a comment and (surprise, surprise) continues to spew misinformation about it.

I've seen nothing supporting it and how would the person he's accusing have access to Bridle's parents' info?

Just more misdirection.

1

Patti @boobooboobunster · 12h

I see your a collegue of Dr. Bridles. Are you in on the smear? And if so why? Is he not a credible scientist? And if not why are you all just coming forward now?

1 2

J Scott Weese
@weese_scott

Replying to @boobooboobunster @diana_c2021 and 3 others

What smear? Many people are simply pointing out all the flaws and misinterpretations.

His information is not credible, as has been pointed out by many people and groups, including the authors of the papers he cites as evidence.

9:30 AM · Jun 21, 2021 · Twitter Web App

← **Tweet**

6 7 16

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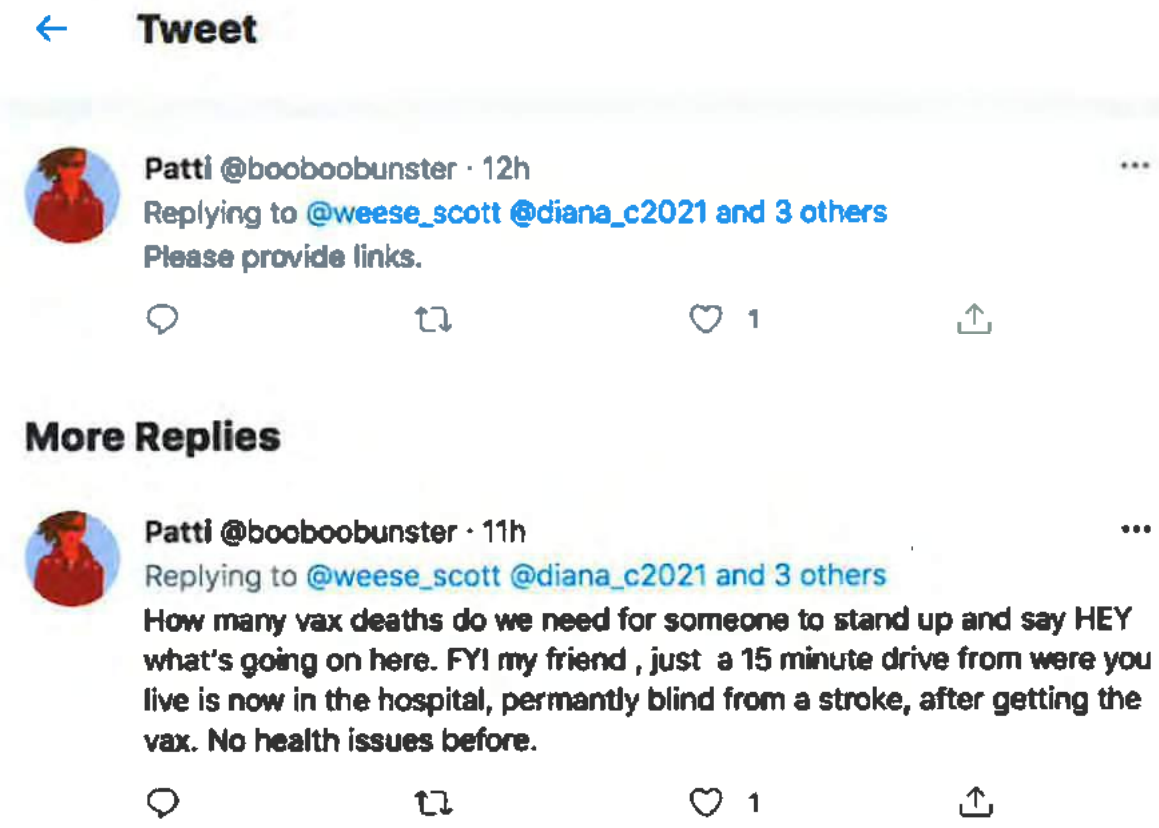
9:30 AM · Jun 21, 2021 · Twitter Web App



← **Tweet**

Patti @booboobunster · 12h

Replying to @weese_scott @diana_c2021 and 3 others

Please provide links.

1

More Replies

Patti @booboobunster · 11h

Replying to @weese_scott @diana_c2021 and 3 others

How many vax deaths do we need for someone to stand up and say HEY what's going on here. FYI my friend , just a 15 minute drive from were you live is now in the hospital, permantly blind from a stroke, after getting the vax. No health issues before.

1

CT Cynic @CTcynic · 12h

Replying to @weese_scott @DFisman and @TorontoStar

Let the man speak. Until more people see the adverse events and stop putting their children at risk.

1 1

Glen Pyle | #GetVaccinated @glenpyle · 12h

We have not said he can't speak. We've simply pointed to the flaws in his arguments, along with the people who did the studies he cites.

lle did not respond to requests for
ıment from The Associated Press. A
ɔ-reply email from his account said
ore comprehensive report on his
ıments would soon be published.

Reuters contacted Bridle about his claims who sent an automatic response saying that he was not accepting media engagements, but rejected a "libellous website" and "public smearing campaign" that resulted from his radio interview.

When USA TODAY reached
ia email for comment, an a
eply addressing his comm
oronavirus vaccines was r

lined to be interviev
when contacted by t
ribune by phone.

1 1 11

← Tweet

Jean Marc Benoit MD @JeanmarcBenoit · Jun 20

#cpso what is competent reply here?
Agree?
Disagree?
Quibble?
Ignore?

> **GV**
>
> What is shameful is playing on parents desire to do the best for their children by coercing through fear, theeatening to exclude kids from school, sports and making them out to be "lepers" that will kill grandma. Parents are then trapped between rock and a hard place.

4 9 38

Rachel Green 🤔 @4bbhb · Jun 20

Shame on the #cpso for not investigating @dfisman for harassing and bullying Dr Byram Bridle, and the sharing of confidential medical information his parents

3 9 42

Jean Marc Benoit MD @JeanmarcBenoit · 23h

Is there proof that this occurred? Was there an admission of action?

1 2

Diana C @diana_c2021 · 23h

Here's website and account discrediting Bridle that Fisman tweets about and RTs. Proof that personal info was released about his parents seems to have only been disclosed by Bridle in the recent cpac conference organized by Derek Sloan. He did not name names...

← **J Scott Weese**
897 Tweets

Follow

J Scott Weese @weese_scott · 1h
WHO doesn't say not to vaccinate 12+.

They say they are lower priority: "less urgent" to vaccinate them. (e.g. Don't vaccine 12+ when you have high risk people unvaccinated.)

who.int/emergencies/di...

> **Daler1** @daler2012 · 16h
> Replying to @weese_scott @DFisman and @TorontoStar
> childrenshealthdefense.org/defender/who-u...

2

J Scott Weese @weese_scott · 15h
It's almost like those vaccine thingys work

Florida coronavirus outbreak: Two employees dead as virus sweeps Manatee County government building - CNN

A coronavirus outbreak hit a Florida government building. Two peopl...
Two people are dead and four of their coworkers were hospitalized

This is Exhibit "J" to the Affidavit of

Bonnie Mallard, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

From: Bonnie Mallard <bmallard@ovc.uoguelph.ca>
Date: Monday, June 7, 2021 at 10:17 PM
To: JJW <jwichtel@uoguelph.ca>
Cc: Shayan Sharif <shayan@uoguelph.ca>
Subject: Re: Facebook censors Byram's interview

Hi Jeff and thanks for your quick response. As professors and scientists we are used to normal scientific debate, but in this case people are not allowing that process to take place. Instead they post websites using his name, send nasty tweets and Facebook

Posts, and now launch a false fact checker post. I have checked the two critical documents in question myself (attached again here), and indeed these reports state what Byram said (mRNA in LNPs at off target locations and spike protein in circulation following immunization).

These slanderous posts essentially state these documents don't exist or are in some way false. They make extremely negative comments about Byram for even mentioning these two documents. This is not how science works. This is something else entirely. This is social media lashing out at opinions they don't appreciate for unknown reasons.

In my 30 years as a faculty member, I have never seen anything like it. I am grateful that you and the UoG are supporting Byram's right to hold any professional position, which in this case was simply to bring these 2 new pieces of information to light last week at a critical time when parents were trying to make the best decisions around vaccination of their children.

By the way, I just finished reading another review paper that sites several other studies that demonstrate that mRNA within LNPs can be delivered to various off target sites. So it is not as if Byram is the only scientist bringing this information forward.

I strongly encourage you and Shayan to at least glance at these documents, if you have not done so already, so you see that this is not false news. Byram has always been a respected and successful member of our faculty, and I am saddened to see people go after him in such a malicious manner on social media including members of our own

faculty. Some have now even removed him from their grant applications. These types of slanderous posts can have a negative impact on his career and should be actively discouraged. As you point out, there is a scientific process to follow and Byram would be happy to discuss these papers with any interested parties. However, he has not been given that opportunity by the people posting against him for no valid reason.

I am sure many of our students are confused and misinformed about all of this. I used to trust fact checkers. I guess that was naive. If you think of anyway we could support Byram further as a college that would be appreciated.

I have already expressed my support to him over the phone. I trust the truth will come out eventually and justice served. I am just saddened by this negative turn of events when everyone is trying their best to help find our way through this pandemic.

2001/672212000_30300AMX00231_I100

All the best during these difficult days. Bonnie

Sent from my iPad

Dr Bonnie Mallard

Professor of Immunogenetics

Ontario Veterinary College

Department Pathobiology

University of Guelph

Guelph, Ontario

Canada

On Jun 7, 2021, at 5:12 PM, Jeffrey Wichtel <jwichtel@uoguelph.ca> wrote:

Hello Bonnie,

Thanks for your question.

The College cannot place itself in a position to referee every scientific discourse in the media involving one of its faculty members. We do not comment on our faculty members' scientific positions, but we of course stand by their right to hold such positions as embodied in our commitment to freedom of expression. The nature of peer-reviewed science is that evidence is weighed by the scientific community itself, not by institutions.

I have already communicated to Byram extensively on the full range of options and supports available to him from the university and my office if he believes any conversation has, in his opinion, moved beyond normative scientific discourse and into the arena of harassment or a human rights violation.

I hope this is a helpful answer.

Thanks,

Jeff

From: Bonnie Mallard <bmallard@ovc.uoguelph.ca>
Date: Monday, June 7, 2021 at 4:18 PM
To: Shayan Sharif <shayan@uoguelph.ca>, JJW <jwichtel@uoguelph.ca>
Subject: Fwd: Facebook censors Byram's interview

Dear Jeff and Shayan - I hope you are both well. I wanted to let you know that I find it very disappointing that after Byram's interview last week the "Fact Checkers" and others on social media etc called this false news when in fact he reported on two important findings: 1 - the Pfizer report to the Japanese government (linked below, see tables on page 6-7) showing that their LNP formulation carrying mRNA is distributed within 15 minutes to most organs and tissues and remains for at least 48 hours. This bio-distribution study was done in rats which is appropriate and another study in primates showed similar results.

In addition, he spoke about an accepted peer reviewed paper by Ogata et al (authors from UoMontreal and Harvard, linked below) that showed the presence of viral spike protein in the circulation of 11 out of 12 health care workers following immunization with the mRNA 1273 vaccine. This substantiates the idea that the mRNA is being translated into spike protein in large enough quantities and finding its way from the local site/draining nodes into the circulation where it can bind to platelets and endothelial cells potentially causing damage.

This is in no way false information. In fact, it is right here in black and white along with a large number of other reports and manuscripts (I attached just a smattering) describing various concerns associated with these nucleic acid vaccines, particularly for use in children.

Why is it all of a sudden a crime or false news when a group of credible scientists offer up their valid concerns to the public, particularly about vaccinating children?

Pfizer's own studies on ~1100 vaccinated and placebo children between the ages of 12-15 years indicates 0.3-0.4% severe reactions. This would translate to about 54,000 kids in Canada. As we all know this age group is at exceedingly low risk of Covid-19. Additionally, it is becoming clear that there are effective treatments for Covid-19 which reduce any risk even further (P Kori et al Therapeutic Advance 2021).

I am wondering if our College will see fit to make some type of counter statement indicating that they do not see this as false claims but a faculty members professional assessment of reports in the literature.

It is inappropriate in my view to let Byram be slandered by all types of false claims and say nothing. I hope you can offer some suggestions to support our colleague.

All the best in these difficult days. Bonnie

https://ijvtpr.com/index.php/IJVTPR/article/download/23/49/106

https://freewestmedia.com/2021/05/26/new-pfizer-study-four-fifths-of-all-vaccinated-children-aged-12-and-over-complain-of-side-effects/

https://www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjU1qat7oXxAhXLTN8KHQXRBCAQuAIwAHoECAgQBg&url=https%3A%2F%2Fwww.youtube.com%2Fwatch%3Fv%3D60pHMK8LTm4&usg=AOvVaw3RPRLGbna0RVfUYUg9cZta

https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keab345/6225015

https://mcusercontent.com/22e41db63deaf4a84be439c0f/files/6a33980b-683f-4ee4-67d4-cc98dc7fcd37/20210601_Guide_to_COVID_19_vaccines_for_parents.pdf

https://www.lifesitenews.com/news/french-drug-assessment-center-demands-removal-of-all-four-widely-used-covid-vaccines

https://www.salk.edu/news-release/the-novel-coronavirus-spike-protein-plays-additional-key-role-in-illness/

https://www.israelnationalnews.com/News/News.aspx/304124

https://legemiddelverket.no/nyheter/expert-group-has-assessed-deaths-amongst-the-frail-elderly-following-covid-19-vaccination

https://www.pecc.org.il/docs/rasheimiflagoteng.pdf

https://www.military.com/daily-news/2021/04/26/pentagon-tracking-14-cases-of-heart-inflammation-troops-after-covid-19-shots.html

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Sent from my iPad

Dr Bonnie Mallard

Ontario Veterinary College

Department Pathobiology

University of Guelph

Guelph, Ontario

Canada

CAUTION: This email originated from outside of the University of Guelph. Do not click links or open attachments unless you recognize the sender and know the content is safe. If in doubt, forward suspicious emails to IThelp@uoguelph.ca

The Facebook censorship group sent me this notice about Byram's interview that I shared. When you click through the link in the politifact message, you get the following article.

https://www.politifact.com/factchecks/2021/jun/07/facebook-posts/no-proof-researcher-claim-covid-19-vaccines-spike-/

<IMG_1877.PNG>

<IMG_1878.jpg>

From: Bonnie Mallard
Sent: 08 June 2021 10:26
To: Jeffrey Wichtel <jwichtel@uoguelph.ca>
Cc: Shayan Sharif <shayan@uoguelph.ca>
Subject: Re: Facebook censors Byram's interview

Thanks again, Jeff. I appreciate your kindness in these difficult days. Social media has turned out to be a bit of a beast to handle.

Best. Bonnie

Sent from my iPad
Dr Bonnie Mallard
Professor of Immunogenetics
Ontario Veterinary College
Department Pathobiology
University of Guelph
Guelph, Ontario
Canada

On Jun 8, 2021, at 8:26 AM, Jeffrey Wichtel <jwichtel@uoguelph.ca> wrote:

I certainly understand how difficult this has been for Byram; it is small consolation, and it is not right, but over the past year, we have had other OVC faculty members withdraw from social media discourse because of actual threats to themselves, because of the scientific positions they have held regarding COVID-19. Sadly, social media sites and apps are not useful places to debate matters of science and truth.

We remain concerned and we have reached out often to Byram over the past weeks with the supports we can offer – Shayan, thank you for being such an empathetic and wise colleague for Byram.

Jeff

---

jwichtel@uoguelph ca
<shayan@uoguelph.ca nkarrow@uoguelph.ca

Thanks, Jeff. I fully understand that you can't get involved. I just wanted you to know that Byram is not alone in his thinking as some would have you believe. As a matter of fact, he is well supported by some outstanding international viral immunologists, geneticists and the like.

I also needed to pass those letters along as requested. There is a group of colleagues that want to show support for Byram, and I totally appreciate that since academic freedom is being threatened if these other faculty get their way.

All the best during these troubling times. Bonnie

Sent from my iPad
Dr Bonnie Mallard
Ontario Veterinary College
Department Pathobiology
University of Guelph
Guelph, Ontario
Canada

On Jul 7, 2021, at 6:50 PM, Jeffrey Wichtel <jwichtel@uoguelph.ca> wrote:

Thanks Bonnie.

I agree that the debate on public health measures to combat COVID-19 has been vigorous and emotionally charged. Sadly, many of our OVC faculty members have been subject to regrettable commentary in the media, social and otherwise, and this has been the case since spring 2020. As an employer we offer the supports we can and of course hold our employees to acceptable standards of professional behaviour when using UofG-sanctioned communication channels with such as email or verbal communication in the workplace, per our established HR policies.

I will repeat my message to you of June 7: the College cannot place itself in a position to referee scientific discourse in the media involving one of its faculty members, and letters of support or detraction for one view or another do not change this. We do not align ourselves with our faculty members' scientific positions, but we of course stand by their right to hold such positions as embodied in our commitment to freedom of

expression. The nature of peer-reviewed science is that evidence is weighed by the scientific community itself, not by institutions. I have already communicated to Byram extensively on the full range of options and supports available to him from the university.

Thanks again for your comments,

Jeff

From: Bonnie Mallard <bmallard@ovc.uoguelph.ca>
Date: Wednesday, July 7, 2021 at 5:18 PM
To: JJW <jwichtel@uoguelph.ca>, Shayan Sharif <shayan@uoguelph.ca>, Vice President Research <vpres@uoguelph.ca>, Cate Dewey <c.dewey@exec.uoguelph.ca>, Tarek Saleh <tsaleh@uoguelph.ca>, Todd Duffield <tduffiel@uoguelph.ca>, Brandon Lillie <blillie@uoguelph.ca>, cyates <cyates@uoguelph.ca>, Gwen Chapman <gwen.chapman@uoguelph.ca>
Cc: "Tenenbaum, Howard" <Howard.Tenenbaum@sinaihealth.ca>, Paul Elias Alexander <elias98_99@yahoo.com>, Niel Karrow <nkarrow@uoguelph.ca>, Ira Bernstein <ira.bernstein@utoronto.ca>, Chris Shaw <cashawlab@gmail.com>, David Ross <davidarossfca@gmail.com>, Dr Michael Palmer <mpalmer@uwaterloo.ca>, Philip Oldfield <philip.oldfield@poldfieldbc.com>, Francis Christian <fchristian@me.com>, "Robert Malone (rwmalonemd@gmail.com)" <rwmalonemd@gmail.com>, Stephen Malthouse <smalthouse@protonmail.com>
Subject: Open Letter Against Prof Byram Bridle

Hi All - I am including you on this email since I think you are already aware of the disruptive open letter against Dr Bridle by several of our faculty. As you can imagine I am extremely disappointed to see the open letter in worms and germs (https://www.wormsandgermsblog.com/) against Byram's view of the literature on the topic of SARS-CoV-2 and related vaccines. It seems some people view his thoughts on the evidence as misinformation, but I can assure you that not all academics have the same opinion. In fact, even Dr Robert Malone, one of the original inventors of the mRNA vaccine platform, agrees with Byram's assessment of the literature (see attached letter from Malone), and recommends some cautions around vaccination of children, as does the WHO. Byram's position is not out of line with that of the WHO and for solid reasons based on emerging data in the literature.

I also have been alarmed to see the false websites, build by unknown people, using Byram's name. There are also members of our faculty that spend large junk of their time on social media twitting out insults about Dr Bridle's credentials and opinions. This is unethical in my opinion, particularly when they have not tried to speak to Byram about the literature or the logic that he is using to comes to his conclusions about the potential toxicity of the spike protein and cautions around vaccinating kids. In fact, it is commonly accepted by most people working in the field that the spike protein has toxic potential and contains a toxic-like epitope (see Lagoumintzis et al., Food and Chemical Toxicology 149:112009, 2021). This is not to be misconstrued that every person coming in contact with the SAR-CoV-2 spike protein will feel toxic effects. In fact, there is still a great deal to learn about this virus and the LNP mRNA vaccines. This is part of the rationale used by Dr Bridle to suggest cautions around child vaccination.

Researchers and physicians from around the world have been contacting me with notes and letters of support for Dr Bridle since they are also alarmed about potential impact on academic freedom. On their behalf, I am attaching a selection of these letters here, so you are aware that he has passionate support from many in the scientific community. I have enjoyed reading these letters and found them very informative. I hope you will take time to do the same.

Many more letters and emails are piling in, and I am sure that Dr Bridle's inbox will be full by the time he comes back from holidays.

I am thankful that the UoG supports academic freedom, but it is disheartening when people call solid scientific evidence, although it may go against the current popular narrative, misinformation. That just is not the case. History will eventually bear out the truth.

I would be happy to discuss this further at any time.

All the best. Bonnie

Dr. Bonnie A Mallard (PhD)
Professor of Immuno-Genetics
Department of Pathobiology
University of Guelph
Guelph, Ontario
N0B 1B0

bmallard@uoguelph.ca

From: Bonnie Mallard
Sent: 09 September 2021 00:22
To: Brandon Lillie <blillie@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>; Jeffrey Wichtel <jwichtel@uoguelph.ca>; Cate Dewey <c.dewey@exec.uoguelph.ca>
Cc: Niel Karrow <nkarrow@uoguelph.ca>
Subject: Fwd: Department of Pathobiology

I totally agree with Niel that this is getting completely out of hand. What a disgrace to our department , college and university.

Scott has been tweeting slanderous comments against Byram for months now and nothing has been done to stop it.

Meanwhile, Byram is the one being accused of harassment. I think the shoe is on the wrong foot here.

In my 30 years as faculty I have never seen such nonsense. To call Byram an anti-Vaxxer is completely ridiculous since his entire career revolves around vaccine production. Showing a picture of a person shovelling manure and implying this is Byram is beyond belief.

Since when do we not accept other faculty with alternative points of view rather than slandering them on social media.

This must stop. Our department and college is becoming a laughing stock. Bonnie

This is Exhibit "K" to the Affidavit

of Bonnie Mallard, sworn before me

on this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

Faculty and staff at the University of Guelph support SARS-CoV-2 vaccine safety

July 6, 2021

We are a science-based faculty and staff at the University of Guelph who support evidence-based decisions and disagree with misinformation being circulated by a member of the faculty at the Ontario Veterinary College.

COVID-19 is an unprecedented pandemic due to a novel coronavirus. Nearly four million people globally have died as a result, and nearly two hundred million have been reported as infected.[1] Many millions more have suffered and continue to suffer from physical and mental illness associated with the pandemic, isolation, poverty, and the long-term effects of the infection.[2]

Vaccines for SARS-CoV-2 were designed, tested and produced at an unprecedented speed and on an extraordinary scale. The ability to quickly develop safe and effective vaccines was made possible through remarkable global co-operation and by concurrently running clinical trials, not by cutting corners. Many countries rapidly authorized vaccines for emergency use. Various types of vaccines are available, including those based on mRNA coding for the viral spike (S) protein, vector-based DNA vaccines coding for the S protein, and recombinant S protein particles. Two doses of the vaccines (type-dependent) have dramatically reduced illness and infections in many parts of the world.[3] The vaccines are highly effective and have very few adverse effects.[4] The coordinated effort of scientists, pharmaceutical companies, public health and regulatory agencies to produce effective vaccines against COVID-19 for billions of people in less than a year is an achievement previously unimaginable.

Dr. Byram Bridle has stated on multiple platforms and numerous outlets that COVID-19 vaccines are unsafe. These statements are contrary to overwhelming scientific evidence. The S protein generated by or incorporated into vaccines is an effective immunogen but does not alter DNA, does not induce infertility or pass through breast milk, and is not a toxin.[5, 6] Adverse vaccine effects do occur but at a similar or lower frequency than for routine vaccines.[4] In the face of this terrible pandemic, widespread vaccination is the best way out of the devastation we currently face. Many people have limited understanding of the complexities of immunization against infectious agents, and rely on scientists in epidemiology and immunology to share their knowledge and experience, especially at times such as these when fear is high. Misinformation spread by individuals such as Dr. Bridle targets uncertainty.

The University of Guelph, including us, supports freedom of expression. However, as scientists and academics we also have a responsibility to counter misinformation, particularly when the misinformation causes harm. A high rate of vaccine acceptance is essential for prevention of SARS-CoV-2 disease and deaths, and for a return to normalcy. In particular, given the high transmissibility of recent variants, very high vaccination rates among people eligible for vaccination are critical. We are very concerned that people who are not seeking vaccination because of misinformation will suffer ill effects from SARS-CoV-2 infection, will infect others, and will slow the return to a more normal life. Academic freedom is important but should not be a license to spread misinformation that has been clearly refuted, including by authors of publications that Dr. Bridle cites in support of his statements.[7] Some may even consider the University of Guelph complicit by failing to provide a clear and effective response to this misinformation

campaign, which is impacting the reputation of the institution and its faculty. Considering the harmful effects of COVID-19 on individuals and communities, the continued spread of misinformation undermines Canadian public health measures, including our vaccine program, and threatens global health security more broadly.

Therefore, we wish to state publicly that as scientists, faculty, and/or staff of the University of Guelph we stand firmly against the continued spread of factually incorrect and misleading information that is being disseminated by Dr. Bridle. We have confidence that the SARS-CoV-2 vaccines approved for use in Canada are safe and effective, and we wish to reassure the public that as members of the University of Guelph community we fully support evidence-based public health, which includes vaccination against COVID-19.

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Supporting signatures from University of Guelph faculty and staff

Name, Credentials	Title	University of Guelph College
Amy Greer, MSc, PhD	Canada Research Chair in Population Disease Modelling and Associate Professor	Ontario Veterinary College
Dorothee Bienzle, DVM, PhD	Professor of Veterinary Pathology	Ontario Veterinary College
Scott Weese DVM DVSc DACVIM FCAHS	Director, Centre for Public Health and Zoonoses	Ontario Veterinary College
Glen Pyle, PhD	Professor of Biomedical Sciences	Ontario Veterinary College
Sarah Adamowicz, PhD	Associate Professor & Director of Bioinformatics Graduate Program, Integrative Biology	College of Biological Science
Emma Allen-Vercoe, PhD	Professor; Canada Research Chair in Human Gut Microbiome Function and Host Interactions	College of Biological Science

Ryan Appleby, DVM, DACVR	Assistant Professor, Clinical Studies	Ontario Veterinary College
Luis G. Arroyo, Lic. Vet Med. DVSc, PhD, DACVIM	Associate Professor, Clinical Studies	Ontario Veterinary College
Daniel Ashlock, PhD	Professor and Chair, Mathematics and Statistics	College of Physical and Engineering Sciences
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DVSc DACVS		
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Steffen Graether, PhD	Professor, Molecular and Cellular Biology	College of Biological Science
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Jutta Hammermueller PhD	Staff, Pathobiology	Ontario Veterinary College
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Paul Hebert PhD, FRSC	Professor & Canada Research Chair in Molecular Biodiversity	College of Biological Science
Stephen Henighan, PhD	Professor, School of Languages and Literature	College of Arts
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Claire Jardine, DVM, PhD	Associate Professor, Pathobiology	Ontario Veterinary College

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Zvonimir Poljak, DVM, PhD	Associate Professor, Population Medicine	Ontario Veterinary College
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Katherine Preuss, PhD	Professor, Research Leadership Chair, and Chair of Chemistry	College of Engineering and Physical Science
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Alex zur Linden, DVM, DACVR	Associate Professor, Clinical Studies	Ontario Veterinary College

This is Exhibit "L" to the Affidavit of

Bonnie Mallard, sworn before me on

this 15th day of December 2023

A Commissioner for Taking Affidavits

Amina Sherazee Barrister and Solicitor

JULY 2021

To whom it may concern,

We offer this letter in support of Professor Bridle's exemplary character and scientific intellect, and, most importantly, his right to express his scientific opinions freely and unfettered. We believe the opinions he has expressed regarding SARS-CoV-2 and the new mRNA/DNA vaccinations have always been underpinned and substantiated by the published literature and deductive reasoning. Although his opinions might appear to be contrary to the prevailing narrative, we state emphatically that this is even more reason for him to be permitted to express his thoughts freely and without fear of official censure and abuse.

The very essence of scientific inquiry is based on the principle of constant interrogative thinking and a healthy degree of skepticism and debate in relation to any one biological phenomenon (which applies to other areas of research as well). However, it is with great alarm and deep concern for the principles of the scientific method that we have seen Professor Bridle's very character impugned as he dared to rely on the accumulative scientific data to support his call for the application of caution in relation to the current nucleic acid-based therapy-based vaccinations for COVID-19. In fact, we are disturbed to see the depths to which those who do not agree with him have sunk, including some of his local colleagues. The critical letters, false websites, tweets and posts being sent to attack his character and qualifications are at best sophomoric, and at worse childish, if not criminal. Is it no longer possible to have scientific disagreements without resorting to character assassination? If this is the case, then the pursuit and application of science is in possible jeopardy. The public, which provides the main source of research funding through various government agencies, will no longer be able to trust that unbiased and open scientific debate surrounding new technologies or data still occurs. If we are fortunate, perhaps science is only in a holding pattern and we can still rescue this noble discipline. However, this will occur only if the scientific community is willing to have open conversations about the facts from all viewpoints without resorting to ad hominem attacks or other forms of unfair and wholly inappropriate acts of overt and often times publicly aired vengeance! A return to 'sober scientific thought and argumentation', is the only way we will be able to rebuild trust among the public.

The COVID-19 pandemic has brought a high degree of uncertainty, along with novel technologies that have not been tested widely in humans until now. We recognize and appreciate that these vaccines were developed with the best of intentions, but when serious signals of injury are being observed (as is the case now, Figure 1), the prudent and wise decision is to pause vaccination programs. This is particularly so with the young who are actually at low risk of serious illness with COVID-19, but are currently developing myocarditis following vaccination at an alarming rate! Unfortunately, those that develop myocarditis do not fully 'recover' and are at increased long term risk for an array of cardiological problems ranging from arrhythmias to cardiomyopathy! This alone can be taken as a sign that issues pertaining to the new vaccines must be elucidated, and the science behind the vaccines must be open to scrutiny and debate.

Yet it has been difficult to challenge some of the new ideas due to the sense of urgency. However, it is exactly at times like his that it is critical for all voices to be heard so that regrettable errors can be detected early to prevent serious clinical roblems that might arise in people who have been vaccinated. We see Professor Bridle as one of those expert voices ncouraging people to think carefully about all the evidence and being willing to change direction as warranted when new ata comes to light. Yet, despite the scientific validity of his concerns (echoed recently by a Senior Editor of the British Medical Journal - Peter Doshi, one of the original inventors of nucleic acid vaccine platforms – Dr. Robert Malone, the WHO, and countless others), his messaging and his professional character are being attacked. We do not object to those who argue with his conclusions as this is the very ethos of scientific inquiry. However, we cannot support those who attack is credentials and character or try to remove his presentations from public view.

y its very nature, drug development, and the science associated with this endeavor require that as new data emerge, new inking, possibly even changing of the course of investigation are critically important. In fact, we applaud Professor ridle's courage to bring a debate forward despite knowing that his message might (and evidently has) result(ed) in harsh

confrontation. Professor Bridle has a proven track record in viral immunology, the two key disciplines most closely aligned with understanding and responding to the SARS-CoV-2 viral pandemic. Professor Bridle's expertise has been recognized nationally and internationally. For example, Professor Bridle was the recipient of the 2020 Zoetis Award for Research Excellence at the University of Guelph. He has also made important and novel contributions to the field of cancer research and vaccinology, especially in the development of novel biotherapies. With this in-depth knowledge and experience in hand, he is well-equipped, perhaps better than most that have argued against him, to discuss the virus and the technologies currently employed for its control.

Although the type of criticism Professor Bridle is receiving is not unexpected, it is grossly unethical to take this opportunity to defame his character or to demand the removal of his funding from agencies by which he has been respected and closely aligned for years. This is in fact contemptible. As fellow scientists, we are appalled to see emails to funding agencies demanding the removal of Dr. Bridle's funding. Where would we be without courageous researchers willing to stand up for their ideas and debate the science openly? Many key discoveries would have been lost if others were not willing to listen and exchange ideas.

It has been deplorable to see colleagues berating Professor Bridle on Twitter and Facebook without so much as contacting him to ask for a discussion of the issues. In fact, not one colleague who signed the recent open letter in the "Worms and Germs" blog (www.wormsandgermsblog.com) has taken the time to contact Professor Bridle to discuss his thinking around the literature that he cites. The core academic group, and many others of us signing this petition have taken the opportunity to personally discuss these ideas with Professor Bridle on numerous occasions. Although we may not always endorse every idea he has put forward, we agree totally with a need for caution around the vaccination of children under 18 years of age, particularly without parental consent. We also fully support his right to freedom of speech and academic freedom so that he can express as freely as possible his scientific ideas, which are motivated by his desire to serve and protect the Canadian public.

We also point out that it seems pusillanimous that many of the complaints against Professor Bridle have come from anonymous 'keyboard warriors'. Those who do not provide their identities and are not willing to engage in a fair and open debate of these ideas in front of the public have no business to deride Professor Bridle, although they too have the freedom to be critical of his opinions, even if they (the detractors) are right or wrong. If they are confident that Professor Bridle and others are incorrect, why are his critics unwilling to participate in an open conversation or even a debate? Along these lines, Professor Bridle and many other colleagues requested that the Premier of Ontario, Doug Ford, and any members of the Ontario COVID Task Force participate in an open forum. This invitation was not acknowledged except by local MPs, and no invitation accepted. Invitations to specific colleagues posting negative comments on social media, including those that initiated the open letter in Worms and Germs, have also not been accepted. We believe, given the critical nature of this matter, the issues surrounding COVID vaccinations should be debated in front of the Canadian public by people with differing views. We are confident in the ability of Canadians to draw their own well-thought out conclusions, provided that they are given the opportunity to listen to and think about all sides of the argument whether or not they agree with Professor Bridle.

We were also shocked that individuals, also unknown, have made websites using his name (e.g. https://byrambridle.com/) to post harmful and slanderous comments about Professor Bridle. This site is replete with disinformation and outright lies, which are being promulgated to defame Professor Bridle. Then there are the 'fact checkers'! What, exactly are their credentials? Who are they? And when one reads their so-called fact-checks, it becomes painfully obvious that apart from attacking Professor Bridle or simply being dismissive of his comments, these ghost-like 'experts' cannot challenge Professor Bridle on any grounds that have any scientific merit.

With respect to his position regarding the spike protein being a concern given its vaccine-induced expression in various tissues, including immune privileged sites, there are now many publications demonstrating precisely that the spike protein can be hazardous. We have provided limited reference here, since we are addressing the bigger issues of academic freedom, but will provide more upon request. However, a few key publications are worth mentioning since the idea of the SARS-CoV-2 spike protein being pathogenic seems to be what is most troubling to Professor Bridle's detractors.

(VIRAL IMMUNOLOGIST -UNIVERSITY OF GUELPH, GUELPH, ONTARIO, CANADA)"

A recent paper by Ogata *et al.* (2021) published in Clinical Infectious Diseases (https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab465/6279075) showed that plasma collected from 11 of 13 health care workers had detectable levels of spike protein and/or S1 antigens as early as one day and up to 28 days (in one individual) following vaccination with the mRNA-1273 Moderna vaccine. Although the amounts of spike proteins were low, it is worthy of further investigation for a number of reasons:

1. Reports of vaccine adverse events such as vaccine-induced thrombocytopenia (VITT) and myocarditis, associated with both the mRNA and DNA vaccines, seem to be due, at least in part, to binding of spike protein to the ACE2 receptor on endothelial cells within the blood vessels. VITT was a key reason why the AstraZeneca vaccine was eventually suspended in Canada and elsewhere.
2. The Pfizer biodistribution data sent to the Japanese regulatory authorities demonstrating in rodents that within 15 minutes of immunization the lipid nanoparticles (LNPs) carrying a mRNA construct could be found in multiple organs and tissues including the blood, bone marrow, brain, ovaries, liver, spleen, adrenal glands and other sites (https://www.naturalnews.com/files/Pfizer-bio-distribution-confidential-document-translated-to-english.pdf). This was of concern, since following traditional vaccination the foreign protein would be expected to stay close to the site of injection and the draining lymph-nodes, but not migrate to various tissues, particularly immune-privileged sites where expression of foreign protein can induce inflammatory damage. These results should at least be confirmed in other species before further vaccination of children. Also, traditional vaccines deliver a known amount of foreign protein, whereas the mRNA and DNA vaccines rely on the host to produce an unknown amount of foreign spike protein. Children may be different than adults with respect to the amount of spike protein they produce due to effects of age and metabolism.
3. The publication by Zhang and Shyy *et al.* (2021) in Circulation Research (https://www.ahajournals.org/doi/full/10.1161/CIRCRESAHA.121.318902) showing that the viral spike protein plays a key role in the disease itself, by allowing attack of the vascular system at the cellular level. This again pointed to a potential concern about any amount of spike protein induction in the circulation.
4. A publication (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7758180/) by Nuovo *et al.* (2021) in the Annals of Diagnostic Pathology showing endothelial cell damage, including within the microvessels of the brain, could readily be induced by viral S1 subunit injection in mice.
5. A recent preprint (https://www.biorxiv.org/content/10.1101/2021.06.25.449905v1) by Patterson *et al.* (2021) showing that human non-classical monocytes capable of causing inflammation, and found in circulation, can carry SARS-CoV-2 S1 protein up to 15 months following infection. In a recent online interview with Dr. Bruce Patterson, he stated that similar observations have been seen post-vaccination. He noted spike proteins carried for many months in monocytic cells associated with long-term effects of COVID-19, and possibly long-term adverse vaccines effects. This requires further investigation.
6. A couple of small studies, one by *Low et al.* (2021) indicated that following BNT162b2 vaccination, there is at least a minimal transfer of vaccine mRNA secretion into human milk (up to 2 ng/ml) (https://doi.org/10.1101/2021.04.27.21256151) and another study by Bertrant *et al.* (2021) documented that a few infants experienced some adverse symptoms, although mild, following suckling from vaccinated mothers. These are small studies imply that vaccine mRNA can be transferred from mothers to infants in breast milk and may cause some symptoms in the children. https://doi.org/10.1101/2021.04.21.21255841).
7. A publication (https://pubmed.ncbi.nlm.nih.gov/33503469/) by Lagoumintzis *et al.* (2021) indicating a small "toxin-like" epitope on the viral spike glycoprotein with homology to a snake venom toxin also requires further investigation.

Many of the troubling features of the SARS-CoV-2 spike protein occur following natural infection, but the difference is that using LNPs has the potential to quickly deliver the mRNA encoding spike to almost all tissues examined. The current mRNA and DNA vaccine platforms are also designed to induce high expression of stable spike on the cell surface, and an inflammatory response is directed against the transfected cells rather than just the virus. Moreover, it seems that whenever the viral spike protein gets into circulation, there is the potential for additional adverse reactions. Even with rare adverse events, this is a large number of people to consider with mass vaccination. We could provide many more publications for discussion, but the aforementioned should be sufficient evidence to help people understand why Professor Bridle suggested

pausing the mass vaccination of children. This recommendation is also in line with a recent WHO cautionary note around the vaccination of children which states "there is not yet enough evidence on the use of vaccines against COVID-19 in children to make recommendation for children to be vaccinated against COVID-19".

These concerning and emerging findings regarding the viral spike protein were unanticipated by all of us, including Dr. Bridle, who admits this openly. However, when Professor Bridle became aware of research showing that the spike protein could be toxic, he concluded that suspending the roll out of these vaccines for children, particularly without parental consent, would be the prudent course of action. Therefore, it is our opinion that Professor Bridle, as an ethical scientist, had no choice but to speak out. His views have not been challenged on a scientific level, and he continues to be open to conversation around these issues. In fact, many world experts agree with his concerns. He participated in international symposia when invited (e.g. COVID Plan B 2020 and 2021, and was hosted by respected colleagues in New Zealand, https://www.covidplanb.co.nz/). He also gave several very informative interviews to the media. The fact that some of these presentations or interviews caused discomfort and debate is not a crime, but is rather a breath of fresh air in what has become a highly censored environment. This environment is tantamount to an echo chamber where those who do not conform are shamed and ridiculed. This is completely anathema to scientific discourse, and is also antithetical to the principles of free speech that are linked inextricably to the maintenance, and improvement of a free and open society.

We also note people's concerns about the variants of concern, including the Delta variant, which is still relatively minor in Canada, but now the most prevalent SARS-CoV-2 strain in England. The current data indicates that although the Delta variant is more transmissible, it is not more virulent. Figure 2 shows that hospitalization rates in England remained low even as the Delta variant became the dominant strain. There is no need for causing further alarm to the public, but rather simply report the facts. Figure 3 indicates death rates in Canada by province also continue to decline. Interestingly, although the overall death rate remains low, the Delta variant appears to be causing more deaths in the vaccinated than the non-vaccinated. The reasons for this are currently being considered, but firm conclusions have not yet been drawn. However, it is well known that the current vaccines do not prevent transmission in a significant portion of vaccinated people.

Another reason for the currently low death and hospitalization rates could be the approach of herd immunity. In fact, several papers point to solid immunity following recovery from COVID-19 (reviewed in https://www.cell.com/cell/pdf/S0092-8674). One publication by a Canadian group reported that >90% of people in the Vancouver area already possessed antibodies to the spike, nucleocapsid and other viral peptides of the SARS-CoV-2 virus (https://insight.jci.org/articles/view/146316). Antibodies are a good indicator of immunity to this virus. Although not every person will produce antibodies following COVID-19, the vast majority will, and since very few people are re-infected one can safely assume that memory cells are also generated. The sophisticated SARS-CoV-2 antibody mapping array described in the paper by Majdoubi *et al.* (2021) was developed in Canada and is an excellent tool that can be used to determine the current level of population immunity in Canada. Immunity from natural exposure to this virus is likely to provide a more broad-based level of protection than vaccine-induce immunity, since the immune system gets to recognize all parts of the virus as opposed to just the spike protein. This could be assessed prior to vaccination, particularly as an alternative vaccinating children until more evidence is available.

Professor Bridle is also well-known for his collaborative research efforts with colleagues at eighteen Canadian institutions. This has best been exemplified by Professor Bridle being a founding member of the highly successful National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx), as well as being one of fifteen members of the pan-Canadian collaborative research network known as the Canadian Oncolytic Virus Consortium (OVC). These collaborations have led to unique opportunities for highly qualified personnel from OVC to gain interdisciplinary training. Further, these collaborative networks have generated several clinical trials and a spin-off company known as Turnstone Biologics. He has also had notably productive collaborations with scientists such as Dr. Grant McFadden at Arizona State University (a leader in the field of oncolytic virotherapy research) and Dr. Jack Lawler at Harvard University (a leader in the field of cancer vascular normalization research); Professor Bridle has co-authored publications with both. We see no reason for funding agencies to suddenly change their minds about the worth of Professor Bridle's contributions or critical thinking skills. Professor Bridle is making unique and important contributions to his discipline, and we can see no reason that this should not continue well into the future. It would be a great loss for our country to defame one of its own topflight scientists, because he is courageous enough to bring forth a difference of opinion. And to reiterate, his opinions relating to the spike

protein, as well as the narrow immunity offered by the mRNA and DNA vaccines are supported by many highly credentialed scientists around the globe, including but not limited to Professor Robert Malone, one of the originators of mRNA technological platforms (https://youtu.be/U1pEtrEr2_s).

Professor Bridle's research over the last several years has been funded by numerous granting agencies including the prestigious Terry Fox Research Institute New Investigator Award, Terry Fox Research Institute Program Project Grant, one Catalyst Grant and one Enabling Grant from BioCanRx, an Innovation Grant that was jointly funded by the Canadian Cancer Society and the CIHR – Institute for Cancer Research (ICR), an Operating Grant that was funded jointly by the Cancer Research Society and the CIHR-ICR), an NSERC Discovery Grant, an operating grant from the Smiling Blue Skies Cancer Fund, and operating grants from the Pet Trust Fund (he was the principal investigator on three and a co-applicant on three). He currently holds government grants to help develop safe and efficacious vaccines against COVID-19. Simply put, he is eminently qualified to speak on this topic.

As colleagues of Professor Bridle, we strongly support his rights to speak as an informed educator and researcher on the topic of COVID-19 vaccination. We fully acknowledge the benefits of vaccination in general, but under the circumstance, support that out of an abundance of caution we should pause mass vaccination of children until we understand the features of the novel nucleic acid vaccines more fully. There are plenty of red flags at the moment and although we are well aware that many governments are moving ahead with mass vaccination of children, we cannot endorse this policy without further investigation.

Figures 1a and b. Number of reported vaccine adverse reactions in US VAERS to June 25, 2021. To date COVID-19-related deaths account for 42% of all vaccine-related deaths in VAERS since it started in 1990 (www.openvaers.com). The reasons for this need to be better understood, but should also be seen as a cautionary sign until further studies are available. It has been estimated that only about 2% of vaccine adverse reactions ever get reported in VAERS.

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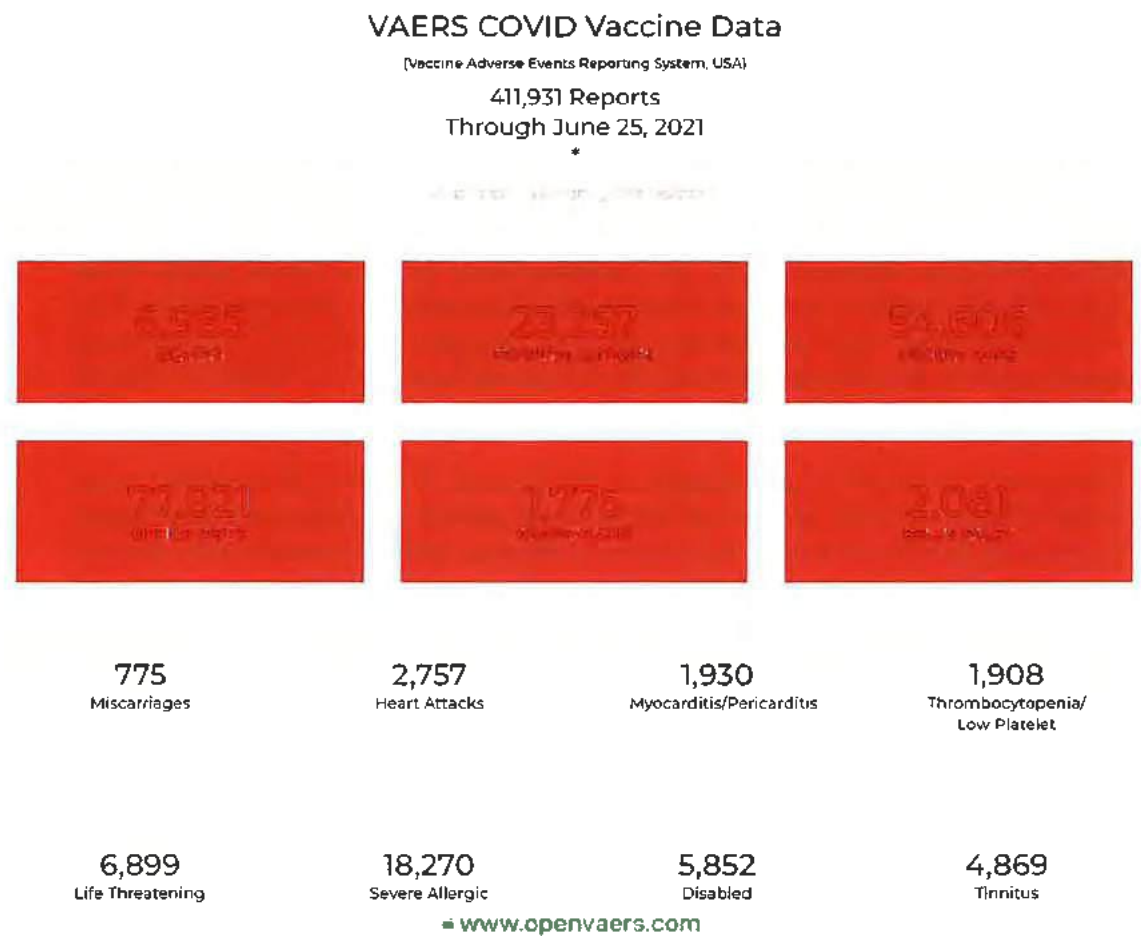


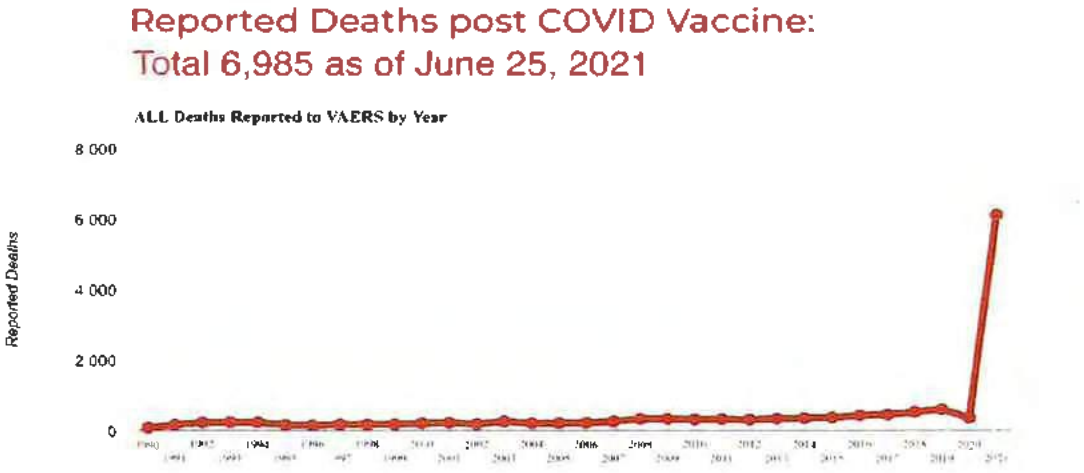


Figure 2. Variant prevalence for all available sequenced cases in England from February 1, 2021 to June 14, 2021 and correlation with hospitalization. Note that the percentage of sequenced SARS-CoV-2 cases corresponding to the Delta variant increased from 5 to 90% from the beginning of April to mid-June (shown in light purple), whereas hospitalization remained low in the same period.

(VIRAL IMMUNOLOGIST -UNIVERSITY OF GUELPH, GUELPH, ONTARIO, CANADA)"

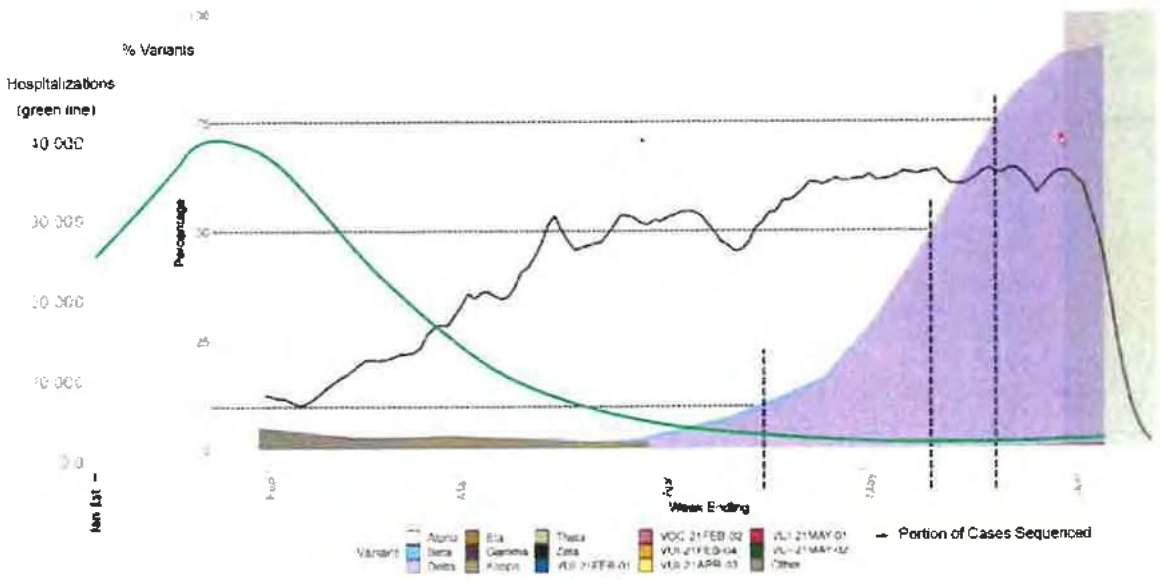
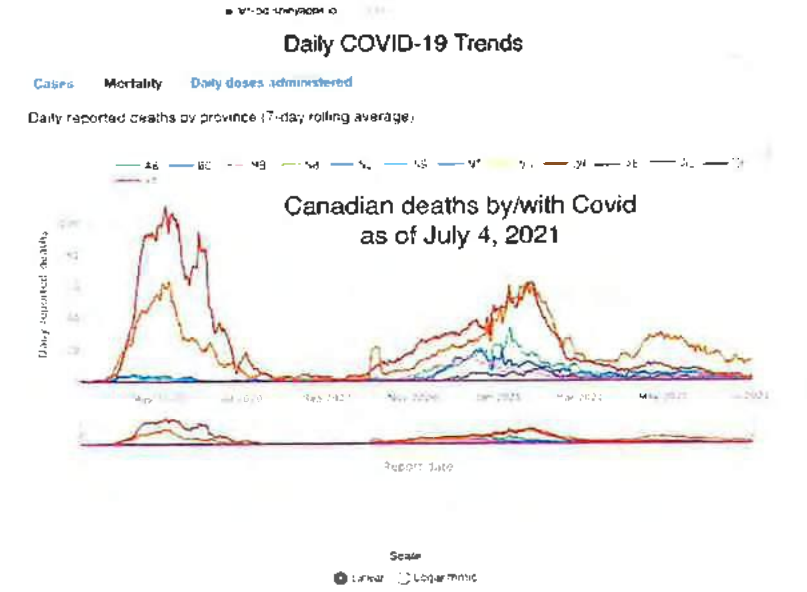


Figure 3. Daily CovidCOVID-19 deaths in Canada by province



These charts may be viewed on a linear scale (the default) or a logarithmic scale. The choice of scale changes the representation of the plot. Select the scale using the button above. Additionally, the total range of data displayed may be changed using the range slider below the plot. By default, the entire range of data is shown.

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Appendix 1. **Signatures from 430 Professionals (Worldwide)** in Support of this "OPEN LETTER IN SUPPORT OF PROFESSOR BYRAM BRIDLE (VIRAL IMMUNOLOGIST -UNIVERSITY OF GUELPH, GUELPH, ONTARIO, CANADA)"

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Shannon Gaetz
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George Gillson MD PhD
Medical Director Rocky Mountain Analytical, LifeLabs
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Laveryne Green BScN
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Roger Hodkinson Pathologist
Dr, Stop the Shot
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Medical Doctor, RETIRED
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Samantha Bailey MBChB
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Pathologist, Southern Community Laboratories,
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Tracy Chandler MB ChB
Dr for 21 years, MCNZ
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Ananish Chaudhuri Ph.D. in Economics
Professor of Behavioural and Experimental Economics; Author: "Nudged into lockdown? Behavioural Economics, Uncertainty and Covid-19", University of Auckland
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Librarian, researcher
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Jessica McEachern Registered Counselling Therapist, RCT-C
Psychotherapist, NSCCT
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Colin Petherick FDS MB BCH
Oral Surgeon, Oral Surgery NHS private/care
United Kingdom

Susan Ratky Ball BSc Biology (UofGuelph)
PhD Biochem (London University)
Retired, Researcher, Clinical Pathology,
Retired, St. Bartholomew's Hospital,
London,
United Kingdom

Mike Yeadon PhD
R&D new medicines professional industry, Own consulting company
United Kingdom

Robert Malone
Original inventor of the mRNA vaccine technology.Consulting Analytics, BiopharmaHebron Valley Rd, Madison, VA, USA
Virginia

Elizabeth Mumper MD
Pediatrician, Advocates for Children
Virginia

Brad Hine PhD, Research Scientist
Immunology, CSIRO, Australia

Appendix 2. **Signatures from 7807 members of the General Public (Worldwide)** in Support of this "OPEN LETTER IN SUPPORT OF PROFESSOR BYRAM BRIDLE (VIRAL IMMUNOLOGIST -UNIVERSITY OF GUELPH, GUELPH, ONTARIO, CANADA)"

Odette Abaco
Alberta

Renata Abramowicz
Alberta

Janet Adair
Alberta

Yvonne Affleck
Alberta

Marjorie Aiken
Alberta

Koula Alder
Alberta

Randy Allan
Alberta

Louise Allison
Alberta

Maureen Amonson
Alberta

Brad Anderson
Alberta

Joyce Anderson
Alberta

Brad Anderson
Alberta

Pat Andrusiak
Alberta

Jill Applegates
Alberta

Catherine Appler
Alberta

Lauren Appleton
Alberta

Lisa Archer
Alberta

Kathy Armes
Alberta

Kevin Armstrong
Alberta

Tannis Arychuk
Alberta

Leo Auger
Alberta

Thea Avis
Alberta

Alison B
Alberta

Christina Babbage
Alberta

Joanne Bacon
Alberta

Wendy Bain
Alberta

Galina Bala
Alberta

Carla Banks
Alberta

Lauren Banman
Alberta

Claudette Barber
Alberta

Jessica Baron
Alberta

P Bart
Alberta

Elaine Beever
Alberta

Richard Beever
Alberta

Susan Bell
Alberta

Randy Bell
Alberta

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Marg Belu Alberta	Cory Bergovich Alberta	Catherine Bergquist Alberta	Apryl Bergstrom Alberta
Judy Bernes Alberta	Leigh Ann Betts Alberta	Martina Bevelaqua Alberta	Richard Beyer Alberta
Rochelke Biffart Alberta	Theresa Bills Alberta	Mary Binette Alberta	Arlene Birnie-Browne Alberta
Avery Bishop Alberta	Andrew Blair Alberta	Margaret Bleakley Alberta	Matthew Bloom Alberta
Walter Boldt Alberta	Scott Bonnar Alberta	Alice Bootsveld Alberta	stefan bossart Alberta
Ken Bouchard Alberta	Connie Boutkan Alberta	Diane Bowen Alberta	WILLIAM BOYCE Alberta
Diana Braine Alberta	Dietmar Brand Alberta	Sharon Branston Alberta	Candace Braun Alberta
ka braun alberta	Amanda Braun Alberta	Grace Breitkreuz Alberta	Richard Breitling Alberta
Lori Briggs Alberta	Charles Briggs Alberta	Ryan Broadfoot Alberta	Anick Brouillet Alberta
Caitlyn Brousson Alberta	Danae Brousson Alberta	Sammie Brown Alberta	Teena Brown Alberta
Annette Brunet Alberta	Deby Bryan Alberta	Terry Burton Alberta	Sherry Butler Alberta

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Verlean Buziak
Alberta

Linda Byram
Alberta

Jeremiah C
Alberta

Kevin Caissie
Alberta

Darlene Callbeck
Alberta

Lorna Calvert
Alberta

Shivonne Cameron
Alberta

Deborah Campbell
Alberta

Rhonda Cannon
Alberta

Carrie Carriere
Alberta

Shelley carrington
Alberta

Tessa Carruthers
Alberta

Pia Casello
Alberta

Sharon Caswell
Alberta

Kenn Chabra
Alberta

Jill Chambers
Alberta

Jess Chase
Alberta

Zhiyi Chen
Alberta

marie cherneske
Alberta

Lisa Chertba
Alberta

Nattolie Chilton
Alberta

George Chorney
Alberta

Kira Christoffersson
Alberta

Marcie Clare
Alberta

Linda Clark
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Brittany Clark
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Kathy Clark
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Brittany Clark
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F. Moira Clarke
Alberta

Terri-Lynn Clement
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Ronald Clements
Alberta

Kylie Clifton
Alberta

Judith Coates
Alberta

Christina Collins
Alberta

Heather Cook
Alberta

Colin Cooper
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Mary Cooper
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Carolyn Corbett
Alberta

Katherine Cornelius
Alberta

Samantha Cote
Alberta

Cheryl Coulton
Alberta

Joyce Cowper-Smith
Alberta

Karen Cox
Alberta

Sebastian Cox
Alberta

Carla Cox
Alberta

Carolin J. Crofts
Alberta

Claudine Crook
Alberta

Robin Crosby
Alberta

Carly Crossbeam
Alberta

Sandra Csizmadia
Alberta

Vaughn Cutts
Alberta

Gail Damico
Alberta

Jim Daskalopoulos
Alberta

Aaron Davey
Alberta

June David
Alberta

Lynn Dawe
Alberta

Rlizabeth Dehghani
Alberta

Manochehr Dehghani
Alberta

David Demeria
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Travis Demey
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Beverley Denby
Alberta

Foon Der
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Jimmy Desbiens
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Brad Devereux
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Norm Dyck
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Margaret Dyck
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Axel Dyckerhoff
Alberta

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Sandy and henry Dykema Alberta	Holly Dyrland Alberta	Miranda Dziuba Alberta	Lois Eagles Alberta
Leanne Elaschuk Alberta	Donna Ellerby Alberta	Veruska Ellestad Alberta	Patti Emelson Alberta
Kristine Emery Alberta	Jeff Enfield Alberta	Steven Engler Alberta	Brett Enns Alberta
David Erfle Alberta	Lisa Evans Alberta	Kim F Alberta	Monica Fairley Alberta
Clay Farnsworth Alberta	Coby Farrelly Alberta	Jesse Fergstad Alberta	Ruth Finch Alberta
Vi Fisher Alberta	Cyril Fitzpatrick Alberta	Penny Flinders Alberta	julie flynn alberta
Jodi Forsythe Alberta	Gary Foucault Alberta	Joseph Fournier Alberta	Gordon Francey Alberta
Katie Fraser Alberta	Murray Fraser Alberta	Katie Fraser Alberta	Lillian Friesen Alberta
Randy Friesen Alberta	Sophie Frigon Alberta	Arianne Fuellos Alberta	Shannon Gaetz Alberta
Michael Gardner Alberta	Louise Garneau Alberta	Marek Gasior Alberta	Conrad Gass Alberta
Lise Gaudet Alberta	Judy Gaudreau Alberta	Michelle Gaulin Alberta	Gail Gay Alberta
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Satchi Gabriel Gold Alberta	Marie Golka Alberta	Regina Goman Alberta	Suzanne Gonsalves Alberta
Cheryl Good Alberta	Myron Good Alberta	Carol Goodkey Alberta	Brian Goold Alberta
Brenda Graham Alberta	Stacy Gray Alberta	Laura Gray Alberta	Colin Gurlitz Alberta
Karthika Guttapalem Alberta	Tanneal Haazen Alberta	Doug Hafso Alberta	Shirley Haggith Alberta
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Chiara Hamel Alberta	Darren Hansen Alberta	Ruth Hansma Alberta	Jane Hanson Alberta
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Alberta

Mervin and Theresa Helmle
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Lori Hendrix
Alberta

Scott Hennessey
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Linda Herman
Alberta

Janice Hermus
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Zeza Hewitt
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Rebecka Hiatt
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Janelle Hilchey
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Ivory Hill
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Dagmar Hills
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Holly Hockley
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Jimmy Hoffa
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John Hokanson
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Brad Holland
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Nikki Holloway
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Jane Holmes
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Bradley Hopcraft
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Conrad Horvath
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Elizabeth Hutchinson
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Dianne Hutton
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Susan Idell
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sharon inkster
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Ronni Ishaky
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Terri Iverson
Alberta

rex jade
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Ron Jones
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Tom Kan
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Kim Karman
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Sharon Kasdorf
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Layn Kattler
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Theo Keet
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Jane Keller
Alberta

judy kempf
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Rick Kershaw
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Carol Kershaw
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Rick Kershaw
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Anita Ketsa
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Elizabeth King
Alberta

Kimberly KIRK
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Donna Kirkpatrick
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Dayton Klein
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Shauna Knee
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Michelle Koenig
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Joy Komarnicki
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Stephanie Konelsky
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Janyce Konkin
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Bernie Konklin
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Eleanor Konrath
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Lori Kotulak
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Gabor Kuhn
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Mattea Kuhn
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Bogumiła Lojko
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Holly Lynch
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Kevin MacGregor
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Sharrell Macleod
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ALLAN MACRAE
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Alberta

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Sianne Martin
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Vanessa Martin
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Nicole Matthews
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Heather Mattjews
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Brandi Mawston
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David Mcadam
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Wendy mcgonigal
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LaVoun McGowan
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Jim McInnes
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Tim Mcmurphy
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Nichola McMurray
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Alexandra McWilliams
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David Meadows
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Joanne Meyers
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William Mikkelson
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Dorreen Miller
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Catherine Miller
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Gail Miller
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shelly minarik
alberta

Jeanna Minkley
Alberta

Janie Minnes
Alberta

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Kayla Mirhashem
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Jon Mitchell
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Grace Moerman
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Brooke Monkman
Alberta

Sierra Moore
Alberta

MaryLou Mordecai
Alberta

Bruce Morgan
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Lloyd Morgan
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Erin Morrison
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Damin Mulalin
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Carol Mulkay
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Monica Munro
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Janice Murphy
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Shelley Mushtuk
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Barbara Nagy
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Linda Nesset
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Verna Neufeld
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John Neustaeter
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Talia Nguyen
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Lana Nicholson
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Lee Nickel
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Jenny Nickel
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Yvonne Nickel
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Willy Nickel
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Micheline Nitschke
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Mona Nottveit
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Gail O'Reilly
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Dean Oakes
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Holly Oickle
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Shanlee Oldfield
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Margaret Oosterhof
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Shawn Palm
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Donald Palm
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Amanda Palmer
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Richard Palmer
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Svetlana Palmer
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Heather Parker
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Cindy Parker
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Lisa Parkins
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Ken Pattison
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Debra Pavelich
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Cheryl Pavlovic
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James Paxton
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Tracey Peckford
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Robyn Pelletier
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Jacqueline Perreault
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Christel Peter
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Wayne Peters
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Jen Peterson
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Kim Petrie
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Lena Phipps
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Beverley Plett
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Glen Pliszka
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Mary Plumley
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Judy Poffenroth
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Elda Pooli
Alberta

Lydia Porubovic
Alberta

Ashley Powelson
Alberta

Monica Prescott
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Sherrie Presseau
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Penny Pretzlaw
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Shirley Pryor
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Elaine Pusch
Alberta

Sharla Quantz
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Patricia Quinlan
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Angela Quon
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Grace Raboud
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Erick Racancoj
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Beverly Rebmann
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James Reid
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Vicki Reid
Alberta

Dallas Reimer
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Pamela Reiser
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Ramona Remesat
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Darla Rennick
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Sheldon Reuther
Alberta

Bruce Richards
Alberta

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Renate Richards
Alberta

Don Richards
Alberta

Kevin Richtscheid
Alberta

Janice Rideout
Alberta

Rachelle Ririe
Alberta

Elaine Ritsema
Alberta

Carrie Roberge
Alberta

Carol Roberge
Alberta

Roland Roberge
Alberta

Laurie Roberts
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Rose Robo
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Leanne Rohrick
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Lisa Romaniuk
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Rhonda Rooks
Alberta

Jayda Rosenthal
Alberta

Alan Ross
Alberta

Brad Ross
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Mireille Rousseau
Alberta

Sondra Roy
Alberta

Debra Rush
Alberta

Mark Rushton
Alberta

Dale Rustebakke
Alberta

Jayne Ruttan
Alberta

Heloisa Sabino
Alberta

Tammie Savage
Alberta

Natsumi Sawada
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Jennifer Scharff
Alberta

Randy Schartner
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daryl scheerer
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Pat Scherf
Alberta

Shelley Schmidtke
Alberta

Walter Schoen
Alberta

Lisa Schommer
Alberta

Lori Schulte
Alberta

Christine Schwab
Alberta

Shelley Scott
Alberta

Dolores Semrok
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Roni-lil Shapka
Alberta

Sue Sharp
Alberta

Wayne Shaw
Alberta

Nick Shearer
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Bernadette Sheedy
Alberta

Robert Sheridan
Alberta

Taira Short
Alberta

Nicholas Simpson
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Judith Skibinsky
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Shane Skrove
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Barbara Sledz
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Barbara Sledz
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Diane Slingerland
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Ted Smedes
Alberta

Daphne Smith
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Rosanna Smith
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Ali smith Smith
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Anneli Smith
Alberta

Kris Smith
Alberta

J'Ana Smith
Alberta

Rosanna Smith
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Jake Smith
Alberta

Adam Smith
Alberta

Madelaine Snell
Alberta

Ashley Snihur
Alberta

Leona Somerville
Alberta

Carol Sonnenberg
Alberta

Daphne Sproule
Alberta

Victoria Stagg
Alberta

Sheila Staggs
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Gail Stamp
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Charma Stang
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Brenda Stang
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Terry Stasiuk
Alberta

Hana Stastny
Alberta

Joan Stauffer
Alberta

David Steckenreiter
Alberta

Charity Steele
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Warren Stephens
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Iain Stewart
Alberta

Debra Stewart
Alberta

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Mike Stokes
Alberta

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Michelle Strebchuk
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Robin Strom
Alberta

Raymond Strom
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Michelle Strudwick
Alberta

Valerie Stubbert
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Kim Suntjens
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Mike Sutherland
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Lynda Swanson
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Robert Sydenham
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peter szeles
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Ken Tansey
Alberta

Jackie Taylor
Alberta

Kathy Taylor
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Duane Terlecki
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Martin Thielmann
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Richard Thirsk
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Catherine Thompson
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Kevin Thompson
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Angela Thompson
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Frank Thompson
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Eileen Thompson
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Sharon Toppe
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Serena Torwalt
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Kathryn Treadwell
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Diane Trithart
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Valerie Trouillot
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Jay Tsougrianis
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Carmen Tuck
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Michael Turcotte
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Corrie Turcotte
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Daryl Turko
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Charles Tutt
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Kyle Ultich
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Colleen Vanderaa
Alberta

Michele VanDerKooi
Alberta

Laura Vanhoutte
Alberta

Julie VanSickle
Alberta

Andrée (University of Guelph Alumni) Verhoog
Alberta

Lise Villeneuve
Alberta

Brenda Vroom
Alberta

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Alberta

Thelea Wagner
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Wanda Wallace
Alberta

Wavey Walsh
Alberta

derek walsh
alberta

Drew Walters
Alberta

Rolf Warner
Alberta

Teresa Wasney
Alberta

Kim Webster
Alberta

lorelee weir
alberta

Sandra Weizman
Alberta

Brian Welling
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Vikki Welshman
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Mark Welshman
Alberta

Ileana Wenger
Alberta

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Tonya Whyte
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Carly Williamson
Alberta

Marilyn Wilson
Alberta

Dr. Christopher Wilson
Alberta

Andria Wilson
Alberta

Kim Wilson
Alberta

:Helen: Wilson.
Alberta

Patricia Withers
Alberta

Dean Wolf
Alberta

Greg Wolf
Alberta

Katie Woodroffe
Alberta

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Brian Woodson
Alberta

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Fella Wright
Alberta

Diane Yackel
Alberta

Darlene Yakimishyn
Alberta

Carol York
Alberta

Mark Young
Alberta

Vance Yung
Alberta

Katherine Zalewski
Alberta

Wonnietta Zarb
Alberta

Bernadette Zelenski
Alberta

Maureen Zelmer
ALBERTA

Therese Ziehr
Alberta

LLOYD ZILINSKY
Alberta

Jana Zverina
Alberta

Nial Adamson
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Shelly Armas
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Marianne Artymko
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Kim Bell
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Shannon Berreth
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Jacobus Bronkhorst
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Kelly Brunet
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Craig Budjak
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Jackie Burbank
Alberta

Natasha Crouser
Alberta

Rene D'Aoust
Alberta

Meleca de Jong
Alberta

Reinhard Dyck
Alberta

Scott Earle
Alberta

James Eklund
Alberta

Lisa Ell
Alberta

Lorraine Evans
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Rita Ewanchuk
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Kent Fisher
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Sandra Flanagan
Alberta

Cheryl folstrom
Alberta

Mary-Jean Gass
Alberta

Betty Gibbs
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Shana Gole
Alberta

Nicola Goundry
Alberta

Natasha Gramatovich
Alberta

Stacey Guynup
Alberta

Leanne Hall
Alberta

Wendy Hazen
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Lois Houcher
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Walter Hunter
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David Idell
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Terrance Jakubowski
Alberta

Carole Johnson
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Ashleigh Johnson
Alberta

Amanda Jones
Alberta

Stania Katrakova
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Jessica Katrakova
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Judy Keet
Alberta

Gillian Kennedy
Alberta

Kirston Killeen
Alberta

Laura King
Alberta

Richard Kraus
Alberta

Pavlina Krayzel
Alberta

Gena LaCoste
Alberta

SUSANNE LARGE
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Marni Lawrence
Alberta

Kathy Layden
Alberta

Cate Laye
Alberta

Maurice Lemay
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Aric Locke
Alberta

Michael Lojczyc
Alberta

Doni MacLellan
Alberta

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ed johnson
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New Brunswick

Edward Clement
New Brunswick

Sarah Comeau
New Brunswick

Vicky Courteau
New Brunswick

Tanya Daechert
New Brunswick

Claudia Gardner
New Brunswick

Terrianne Humby
New Brunswick

Helena Janik
New Brunswick

Laura Jean
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New Brunswick

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New Brunswick

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Tristan Tardif woolgar
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Newfoundland and Labrador

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Newfoundland and Labrador

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Delano Flowers
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Newfoundland and Labrador

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Northwest Territories

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Nova Scotia

Michael Anthony
Nova Scotia

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Nova Scotia

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Nova Scotia

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Nova Scotia

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Jessica Bearden
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Michael Bingley
Nova Scotia

Hunter Blair
Nova Scotia

William Bohdan
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Kelly Bond
Nova Scotia

William Bond
Nova Scotia

Zara Bourgeois
Nova Scotia

Robin Bourque
Nova Scotia

Vaughn Bourque
Nova Scotia

Dan Bourque
Nova Scotia

Falen Boutilier
Nova Scotia

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Nova Scotia

Jaclyn Boyd
Nova Scotia

Jackie Brown
Nova Scotia

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Nova Scotia

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Brent Butler
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Shawn Coates
Nova Scotia

Heather Cook
Nova Scotia

Chris Cottrell
nova scotia

Heather Creamer
Nova Scotia

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Nova Scotia

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Nova scotia

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Roy Dillman
Nova Scotia

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NOva scotia

patti fraser
nova scotia

Scott Fraser
Nova Scotia

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Nova Scotia

sharron langille
nova scotia

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Nova Scotia

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Nunavut

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Nunavut

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Doreen Agostino
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Ontario

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Linda Arone
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Lily Arpa
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Nick Arrizza MD ret'd
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Dina Arvanites
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Sean Ashworth
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Chris Asima
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Heather Asmussen
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Ontario

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Kim Atherton
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Ontario

suppinder bains
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gary banderob
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Tania Barbe
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helena barbesin
Ontario

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Gefen Bar-On Santor
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Kelsie Beck
Ontario

Elizabeth Beck
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Ontario

georgette bedard
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Lisa Benhaim
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Holly Belinda Benn
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carole benoit
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Ken Benoit
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Ontario

Lillian Buhl
Ontario

cindy buikema
Ontario

Carol Bukoski
Ontario

Brenda Bulmer
Ontario

Sheryl Bunting
Ontario

Annika Burden
Ontario

Tammy Burdett
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Lynn Burke
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Ontario

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Ontario

Lindsey Burke
Ontario

Trish Burke
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Carol Burke
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Eugene Burles
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Suzanne Burnie
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Ontario

Laura Burns
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Mark Burns
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Linda Burns
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Lynda Burns
Ontario

Shannon Burns
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Scott Burrows
Ontario

Karrie Burrows
Ontario

Kym Burt
Ontario

peter burtoft
Ontario

barbara burtoft
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Diana Buruma
Ontano

Ina Burwell
Ontario

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Nick Busigin
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Ximena Butko
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Shannon Butler
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Carolyn Butler
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Diana Butler
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Cathy Butler
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Angela Butt
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Patrice Butterfield
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Katerina Bylen
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Rita Byra
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Brian C
Ontario

Matthew Cabral
Ontario

maria cabral
Ontario

Marylene Caccioia
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Paul Cachia
Ontario

Max Cafissi
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Sabrina Cameron
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Robert Campanella
Ontario

Callon Campbell
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Stephen Campbell
Ontario

Deborah Campbell
Ontario

Doug Campbell
Ontario

Pam Campbell
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Linda Campbell
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Kristy Campbell
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Ontario

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Lena Cardoso
Ontario

Lisa Cardoza
Ontario

Frank carere
Ontario

Thomas Carere
Ontario

Bonita Carere
Ontario

Diana Carlini
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Andrea Carmichael
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Nora Carnegie
Ontario

Dan Caron
Ontario

Ginette Carrier
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Joseph Carriero
Ontario

Helene Carriero
Ontario

Alex Carriero
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Lise Carruthers
Ontario

David Carson
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Sharon Carson
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Alex Carson
Ontario

Luke Carson
Ontario

Betty Carter
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Shannon Carter
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John Carter
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Linda Carter
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Greg Carter
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Claire Casola
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Celine Cassar
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Aleigha Catherine
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Peter Catoni
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Natasha Chambers
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Linda Chambers
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Vicky Chan
Ontario

Lily Chan
Ontario

Esther Chan
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Heather Chapman
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Hannah Charters
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Julian Cirotto
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Carey Clark
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Christine Clark
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Leigha Clarke
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Navy Clarke
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Teresa Clarke
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Vince Clements
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Jordan Cooper
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Pat Cooper
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Patricia Cooper
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Cesar Costa
Ontario

Donna Costa
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Maria Costanza
Ontario

Rosa Costanzo
Ontario

Thomas Costin
Ontario

Albert Cote
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Mike Couling
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Andrea Coulter
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Catherine Courtine
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Rory Craig
Ontario

Maureen Craig
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Danielle Crawford
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Terrie Crawford
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Kyle Cresswell
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Crina Cretu
Ontario

Theodor Cretu
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Tygr Cummings
Ontario

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Daria Czauderna
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Ontario

Inez Czerwinski
Ontario

Tomasz Czerwinski
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Donna Da Silva
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Brian daCosta
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Darlene Dacuk
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Theresa Dagenais
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Holly Dahmer
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Giacomo Dale
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Jacoby Dale
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Mary Daly
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Ana Daly
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Ontario

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Ontario

Sue Daniels
Ontario

Sharon darcey
Ontario

Jill Darnell
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Melissa Daunt
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Fira Dav
Ontario

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Ontario

Colleen Davidson
Ontario

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Ontario

Russell Davies
Ontario

Mary Davis
Ontario

C. DAWN Davis
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Mary C Davis
Ontario

Jonathan Davis
Ontario

Edward Daw
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Marzena Dawid
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James De Andrade
Ontario

Simon de Boer
Ontario

Jennifer De Giovanni
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Minnie de Jong
Ontario

Kevin de Jong
Ontario

Robert de Lint
Ontario

Michael de Lint
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Rose De Marco
Ontario

Lizzy de Martino
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Cecilia De Martino
Ontario

Michele De Minico
Ontario

Joanne de Montigny
Ontario

Andreea De Saint
Ontario

Natalie De Sousa
Ontario

Becky Dean
Ontario

Carole DeBarry
Ontario

Kari Deckert
Ontario

Marie France Dedieu
Ontario

Ron deGagne
Ontario

Carol Deganis
Ontario

Andy Degroot
Ontario

Kelly DeJong
Ontario

Jackie DeKnock
Ontario

Kerri Del Medico
Ontario

Kim Del Medico
Ontario

Nadia Del Rosso
Ontario

Jeresa Delic
Ontario

Paul Deluca
Ontario

Deena DelZotto
Ontario

Thelma Demers
Ontario

Elena Demetriou
Ontario

geraldine dempsey
Ontario

Nicole DenHartogh
Ontario

Shanine Dennill
Ontario

Robert Denomme
Ontario

Sharon Denomme
Ontario

Stacy Denunzio
Ontario

Linda D'EON
Ontario

Leo Derikx
Ontario

Rob Dermott
Ontario

Dana Deschenes
Ontario

lucas deshayes
Ontario

Tino Desideri
Ontario

Bryce Desjarlais
Ontario

sharon deslauriers
Ontario

VERONIKA DESPINS
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Cathy Desrochers
Ontario

Daniel Desrochers
Ontario

Janet Desroches
Ontario

Kim DeThomasis
Ontario

Kimberly DeThomasis
Ontario

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Julia Di Lollo
Ontario

Chris Di Lullo
Ontario

Jack Di Nardo
Ontario

Jessica Di Rezze
Ontario

Ramona Diaconescu
Ontario

Alin Diaconescu
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Matina Dianos
Ontario

Karrie Dickert
Ontario

Marilyn Dickinson
Ontario

Bruce Dickson
Ontario

Lynne DiCocco
Ontario

Esther Dietsche
Ontario

elke dietz
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Cynthia Dika
Ontario

Irina Dikun
Ontario

Dina Dileonardo
Ontario

Gina Dillon
Ontario

Margaret Dima
Ontario

Sophia Dimanche
Ontario

assunta dimarcantonio
Ontario

Adriana DiMaria
Ontario

Diana Dimech
Ontario

Goran Dimitrijevik
Ontario

John Dinan
Ontario

Corinne Dinan
Ontario

Shawna Dingman
Ontario

Antoaneta Dinkova
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Kara Dionisio
Ontario

Ted Dionne
Ontario

Jessica DiPasquals
Ontario

Michelle Diskic
Ontario

DANIELLE DIVINCENZO
Ontario

Sonya DiVito
Ontario

Wendy Dixon
Ontario

Joanne Dixon
Ontario

Olivera Djordjic
Ontario

Stephen Dobos
Ontario

Susanne Dobos
Ontario

Mike (Mihai) Dobrin
Ontario

Juliana (Monica) Dobrin
Ontario

Mike Dobrin
Ontario

Monica Dobrin
Ontario

Drazen Dodig
Ontario

Carissa Doherty
Ontario

Susan Doherty
Ontario

Nicole Doire
Ontario

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Ontario

Joe Dolan
Ontario

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Ontario

Lydia Dominguez
Ontario

Calin Domosaru
Ontario

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Karen Donenico
Ontario

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Ontario

Cynthia Donnelly
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Virginia Donofrio
Ontario

Luisa Donofrio
Ontario

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Ontario

Luisa Donofrio
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Ontario

Lana Douglas
Ontario

Chris Douros
Ontario

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Ontario

Vi Dowell
Ontario

Kim Dowling
Ontario

Bea Doyle
Ontario

Natalie Doyle
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Ontario

Rhonda Draper
Ontario

Dexter Draper
Ontario

Dana Driesman
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Bojan Drkaul
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Ontario

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Ontario

Cathy Drury
Ontario

hali duba
Ontario

Julie Ducharme
Ontario

Susan Duff
Ontario

Tara Duff Cloez
Ontario

Kimberly Duffner
Ontario

Carol Duffy
Ontario

Irina Dumitrache
Ontario

VLAD DUNAEVSKY
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Rosemary Duncan
Ontario

Julie Duncombe
Ontario

Denise Dupuis
Ontario

Dragica Durajlija
Ontario

Julie Durnford
Ontario

Ken Durnford
Ontario

David Durnford
Ontario

Dawn Dwyer Pappas
Ontario

Pete Dychtiar
Ontario

Maria Dyck
Ontario

Beverley Dyck
Ontario

Elisabeth Dykema
Ontario

Marty Dymel
Ontario

Billea Dyson
Ontario

Cheyanne Eagle
Ontario

Deanna Eagles
Ontario

Sheila Earl
Ontario

Stacey Eason-Bondy
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Gwen Easson
Ontario

Jeannette Eastin
Ontario

Samuel Eastman
Ontario

Nicole Easton
Ontario

Jordan Eastway
Ontario

Nancy Eckert
Ontario

Erica Eckstrand
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Ian Edghill
Ontario

Denise Edmondson
Ontario

Anita Edralin
Ontario

H. Gayle Edward
Ontario

Sandra Edwards
Ontario

Maureen Eede
Ontario

Avia Eek
Ontario

Ed Effinger
Ontario

Kristine Egeland
Ontario

Eunice Egerhazi
Ontario

Katherine Egleston
Ontario

Horst Eichholzer
Ontario

Sonya Eikelboom
Ontario

Eveline Eilert
Ontario

Nassim EL Hindi
Ontario

Tasha Eland
Ontario

Dana Elarte
Ontario

Grace Elema
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Christina Eliadis
Ontario

Christina Elias
Ontario

Mark Elias
Ontario

Rola Elias
Ontario

Giovanna Elias
Ontario

donna ellis
Ontario

Louise Ellis
Ontario

Karen Ellis
Ontario

Dan Ellison
Ontario

Lori Emerson
Ontario

Florian Ene
Ontario

C Engel
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Renée English
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Rick English
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Melanie Epp
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Lisa Erickson
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Heather Erickson
Ontario

Heather Erickson
Ontario

Kristine Ericson
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Darrell Ernst
Ontario

Cheryl & Egon Ernst
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Tracey Etwell
Ontario

carmel Euwen
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Ontario

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Barb Everatt
Ontario

Denise Exler
Ontario

Dylan F
Ontario

Tracy Fadden
Ontario

Emanuel Fagundes
Ontario

Edwidge Fairweather
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Tany Falardeau
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Kimberly Fallis
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Roy Fam
Ontario

Karen Fangrad
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Marinette Fargo
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Nicole Farrar
Ontario

Keith Farrar
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Erica Farrell
Ontario

Mitchell Farrell
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Liza Farrell
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Ontario

Glenn Farris
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Reda Fayek
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Ilka Fedor
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Nadezhda Fedotova
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Greg Feldman
Ontario

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Andrew Fera
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Barbara Fera
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Catherine Feren
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antonina ferenc
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Michael Ferfolia
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John Ferguson
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Sheri Ferguson
Ontario

James Ferland
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Jeffrey Ferland
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Jimmy Fernandes
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Flora Fernandes
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Pedro Fernandez
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Michael Ficker
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Gayle Fielding
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Julia Filomen
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Melisa Filson
Ontario

Melisa Filson
Ontario

:laura finch
Ontario

don findlay
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Jennifer Fischer-Jenssen
Ontario

steve fish
Ontario

Jan Fisher
Ontario

Ginny Fisher
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Ontario

David Fisman
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Jennifer Fonseca
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Ontario

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Ontario

Silvia Fomataro
Ontario

Lindsay Forsey
Ontario

Barbara Forthuber
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Lesley Fortner
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Lois Foster
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Lorna Foster
Ontario

Kate Foster
Ontario

Jocelyn Fournier
Ontario

Jocelyne Fox
Ontario

Doris Fox
Ontario

Carllie B Fox
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Bessie Fragis
Ontario

Niko Fragis
Ontario

Melissa Fralick
Ontario

Carrie Francis
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Robin Francis
Ontario

Elise Francis
Ontario

Alex Franco
Ontario

Joseph Frangione
Ontario

Laura Frangione
Ontario

Alan Frank
Ontario

Mata Franklin
Ontario

J K Franklin
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Rod Fraser
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Susie Fraser
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Patricia Frazier
Ontario

Tim Freeland
Ontario

Alexandra Freeman
Ontario

Michelle French
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Duane Frey
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Les Frey
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Vincent Frey
Ontario

Lowell Frey
Ontario

Andrea Frey
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Pamela Friendly
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Darika Friesen
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Amy Frith
Ontario

Stacey Fritsch
Ontario

Leanne Fromhold-Treu
Ontario

Del Frost
Ontario

Tina Fryer
Ontario

Esther Fulford
Ontario

Rachel Fullerton
Ontario

Cristian Fulop
Ontario

Lauren Fulop
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Sylvie Fulson
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Rachel Funk
Ontario

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Angela Furia
Ontario

Sharon Furlong
Ontario

Richard Fyvie
Ontario

Marcela G
Ontario

Ian Gadal
Ontario

Randy Gadal
Ontario

Jacqui Gadal
Ontario

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Ontario

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Ontario

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Ontario

Kristin Gardiner
Ontario

Dave Gardner
Ontario

Josie Garner
Ontario

Janice Garner
Ontario

Bonnie Garner
Ontario

Mark Garner
Ontario

Bonnie Garner
Ontario

Chuck Garner
Ontario

Jennifer Garritsen
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Carolina Gary
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Rosalie Gascho
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Maria Gatt
Ontario

Frederick Gatt
Ontario

Sheryl Gatzke
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Myriam Gaudet
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Monique Gaudet
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Len Gauthier
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Beth Gawley
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Wade Gender
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Wagdy Gendy
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Joe Genovese
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Joseph Genovese
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Carm Genuardi
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C Gies
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anna gindin
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Ontario

barb glover
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Taylor Glover
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B Gough
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Margo Green
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Kristin Greenacre
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Christine Greening
Ontario

Tim Greening
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Courtney Greer
Ontario

Hannah Greig
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Jennifer Greig
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Solveig Greppmayr
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Patrick Grier
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Ian Grierson
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Luke Griffin
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Adrian Gugiuman
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Yvonne Guldie-Schepens
Ontario

L M Gunn
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June Gunter
Ontario

clint gunter
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Abby Guy
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Pawel Haber
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Kathryn Hackner
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Jenilee Haddon
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Jack Hakoun
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Karren Hammond
Ontario

Sandrs Hammond
Ontario

Gerda Hammond
Ontario

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Ontario

Lourdes Hanlon
Ontario

Jen Hannon
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Ontario

Scott Hanson
Ontario

Catherine Harding
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Ontario

Jocelyn Harpell
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Wendy Harris
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Charlotte Harris
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Bryant Harris
Ontario

Stephen Harris
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Gary Harrison
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Jennifer Harrison
Ontario

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Judi Hartlin
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Vicki Hartman
Ontario

David Hartman
Ontario

sandy hartman
Ontario

Stacey Hartwick
Ontario

Karen Hartwick
Ontario

Brenda Harvey
Ontario

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Ontario

Krystal Hass
Ontario

Kim Hass
Ontario

Alex Hasse
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John Hasyn
Ontario

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Ontario

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Ontario

Marion Haughton
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Sarah Haunts
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Kailey Hawthorn
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Sarah Hawthorn
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Alana Hawthorn
Ontario

Jessie Hawthorn
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Ontario

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Steve Hayhurst
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Janice Hayhurst
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Carolyn Hayman
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Ann Hayward
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Daniel Heaney
Ontario

Nancy Heaney
Ontario

Lisa Heard
Ontario

chris heeney
Ontario

Ken Heimbuch
Ontario

Myrna Heinbuch
Ontario

Janet e Heisey
Ontario

Sandra Hek
Ontario

Julianna Hekker
Ontario

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Ontario

John held
Ontario

Apolonia Henderson
Ontario

Shayne Henderson
Ontario

Sarah Henderson
Ontario

Shelley Henderson
Ontario

Jamie Henderson
Ontario

Gary Henderson
Ontario

S. Henderson
Ontario

Conrad Henry
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Mary Herder
Ontario

Yolanda Hermack
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Keith Hermack
Ontario

Ryan Hermack
Ontario

Zoltan Hernadi
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Mason Hersh
Ontario

Tracy Hexemer
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Stephanie Hickey
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Ontario

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Ontario

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Ontario

Amanda Hill
Ontario

Amy Hill
Ontario

Keith Hill
Ontario

Julie Hill
Ontario

Jessica Hill
Ontario

Elizabeth Hill
Ontario

Melanie Hill
Ontario

Stephen Hill
Ontario

Michelle Hilton
Ontario

Kerry Hinzman
Ontario

Tim Hirtle
Ontario

Frank & Peggy Hlisic
Ontario

Peggy & Frank Hlisic
Ontario

Lorna Hnat
Ontario

Ury Ho
Ontario

Mary-Ann Hobe
Ontario

Claudine Hodge
Ontario

Jonathan Hodgson
Ontario

Michael Hoepfner
Ontario

Michael Hoffbauer
Ontario

Angela Hoffbauer
Ontario

Amanda Hoffman
Ontario

Rita Hoffman
Ontario

Riette Hofhuis
Ontario

Kathie Hogan
Ontario

Margaret Hogan
Ontario

Bob Hogge
Ontario

Susan Hogue
Ontario

Shirley and Doug Hohl
Ontario

Kate Hollender
Ontario

Robert Hollis
Ontario

Kailan Hollywood
Ontario

Karen Holme
Ontario

Jen Holmes
Ontario

Marlene Holt
Ontario

Michael Holubik
Ontario

Jessica Honcoop
Ontario

Rod Hoover
Ontario

Joanne Hordyk
Ontario

Len Hordyk
Ontario

Erica Horgan
Ontario

Jessie Horowitz
Ontario

Dayna Horst
Ontario

Sharon Horst
Ontario

Melanie Horton
Ontario

Melanie Horton
Ontario

Isabel Horvath
Ontario

roza horvath
Ontario

Sophie Hotoyan
Ontario

Amy Hou
Ontario

Joanne Hough
Ontario

Diane Houle
Ontario

Colleen House
Ontario

Allison House
Ontario

Anita Howald
Ontario

Helene Howard
Ontario

Annmarie Howard
Ontario

Dr. Sandra Howlett
Ontario

Wendy Hoy Bright
Ontario

Jennifer Hrebicek
Ontario

Diane Hruska
Ontario

Sandy Hruska
Ontario

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Ontario

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Ontario

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Ontario

Graham Hubert
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Anna Hucman
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Christi Huculak
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Darcy Huda
Ontario

Faisal Huda
Ontario

Stephen Hughes
Ontario

Joan Hughes
Ontario

Ryan Hughes
Ontario

Lorraine Hughes
Ontario

Laura Hughes
Ontario

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Ontario

Katarzyna Hulicki
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Ontario

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Ontario

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Ontario

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Ontario

Jason Hunt
Ontario

Thora Hunter
Ontario

Katherine Hunter
Ontario

Adam Hurlburt
Ontario

Eva Hutchinson
Ontario

Patricia & John Hutchinson
Ontario

Darren Hutton
Ontario

Jocelyne Hyland
Ontario

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Ontario

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Ontario

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Ontario

Jesse Ibañez
Ontario

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Ontario

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Tanya Ireson
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Ontario

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Ontario

Susan Jackson
Ontario

Brian Jackson
Ontario

Sharon Jackson
Ontario

cindy jackson
Ontario

Marcy Jackson
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Sharon Jackson
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Sarah Jacobson
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Ontario

Miroslawa Jacyniak
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Ontario

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Ontario

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Irma Johnson
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Marg Johnson
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Ontario

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Martin Jones
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Heather Jones
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Alex Jones
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Shayne Jose
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Rose Joseph
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Jason Joseph
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Sebastian Jug
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Jon Jukes
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M June
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Ontario

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Ontario

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Ontario

Viktor K
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Ivana Kacianova
Ontario

Julia Kakish
Ontario

staney kalathilparambil
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Kim Kalil
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Rosalia Kalisz
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Soula Kallinis
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Anesti Karantakis
Ontario

Vicki Karpiak
Ontario

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Ontario

Romanos Katchmar
Ontario

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Berge Kazazian
Ontario

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Judy Keffer
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Faten Kella
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Shirley Kellerstein
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Inez Kelly
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Shirleen Kelly
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john kennedy
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Ontario

dave kersey
Ontario

Emma Kessler
Ontario

Vesna Khalaf
Ontario

MAROUN KHALIL
Ontario

F Khan
Ontario

Neeta Khanna
Ontario

Anchika Khanna
Ontario

Faten Khelfa
Ontario

Chantha Khem
Ontario

Elizabeth Khosla
Ontario

Yashar Khosroshahi
Ontario

Neveen Khouzam
Ontario

michael kidd
Ontario

Moira Kiedrowski
Ontario

Kathy Kiefte-(nee-Harrison)
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Lucinda Kiessling
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Eileen Kilbreath
Ontario

Rochagne Kilian
Ontario

John Kilkenny
Ontario

Joanne Kilpatrick
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Colleen Kinden
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Tara King
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Samantha King
Ontario

DWAYNE KING
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Henrietta Kingshott
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Natasha Kingsmore
Ontario

Colin Kingsmore
Ontario

Nat Kipling
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Laura Kissmann
Ontario

Kristin Kiviranta
Ontario

Joann Kjeldsen
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Elaine Klafuric
Ontario

Heidi Klaming
Ontario

Fran Klassen
Ontario

Silvia Klassen
Ontario

Christian Klein
Ontario

Julie Klein
Ontario

Ken Klinaftakis
Ontario

Arla Klooster
Ontario

William Klooster
Ontario

Chris Klotz
Ontario

Hattie Klotz
Ontario

Rachel Knight
Ontario

Andrea Knight
Ontario

Derek Knight
Ontario

Mary Knipf
Ontario

Rob Knipf
Ontario

ann knutton
Ontario

Winnie Ko
Ontario

Beata Kobelak
Ontario

Wendy Kochaniec
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Lida Kocis
Ontario

Vera Kolaritsch
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Ontario

Andrea Kombe
Ontario

Anne Garber Kompaore
Ontario

Kristen Koning
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Josie konstantini
Ontario

Julita Koprianiuk
Ontario

Josie Korimsek
Ontario

Kara Kortegaard
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Judy Korten
Ontario

Marta Kosek
Ontario

Helena Kosin
Ontario

Sur Kosokowsky
Ontario

Wilhelmina Kosowan
Ontario

Rad Kostka
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Tom Kotarac
Ontario

Maria Kotenko
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Nenad Kovacevic
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Julie Kovarski
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Danuta Kozak
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Ontario

Carol Kraft
Ontario

Larry Kraskevich
Ontario

Laura Kraskevich
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Jennifer Kravis
Ontario

Ingrid Kravis
Ontario

Donna Krebs
Ontario

Adrian Kremblewski
Ontario

Kathy Kristof
Ontario

Karel Kromar
Ontario

Michael Krpan
Ontario

Ljubica Krpan
Ontario

Jacqueline Krstic
Ontario

Naomi Krucker
Ontario

keshia krucker
Ontario

Eve Krupp
Ontario

Matt Krusky
Ontario

Peter Krygsman
Ontario

Monika Krysinska
Ontario

Marek Krzton
Ontario

Olga Kudritska
Ontario

Elena Kudryavtseva
Ontario

Adrian Kudzma
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Pamela Robinson
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S. Beauchamp
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Québec

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véronique bérubé-roussy
Québec

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Tan Bokhari
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Québec

Chagit Bouzaglou
Québec

Julie Brady
Québec

Drew Brazil
Québec

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Québec

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Leslie Carlyle
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Mario Caruso
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Christine Woestmann
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Québec

Qing Zhang
Québec

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Saskatchewan

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Saskatchewan

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Saskatchewan

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Susan Lechman
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Darrell Lechman
Saskatchewan

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Saskatchewan

Debbie Mihalcea
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Brad Peters
Saskatchewan

Brenda Roenspies
Saskatchewan

Monica Roussin
Saskatchewan

Garth Smith
Saskatchewan

Bruce Thompson
Saskatchewan

Sandra Warnock
Saskatchewan

Stefan Angerer
Yukon

Jill Ford
Yukon

Dorothy Lebel
Yukon

Elke Sinclair
Yukon

Sue Meadows
Alabama

Karen Langran
Arizona

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Australia

Fi Jolli
Australia

Aidan Martin
Australia

Glenn Taylor
Australia

Vicky Kermogianni
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Saskatchewan

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Saskatchewan

Jen Rollins
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Craig Stein
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Cheryl Thoreson
Saskatchewan

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Saskatchewan

Ursula Angerer
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Michelle Gregory
Yukon

Ellen Oppold
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Joline Williams
Yukon

Edgar Russo
Argentina

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Arizona

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Australia

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Australia

Sylvia Wernicke
Australia

Gerold Weber
Austria

Roxanne Liebrecht
Saskatchewan

Jackie McCaig
Saskatchewan

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Saskatchewan

David Rollins
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Saskatchewan

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Lana Van Dijk
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Nolan Weinmaster
Saskatchewan

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Yukon

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Dena Zavier
Yukon

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Arizona

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Australia

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Saskatchewan

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Saskatchewan

James Roulston
Saskatchewan

Elin Shearer
Saskatchewan

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Gabriel Varkonyi
Saskatchewan

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Yukon

Cathy Evelyn
Yukon

Sasha Kallos
Yukon

SUNJE PETERSEN
Yukon

Shane Wolffe
Yukon

Suzanne Higgins
Arizona

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Australia

Maureen Fox
Australia

Manuel Martin
Australia

Carla Sharpe
Australia

Edurne Bengoetxea
Australia

David Adams, Ph.D.
California

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California

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California

Denise Buslach
California

Anissa Campbell
California

Maritza Cisneros
California

Jody Deaderick
California

Melody Harwood
California

Lizs Kosinski
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Irene Makris
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Pegy Manfredi
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Elizabeth Ray
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Christy Wolfe
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Justin Glessner
California

Rebekah Harris
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Cathey Painter
California

lendri purcell
california

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David Kulas
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Czech Republic

Simon Reich, MD
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Claus Hetting
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Glen Wyborn
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Elizabeth Cutajar
Europe

Delphine Bulcke
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Ladynez Jimenez
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tyler kalmer
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Missouri

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New York

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New York

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Gina Reece
Oregon

Eli Dumitru
Oregon

christy parry
pennsylvania

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Rhode Island

Iveta Cajchanova
Slovakia

Joan Holds
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Missouri

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Muscat oman

M. van Gennep
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Texas

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Lincoln Earle-Centers
Vermont

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dave bourgon

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Blake Mombourquette	Mary Anne Neufeld	L Orth	Tegan Osmond
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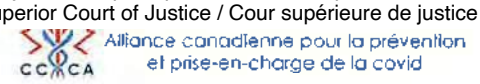
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Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000

Court File No.: **CV-22-0069-1880-0000**

Dr. BYRAM BRIDLE	-and-	Glen PYLE et al
Plaintiffs		Defendants

ONTARIO
SUPERIOR COURT OF JUSTICE
PROCEEDING COMMENCED AT TORONTO

AFFIDAVIT OF DR. BONNIE MALLARD

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TAB 6

Court File #: CV-22-0069-1880-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

BETWEEN:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

AFFIDAVIT OF DR. DAVID J. SPEICHER

I, Dr. David J. Speicher, of the City of Hamilton, in the Province of Ontario, MAKE OATH AND SAY:

1. I am a Senior Research Associate at the University of Guelph and an academic and professional colleague of the Plaintiff, and as such, have knowledge of the matters contained in this Affidavit.

Professional, Academic and Research background

2. I am a Canadian molecular virologist with a Bachelor of Science with honours in Biology (major) and Chemistry (minor) from Redeemer University College (Canada). I also have a masters of science with honours in Clinical Microbiology with research focused on the diagnostics and characterisation of human coronaviruses (HCoVs) and a PhD in Virology with research focused on Human Herpesvirus type 8 (HHV-8), both from Griffith University (Australia).
3. Attached and marked as **Exhibit A is a copy of my CV**.

4. I have published just over 30 peer-reviewed scientific manuscripts in the field of infectious diseases.
5. I have obtained just over $1 million in competitive research grants including a $500,000 New Frontiers in Research Fund - Special Call 2022 by Social Sciences and Humanities Research Council (SSHRC), Canada to investigate Canada's response to the COVID-19 pandemic, for work under a project entitled: Project title: Transparency and Shared Responsibility for Sustainable Post-Pandemic Recovery and Evidence-Informed Decision-Making During Future Global Emergencies.
6. I have performed scientific research on a range of infectious diseases including, but not limited to, HCoVs including SARS-CoV-2/COVID, Human Herpesviruses (HHV), Human Papillomavirus (HPV), *Clostridium difficile, Mycoplasma genitalium*, and malaria in Canada, Australia, Kenya, India, and Cambodia.
7. I completed two postdoctoral fellowships at McMaster University/St Joseph's Healthcare Hamilton in Clinical Microbiology and Molecular Epidemiology, and in 2020 received the McMaster University Faculty of Health Sciences Postdoctoral Leadership Award.
8. I was a Sessional Assistant Professor of Biology and Health Sciences (2022-2023) at Redeemer University where I taught courses on Microbiology, Genetics, and Advanced Molecular Methods.
9. I have served as a Senior Research Associate at the University of Guelph under the supervision of Dr. Byram Bridle since September 2021.

Research and Expertise on COVID-19 and COVID-19 vaccines

10. At the start of the pandemic, during my time with McMaster University I designed methods used to sequence SARS-CoV-2[1][2][3].

11. In 2020, I published two manuscripts outlining the federal (Canadian) and provincial (Ontario) response to the COVID-19 pandemic[4][5].

12. I served, from February to April 2021, as the Laboratory Director of Epitome Genomics, which performed up to 10,000 PCR tests per week on asymptomatic people for FH Health.

13. During the pandemic I served, from February to April 2021, as the Laboratory Director of Multiplex Genomics, which performed up to 15,000 PCR tests per week on asymptomatic people for LifeLabs.

14. I have served with Dr. Byram Bridle on the Scientific and Medical Advisory Committee of the Canadian COVID Care Alliance (CCCA) since April 2021. This is a panel of biomedical scientists, medical doctors and other health practitioners that meet weekly on zoom and discuss the science surrounding SARS-CoV-2/COVID-19 including, but not limited to, topics like virology, all cause mortality, COVID vaccines, etc. On this committee Dr. Bridle and I were a part of a team that co-published a critique of the original

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1 https://www.cbc.ca/news/canada/hamilton/mcmaster-coronavirus-sequencing-tool-1.5479663

2 Speicher DJ, Nasir JA, Zhou P, Anderson DE (2021) Whole-Genome Sequencing of Pathogens in Saliva: A Target-Enrichment Approach for SARS-CoV-2. In: Adami G.R. (eds) The Oral Microbiome. Methods in Molecular Biology, vol 2327. Humana, New York, NY. https://doi.org/10.1007/978-1-0716-1518-8_8

3 https://www.preprints.org/manuscript/202002.0385/v1

4 Bielska IA, Manis DR, Schumacher C, Moore E, Lewis K, Agarwal G, Mondoux S, Jewett L, Speicher DJ, Liu RH, Leyenaar M, McLeod B, Upadhye S (2020) Health Sector responses to the COVID-19 pandemic in Ontario, Canada – January to May 2020. Zdrowie Publiczne i Zarządzanie [Public Health and Management] 18(1):106-120. doi:10.4467/20842627oz.20.010.12664.During the pandemic

5 Bielska IA, Embrett M, Jewett L, Buote R, Manis DR, Parikh M, Speicher DJ, Agarwal G, Nartowski RO, Finnegan H, Bandara T, Hamilton CB, Moore E, Liu RH, Roher SIG, Lopatina E, Nguyen DTK, Lawrence L, Lukewich J (2020) Canada's multi-jurisdictional COVID-19 Public Health response January to May 2020. Zdrowie Publiczne i Zarządzanie [Public Health and Management] 18(1):88-105. doi:10.4467/20842627oz.20.009.12663.

6-month clinical study performed by Pfizer/BioNTech on their BNT162b2 RNA vaccine[6]. As part of this committee, I also co-authored a related piece on the manufacturing and quality issues associated with the BNT162b2 mRNA COVID-19 vaccine[7].

15. At the University of Guelph Dr. Bridle and I have co-supervised a PhD candidate, Mr. Jason Knapp, which lead to the co-publishing of a peer-reviewed, review paper[8] and a presentation[9] on oncolytic viral therapy.

16. I was also the lead author and principal investigator on a study that confirmed residual plasmid DNA in both Pfizer and Moderna COVID-19 modified RNA (modRNA) vaccines, and the SV40 enhancer and promoter in the Pfizer COVID-19 vaccine[10].

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6 Bridle, B.W., Martins, I., Mallard, B.A., Karrow, N.A., Speicher, D.J., Chaufan, C., Northey, J.G.B., Pelech, S., Shaw, C.A., Halgas, O. (2021) Concerns regarding the efficacy and safety for BNT162b2 mRNA coronavirus disease (COVID-19) vaccine through six months. www.CanadianCovidCareAlliance.org (January 10, 2022) 1-10 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/01/Final-CCCA-Critique-Thomas-COVID-19-Vaccines-6-months-NEJM-Jan-10-22.pdf

7 Gutschi, M., Speicher, D. J., Natsheh, S., Oldfield, P., Britz-McKibbon, P., Palmer, M., Karrow, N., Massie, B., Mallard, B., Chan, G. Pelech, S. (2022) An independent analysis of the manufacturing and quality control issues of the BNT162b BioNTech/Pfizer vaccine identified by the European Medicine Agency. www.Canadian Covid Care Alliance.org (October 29, 2022) 1-5 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/11/22OC29_EMA-Analysisof-BNT162b-Manufacture.pdf

8 Knapp, JP, Kakish, JE, Bridle, BW, Speicher, DJ (2022) Tumor Temperature: Friend or Foe of Virus-Based Cancer Immunotherapy. Biomedicines 10, (8).

9 Knapp JP, Van Vloten J, Mutsaers A, Meng B, Speicher DJ, Bridle BW. Exploring the heat sensitivity and heat-adaptation of oncolytic vesicular stomatitis virus for improved cancer immunotherapy. BioCanRx, Summit for Cancer Immunotherapy Conference. Ottawa, Canada, October 1-4, 2023.

10 Speicher, D.J., Rose, J., Gutschi, L.M., Wiseman, D.M., McKernan, K. (2023) DNA fragments detected in monovalent and Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada: Exploratory dose response relationship with serious adverse events. OSF Preprints. Retrieved from https://osf.io/mjc97/

Dr. Bridle's claims were not and are not "misinformation".

17. When Dr. Bridle did the interview with Alex Pierson, I had only known him for about 1 month.

18. I heard Dr. Bridle's radio interview on Global News Alex Pierson Show on AM640 when it was first aired on May 28, 2021, and again on December 11, 2023, in preparing this affidavit.

19. Dr. Bridle is a viral vaccinologist who is pro-vaccine and pro-evidence-based medical science. Dr. Bridle has very strong moral convictions and is against causing undue harm to any human or animal. Dr. Bridle is a firm advocate of evidence-based science and teaches his students and colleagues to think critically about existing knowledge and the published literature.

20. Dr. Bridle identified the following concerns about the COVID19 vaccines during the interview:

    a. The spike protein is a poor target for COVID vaccines because it's a pathogenic toxic protein.

    b. The COVID vaccine does not stay at the site of injection like first claimed but travels throughout the body.

    c. The spike protein can cross the blood brain barrier and cause harm.

    d. The spike protein can pass in breast milk from a vaccinated mother to a breastfeeding baby.

21. Every single claim made by Dr. Bridle in the interview is correct and accurate. I have re-iterated the facts with the published literature below.

a. Spike protein: There have been many reports that the spike protein is a pathogenic toxic protein that can trigger inflammatory[11,12,13] and neurological conditions[14] without being part of the virus itself.

b. Vaccine Biodistribution: Dr. Bridle's claims about the biodistribution of the COVID-19 vaccine was founded from data in the Japanese study government regulatory study that Dr. Bridle had translated[15]. That same data was submitted and summarized by the European Medicines Agency (see page 47 of the EMA Assessment report for Comirnaty)[16]. This regulatory study is part of the Common Technical Data (CTD), a common set of regulatory documents used by the major regulatory agencies in the western world. The CTD is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries such as the EMA, SwissMedic, MHRA, HC, FDA and Japan[17].

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[11] Dosch, S.F., Mahajan, S.D., Collins, A.R. (2009) SARS coronavirus spike protein-induced innate immune response occurs via activation of the NF-kappaB pathway in human monocyte macrophages in vitro. Virus Res. 142(1-2):19–27. doi:10.1016/j.virusres.2009.01.005

[12] Barhoumi, T., Alghanem, B., Shaibah, H., Mansour, F.A., Alamri, H.S., et al. (2021) SARS-CoV-2 coronavirus Spike protein-induced apoptosis, inflammatory, and oxidative stress responses in THP-1-like-macrophages: potential role of angiotensin-converting enzyme inhibitor (Perindopril). Front Immunol. 20(12):728896. doi:10.3389/fimmu.2021.728896

[13] Theoharides, T.C, Conti, P. (2020) COVID-19 and multisystem inflammatory syndrome, or is it mast cell activation syndrome? J Biol Regul Homeost Agents. 34(5):1633-1636. doi:10.23812/20-EDIT3

[14] Seneff, S., Nigh, G., Kyriakopoulos, A.M., McCullough P.A. (2022) Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs. Food Chem Toxicol. 164:113008 doi:10.1016/j.fct.2022.113008

[15] (2021) SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048) 2.6.4 薬物動態試験の概要文 (translation: "Summary of pharmacokinetic study")" Retrieved from https://pandemictimeline.com/wp-content/uploads/2021/07/Pfizer-report_Japanese-government.pdf

[16] EMEA/H/C/005735/0000. 2021. Comirnaty European Public Assessment Report (EPAR) [Online]. Available: https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf.

[17] https://www.ich.org/page/ctd

c. Blood brain barrier: There have been reports that the SARS-CoV-2 spike protein can act like a prion and cross the blood brain barrier[18,19]. Dr. Bridle published a peer-review manuscript showing that the SARS-CoV-2 spike protein can affect the brain and the potential implications of modRNA vaccine spike[20].

d. Breastmilk: The COVID mRNA spike can be transferred to a baby via breast milk following vaccination of a lactating mother[21].

22. This is not the first time Dr. Bridle has accurately predicted problems, stemming from his articulated concerns, surrounding the COVID-19 vaccines, and government measures, such as masking, lockdowns, and PCR testing. Dr. Bridle is a lab-based immunologist and scientist who thinks critically about existing knowledge.

Dr. Fisman's asertions against Dr. Bridle are false

23. Dr. David Fisman has a Doctor of Medicine (MD) and a Master's degree in Public Health (MPH). Dr. Fisman does not hold a PhD and does not specialize in the research and development of vaccines. Dr. Fisman is a tenured professor specializing in epidemiology and the mathematical modeling of infectious diseases.

24. Dr. David Fisman (@DFisman) is someone who I follow on Twitter and am surprised at his continuous discrimination against the unvaccinated. Dr. Fisman continuously uses his Twitter account to communicate these opinions and dislike of "anti-vaxxers". Dr. Fisman's Twitter bio states "Notoriously unfair to … anti-vaxxers". He has often blamed the "anti-vaxxers" for increased viral transmission, and has openly stated that "anti-vaxxers" should

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[18] Krasemann, S., Haferkamp, U., Pfefferle, S., Woo, M. S., Heinrich, F., Schweizer, M., . . . Pless, O. (2022). The blood-brain barrier is dysregulated in COVID-19 and serves as a CNS entry route for SARS-CoV-2. Stem Cell Reports, 17(2), 307-320. doi:10.1016/j.stemcr.2021.12.011

[19] Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J. P., Schröder, A. S., Edler, C., . . . Glatzel, M. (2020). Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol, 19(11), 919-929. doi:10.1016/s1474-4422(20)30308-2

[20] Oldfield, P. R., Hibberd, J., & Bridle, B. W. (2021). How Does Severe Acute Respiratory Syndrome-Coronavirus-2 Affect the Brain and Its Implications for the Vaccines Currently in Use. Vaccines (Basel), 10(1). doi:10.3390/vaccines10010001

[21] Fu, W., Sivajohan, B., McClymont, E., Albert, A., Elwood, C., et al. (2022) Systematic review of the safety, immunogenicity, and effectiveness of COVID-19 vaccines in pregnant and lactating individuals and their infants. Int J Gynaecol Obstet. 156(3):406-417. doi:10.1002/ijgo.14008

"stay home" and don't deserve to live in a free society, and that vaccine passports and mandates should be enforced. While he will often refute arguments put forth by those he disagrees with, Dr. Fisman only allows those who @DFisman follows or mentions to reply. Dr. Fisman also referred to "anti-vaxxers" as "cult-like" and that their behaviour "may cause lasting damage to vaccine programs." On October 22, 2021 Dr. Fisman agreed with Geoffrey Johnson that "the anti-vaccine online thugs are increasingly desperate" and that he was going to make "a toast with a glass of anti-vaxxer tears." See **Exhibit B** as a sample of Dr. Fisman's tweets against the unvaccinated.

25. I have read the affidavit of Dr. Fisman filed in the within motion. Dr. Fisman states that Dr Bridle's claims were:
    a. "contrary to overwhelming majority of scientists"; (paragraph 13);
    b. "had potential to harm or halt Ontario's vaccine roll out" (paragraph 15);
    c. "not data-based" (paragraph 19);
    d. "spreading misinformation"; (paragraphs 20, 23, 28, 40);
    e. "not evidence based" (paragraph 25);
    f. "implausible and not data based" (paragraph 30);
    g. "not scientifically sound" (paragraph 41);
    h. "Dr. Bridle's speaking engagements, interviews and articles posed a risk to the public" (paragraph 42);
    i. "Dr. Bridle is suggesting that a study that noted minuscule quantities of spike protein in blood after first dose represent a health hazard. That is poppycock: biologically implausible and not data based." (paragraph 30, Exhibit N, page 184);
    j. "His (Dr. Bridle's) assertions re: accumulation in ovaries is based on an odd document, the original of which is apparently not available, and which looks like it may be a safety study for lipid nanoparticles, not spike as Bridle asserts. This is some kind of drug safety study in rats, not people, and its not possible to assess what was being done here, or even whether it's a real document." (para 30);
    k. "This seems to be an organized disinformation op aimed at undermining vaccine confidence" (para 30);
    l. "…Dr. Bridle…seems to have been headed more and more in the "anti-vax" direction…" (para 30) ;

26. Dr. Fisman has a due diligence as a physician providing expert opinion for public health orders to ensure he is accurate and thorough. Data on biodistribution was available at the time of the Interim Order from Health Canada since they had access to the a Common Technical Document as every regulator. A summary was included in the European Public Assessment Report (EPAR)[22]. Dr. Bridle obtained the full report from Japan. It has since been published by PHMPT (Aaron Siri site) and is now publicly available[23].

27. Dr. Fisman has been pushing the COVID vaccines hard and is discriminatory against the unvaccinated, and Dr. Bridle. Despite several attempts by Dr. Bridle to have a professional scientific discussion with Dr. Fisman, no offer has ever been accepted. In response to Dr. Fisman's allegations I provide the following evidence that Dr. Fisman's claims are false:

    a. With respect to paragraph 13: It was known as early as 2009 that the viral spike protein was toxic[24], and there is no evidence showing that a vaccine version of the spike protein would be any less toxic. The article that Dr. Fisman references a news article that refers to **no** published literature proving that the vaccine spike is different from the virus spike in terms of toxicity. Dr. Fisman, referred to the opinions of "experts" on the field but refers to Dr. Pyle who is not an immunologist let alone an expert on vaccines. However, Dr. Fisman refused to acknowledge that Dr. Bridle as an expert.

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[22] EMEA/H/C/005735/0000. 2021. Comirnaty European Public Assessment Report (EPAR) [Online]. Available: https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf.
[23] (2021) SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048) 2.6.4 薬物動態試験の概要文 (translation: "Summary of pharmacokinetic study")" Retrieved from https://pandemictimeline.com/wp-content/uploads/2021/07/Pfizer-report_Japanese-government.pdf
[24] Dosch, S.F., Mahajan, S.D., Collins, A.R. (2009) SARS coronavirus spike protein-induced innate immune response occurs via activation of the NF-kappaB pathway in human monocyte macrophages in vitro. Virus Res. 142(1-2):19–27. doi:10.1016/j.virusres.2009.01.005

b. With respect to paragraph 15: It puzzles me as to how Dr. Fisman believes that despite the mainstream media and the government pushing for the entire public to get vaccinated that one man, Dr. Bridle, has that much influence to topple the entire vaccine campaign. Informed consent is the cornerstone of medical care yet when Dr. Bridle brings forth the information that he knows Dr Fisman insists on Dr. Bridle being silenced.

c. In several instances (e.g. Paragraphs 19, 20, 23, 28, 40) Dr. Fisman claims that Dr. Bridle's claims are "not data based" and that Dr. Bridle is spreading misinformation. Yet, in all of Dr. Bridle's presentations Dr. Bridle shows a plethora of publications supporting his argument. On the contrary, Dr. Fisman in his affidavit does not produce any scientific evidence for his claim and refers to quotes on social media to support his argument that Dr. Bridle is spreading misinformation rather than openly discuss the scientific literature. Dr. Fisman even admitted that he was unwilling to discuss the science with Dr. Bridle (Paragraph 34).

d. With respect to paragraph 30, Exhibit N, page 184, in regards to Dr. Bridle's claims that miniscule quantities of spike protein in the blood can present a health hazard, note that picogram and fentograms of proteins are toxic, such as botulinum toxin and endotoxin. Therefore the amount of protein available in the blood is not an accurate predictor of its ability to cause harm to human cells.

e. In regards to Dr. Bridle's assertions re: accumulation in ovaries, part of the regulatory submission to which Dr Fisman seems to be unaware which is usually then followed up by subsequent human studies which were not performed.

28. Additionally, each scientific point made by Dr. Bridle during the interview was confirmed by scientists during a panel presentation and discussion at The Future of Medicine: Beyond mRNA vaccines on June 1, 2023 at McGill University (https://www.mcgill.ca/sbms/channels/event/future-medicine-beyond-mrna-vaccines-348383), which I attended live. The replay of that is widely available to the public (https://e1.envoke.com/ext/pages/8168da7a57652e4f6e26474fe17ca814). During this presentation, Anastasia Khvorova (RNA Therapeutics Institute, UMass Chan Medical School) and others admitted that there were issues with the biodistribution (even referred to the Japanese study), and informed consent when rolling out the COVID-19 modRNA vaccines. Prof Mohamad-Gabriel Alameh (Penn Institute for RNA Innovation) stated that the lipid nanoparticles (LNPs) are strong adjuvants, and they need to make them immunologically silent. This is important since the LNPs were assessed by the regulators as novel excipients, which means they are pharmacologically inactive by themselves. This is part of the basis to use the LNPs of the vaccine as platform technology. If classified as an adjuvant, they need different studies for regulatory approval than does excipients. Dr. John Androsavic (Global Head, RNA Medicine Lead, Pfizer) admitted that the "rare" side effects of the vaccine were all due to the spike so don't worry, the next mRNA vaccines will be even safer especially if they can make the LNPs immunologically silent.

29. I have expertise to opine that what was attributed to Dr. Bridle as "misinformation" by Dr. Fisman was in fact scientifically truthful and accurate. The information Dr. Bridle provided did not constitute false or misleading opinions.

False claims of scientists spreading "misinformation" is not in the Public Interest

30. The claims by Dr. Bridle were not "misinformation" but were scientifically sound based on available scientific data. In every instance where Dr. Bridle went public with a statement, he was well researched and presented the facts that he knew. In the scientific method an observation is made, a hypothesis is formulated, tested either empirically in the laboratory or through critically examining the published literature, and then presenting and discussing the findings. Good scientific discussion/debate in the public arena is essential. To stifle scientific discussion or to only listen to one side of the argument is detrimental to the advancement of science and could be harmful to the public, especially during a pandemic. As Premier Doug Ford said, "we need all hands-on deck" and this includes experts in vaccinology like Dr. Byram Bridle.

31. There are several instances during the pandemic where even Health Canada admitted that they made decisions without having all the information. For example, on October 19, 2023 I released a preprint showing excessive residual plasmid DNA in the Pfizer and Moderna COVID-19 modRNA vaccines and an SV40 enhancer-promoter in the Pfizer COVID-19 modRNA vaccines[25]. This work confirmed the initial findings of Kevin McKernan[26] and Dr. Philip Buckhaults[27]. Six hours after the release of my preprint, through an Epoch Times Canada article[28], Health Canada confirmed the presence of DNA

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[25] Speicher, D.J., Rose, J., Gutschi, L.M., Wiseman, D.M., McKernan, K. (2023) DNA fragments detected in monovalent and Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada: Exploratory dose response relationship with serious adverse events. OSF Preprints. Retrieved from https://osf.io/mjc97/

[26] McKernan, K., Helbert, Y., Kane, L. T., & McLaughlin, S. (2023). Sequencing of bivalent Moderna and Pfizer mRNA vaccines reveals nanogram to microgram quantities of expression vector dsDNA per dose. OSF.io. doi:10.31219/osf.io/b9t7m

[27] South Carolina Senate. (2023, 2023-09-13). SC Senate Hearing - USC Professor Dr. Phillip Buckhaults. Retrieved from https://www.youtube.com/watch?v=IEWHhrHiiTY

[28] https://www.theepochtimes.com/world/exclusive-health-canada-confirms-undisclosed-presence-of-dna-sequence-in-pfizer-shot-5513277

in the Pfizer COVID-19 vaccines that what was previously considered "misinformation" but was in fact accurate.

32. My research study and publication was reported by The Epoch Times on November 7, 2023[29].

33. On October 31, 2023. I was interviewed by Mathew Horwood and Noe Chartier, and on November 27, 2023. I was provided with an email exchange between Mr. Horwood of The Epoch Times and Ms. Ann Madison at Health Canada.

34. Attached and marked as **Exhibit C** is the email exchange between Mr Horwood and Ms. Madison. Additionally on November 28, 2023, I requested access to this information under the *Access to Information Act*, attached as **Exhibit D**. The request is pending.

35. The conclusions I reached as an expert may have been contrary to Public Health or Health Canada information, or "to the overwhelming majority of scientific opinion" but they were accurate. I was also subject to the allegation of "misinformation" by academics commenting outside the ambit of their expertise. Those claims were false.

36. It is therefore not in the public interest to not have scientists and their opinion labelled as "misinformation".

Harms for alleging Dr. Bridle is "an immunologist spreading misinformation"

37. Despite standing on the scientific evidence, people like Dr. Fisman wrongly labelled Dr. Bridle as "spreading misinformation" and "anti-vaxxer" has been detrimental Dr. Bridle's research group, funding, and reputation as a scientist. Prior to the pandemic Dr. Bridle had a growing and very productive research team that was well funded. Since the pandemic

[29] https://www.theepochtimes.com/health/billions-of-copies-of-dna-impurities-and-contaminants-in-a-single-dose-of-covid-19-mrna-vaccine-preprint-5515324?utm_source=partner&utm_campaign=ZeroHedge&src_src=partner&src_cmp=ZeroHedge

and Dr. Bridle's evidence-based scientific stance Dr. Bridle has not been able to obtain new funding. His present research funding is drained, and he is having difficulty getting more research funding to the point where the university is laying off all those employed by Dr. Bridle at the University of Guelph. Even Dr. Bridle's students and colleagues, like me, who have supported him are being unfairly treated due to our association with Dr. Bridle.

38. The damage to Dr. Bridles reputation is not just him but future scientists, such as myself as his former student. I benefited from the depth of his knowledge, the excellence of his teaching methods and the rigor of his research. It is a great loss to the study of research of sciences in Canada as Dr. Bridle is one of the country's leading viral immunologists.

SWORN BEFORE ME by David Speicher in the City of Hamilton, in the Province of Ontario, on this 13th day of December, 2023, in accordance with O. Reg. 431/20 Administering Oath or Declaration Remotely

A Commissioner for Taking Oaths
Rocco Galati B.A. LL.B. LL.M

Dr. David Speicher

This is Exhibit "A" to the Affidavit of
Dr. David Speicher, sworn before me on
this 13th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

CURRICULUM VITAE

David J. Speicher, PhD DTM
Visiting Professor of Biology and Health Sciences
h-index = 14 (Google Scholar)

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Educational Background

2018 – 2020
Post-doctoral Fellow (Bioinformatics and Molecular Epidemiology)
McMaster University, Department of Biochemistry and Biomedical Sciences
M.G. DeGroote Institute for Infectious Disease Research
Hamilton, Ontario, Canada
"*Clostridioides difficile* strain divergence and transmission in Southern Ontario"
Supervisor: Dr. Andrew G. McArthur

2016 – 2018
Post-doctoral Fellow (Molecular and Clinical Microbiology)
McMaster University, Department of Pathology and Molecular Medicine
M.G. DeGroote Institute for Infectious Disease Research
Hamilton, Ontario, Canada
"Oral diagnostics of viruses" and "*C. difficile* and associated phages"
Supervisor: Dr. Marek Smieja

2007 – 2012
PhD (Virology)
Griffith University, Department of Dentistry and Oral Health
Menzies Health Institute Queensland
Gold Coast Campus, Gold Coast, Queensland, Australia
"Characterization of Human Herpesvirus 8 in Australia and Kenya"
Supervisor: Professor Newell W. Johnson CMG

2005 – 2006
MSc with Honours (Clinical Microbiology)
Griffith University, School of Biomolecular and Biomedical Sciences
Sir Albert Sakzewski Virus Research Centre (Royal Children's Hospital)
Brisbane, Queensland, Australia
Project 1: "Incidence and emergence of respiratory viruses in QLD, Australia."
Project 2: "Expression and purification of Coronavirus nucleocapsid proteins."
Supervisor: Associate Professor Theo Sloots

1999 – 2003
BSc. with Honours (Maj: Biology; Min: Chemistry)
Redeemer University College, Ancaster, Ontario, Canada
Undergraduate Project on *Rhodnius prolixus*
Supervisor: Dr. Gary Chiang

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Certificates

2019	Canada Good Clinical Practice (GCP) Certification, CITI Program, Canada
2018	Distinguished Toastmaster, Toastmasters International
2018	Teaching and Learning Scholar, Macpherson Institute, McMaster University, Hamilton, ON, Canada
2018	Foundations of Project Management, Mitacs, McMaster, University, Hamilton, ON, Canada
2017	Teaching and Learning Foundations, Macpherson Institute, McMaster, University, Hamilton, ON, Canada
2014	Advanced Safety in the Field (ASITF), United Nations Department of Safety and Security
2014	Basic Safety in the Field II (BSITF II), United Nations Department of Safety and Security

Honours, Awards, and Scholarships

2022	Local Volunteer of the Year Award, Delta Waterfowl
2022	$5,000. 3rd place, 7th Sunstar World Perio Research Awards. Sunstar Foundation in collaboration with the Journal of Clinical Periodontology, Journal of Dental Research, Journal of Periodontology, Journal of Periodontology Research.
2020	Faculty of Health Sciences Postdoctoral Leadership Award, McMaster, University, Hamilton, ON, Canada
2016	Research Institute Post-Doctoral Fellowship Award, St Joseph's Healthcare Hamilton, Hamilton, ON, Canada
2014	Best Poster, 7th World Workshop on Oral Health & Disease in AIDS. Hyderabad, India. November 6-9, 2014.
2009	Travel Grant, The Mouth and AIDS: The Global Challenge, April 21-24, 2009, Beijing, China
2010 – 2011	Completion Assistance Postgraduate Research Scholarship, Griffith University, QLD, Australia
2008 – 2010	Griffith University Postgraduate Research Scholarship, Griffith University, QLD, Australia
2007 – 2012	Griffith University International Postgraduate Research Scholarship, Griffith University, QLD, Australia
2007	School of Dentistry and Oral Health Postgraduate Research Scholarship, Griffith University, QLD, Australia
2006	Griffith Award for Academic Excellence 2006, Griffith University, QLD, Australia
2005	Griffith Award for Academic Excellence 2005, Griffith University, QLD, Australia

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Professional Organizations

2021 – Present	Scientific and Medical Advisory Committee, Canadian COVID Care Alliance
2007 – Present	American Society for Microbiology
2005 – Present	Toastmasters International
2019 – 2020	Canadian Association of Postdoctoral Scholars
2016 – 2020	Association of Medical Microbiology and Infectious Disease Canada (AMMI)
2006 – 2014	The Australian Society for Microbiology Inc

Employment History

Academic

2021 – Present	Senior Research Associate, University of Guelph, Guelph, ON, Canada
2015 – Present	Honorary Professor, Sree Balaji Dental College& Hospital, Balaji University, Chennai, Tamil Nadu, India
2022 – 2023	Visiting Professor, Redeemer University, Ancaster, ON, Canada
2022 – 2023	Sessional Assistant Professor, Redeemer University, Ancaster, ON, Canada
2022 – 2022	Director of Scientific Operations, Novometrix Research Inc, Guelph, ON, Canada
2021 – 2022	Lab and R&D Director, Multiplex Genomics, Guelph, ON, Canada
2021 – 2021	Laboratory Scientist, Epitome Genetics, Kitchener, ON, Canada
2018 – 2022	Research Associate, St Joseph's Healthcare Hamilton, Hamilton, ON, Canada
2014 – 2022	Senior Research Fellow (Adj), Menzies Health Institute Queensland, Griffith University, QLD, Australia
2014	Senior Research Fellow, Griffith Health Institute, Griffith University, Australia
2011 – 2013	Research Fellow, Griffith Health Institute, Griffith University, QLD, Australia
2001 – 2004	Laboratory Technician, Redeemer University College, Ancaster, ON, Canada

Scholarly & Professional Activities

Executive Positions

2018 – 2020	Co-chair, Executive Committee, Faculty of Health Sciences Postdoctoral Association, McMaster, University, Hamilton, ON, Canada
2016 -- 2018	Inter Campus Liaison Officer, Executive Committee, Faculty of Health Sciences Postdoctoral Association, McMaster, University, Hamilton, ON, Canada

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Professional Development

2021 Project Management for Research and Evaluation, RPM, Toronto, ON, Canada

2021 Grant Writing Webinar Series, American Society of Microbiology

2021 Manuscript Writing and Publishing for Scientists, American Society of Microbiology

2019 23rd Biennial Evergreen International Phage Meeting. Olympia, WA, USA.

2019 High Performance Computing & Machine Learning, SHARCNET and University of Toronto, McMaster, University, Hamilton, ON, Canada

2018 Software/Data Carpentry Workshop, McMaster, University, Hamilton, ON, Canada

2018 'OMICS and Epidemiology workshop, McMaster, University, Hamilton, ON, Canada

2017 12 Irrefutable Laws of Leadership, The John Maxwell Team

2017 Instructional Skills Workshop, Macpherson Institute, McMaster University, Hamilton, ON, Canada

2017 Essentials of Productive Teams, Mitacs, McMaster University, Hamilton, ON, Canada

2016 2nd Global Health Diagnostics Course, McGill Summer Institute in Infectious Diseases and Global Health, McGill University, Montreal, Quebec, Canada

2007 Virology Master Class, June 18-29, 2007, University of Adelaide, South Australia, Australia

Journal Editorships

2023 MDPI biomedicines, Special Issue "Molecular Detection of Infectious Diseases"

Journal Referee (ad hoc)

BMC Cancer - 2023

BMC Oral Health - 2023

Clinical Case Reports (Wiley) - 2020

Computational and Structural Biotechnology Journal - 2020

Current Gene Therapy (Bentham Science Publishers) - 2017

Diagnostic Microbiology and Infectious Diseases (Elsevier) - 2014

International Journal of Molecular Sciences - 2020

Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology (Elsevier) - 2020

Pathology (Elsevier) – 2015

Infection (Springer Nature) - 2023

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Teaching and Supervision

Courses Taught

Teaching portfolio available upon request.

Undergraduate

BIO-463/CHE-463	Advanced Techniques in Biochemistry & Molecular Biology (2023), Redeemer University, Canada
BIO-261	Genetics (2023), Redeemer University, Canada
BIO-351	Microbiology (2022), Redeemer University, Canada
2015MSC	Laboratory Instructor (February to April 2007), Griffith University, Australia

Supervisorships

PhD Students (completed)

Surani Fernando — School of Dentistry and Oral Health, Griffith University, QLD, Australia
"Assessing maternal, environmental, and individual risk factors for dental caries in a population of children from Queensland, Australia.
Supervisors: Newell W. Johnson, Paul Scuffham, Rodney Lea, **David J. Speicher**
2015 – 2018

MSc Students (completed)

Bradley McInnes — School of Dentistry and Oral Health, Griffith University, QLD, Australia
"Production of a plasmid construct to produce a new qPCR assay for the detection of Human Herpesvirus 8"
Degree: MSc in Clinical Microbiology
Supervisors: Newell W. Johnson and **David J. Speicher**
July – October 2009

Undergraduate Students (completed)

Victoria Kashchuk — School of Dentistry and Oral Health, Griffith University, QLD, Australia
"Prevalence of HHV-8 in an HIV-negative population in Gold Coast, Australia"
Degree: BDS with Honours
Funding: Colin Cormie Grant via the Australian Dental Research Foundation
Supervisors: Newell W. Johnson and **David J. Speicher**
February 2014 – September 2015

External Examiner - PhD Defense

Laura Gilbert — June 2022 — Memorial University
Recent developments in early detection strategies and population-based screening: the perspectives of cervical cancer and COVID-19

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Guest Lecturing

"Respiratory Viruses and COVID-19" (Nov 14, 2023) in Microbiology (BIO-351), Redeemer University

"Immunology" (June 26, 2019) in Human Physiology (KINE 2P09), Brock University

Research Funding

Principal investigator(s) name underlined on grants listed below. My name is in **bold.**

Project Grants Under Review

None

Project Grants Funded

2022	Funding Agency:	Social Sciences and Humanities Research Council (SSHRC), Canada
	Program Type	New Frontiers in Research Fund - Special Call 2022
	Amount:	$500,000
	Project Title:	Transparency and shared responsibility for sustainable post-pandemic recovery and evidence-informed decision-making during future global emergencies.
	Investigators:	Rinner C, Chaufan C, Chow C, Weirsma E, Rangel J, Wang Y, Aversa J., Francis D, Klakura J, Manwell J, **Speicher D**, Zimmerman J, Valente A, Grandsman A, Welsh D.
2016 (Completed)	Funding Agency:	Australian Dental Research Foundation Inc., Australia
	Amount:	$14,821
	Project Title:	Identifying inherited epigenetic and microbiomic influences of dental caries.
	Investigators:	Fernando S, **Speicher DJ**, Lea RA, Johnson NW
2013 (Completed)	Funding Agency:	Griffith Health Institute, Griffith University, Australia
	Amount:	$15,000
	Project Title:	Maternal, paternal, environmental and genetic influences on dental caries in children.
	Investigators:	Johnson NW, Scuffham PA, Griffiths LR, Fernando S, Lea RA, **Speicher DJ**
2012 (Completed)	Funding Agency:	School of Dentistry and Oral Health, Griffith University, Australia
	Amount:	$5,000
	Project Title:	Detection of Human Immunodeficiency Virus, Human Herpesviruses and Human papillomavirus in Oral Fluids from HIV-positive Patients in Chennai, India.
	Investigators:	**Speicher DJ** and Johnson NW
2012 (Completed)	Funding Agency:	Griffith Health Institute, Griffith University, Australia
	Amount:	$15,000
	Project Title:	Development of a serological algorithm for carriage of, or infection with, HHV-8 for use in Australia, India, and Papua New Guinea.
	Investigators:	**Speicher DJ** and Johnson NW

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Project Grants Funded continued...

2012 (Completed)	Funding Agency:	DNA Genotek Grant Program, Canada
	Amount:	$25,000 plus 400 collection kits.
	Project Title:	Salivary diagnosis of HIV, HHV-8 and HPV in two distinct HIV-positive populations: Port Moresby, Papua New Guinea and Chennai, India.
	Investigators:	**Speicher DJ** and Johnson NW
2011 (Completed)	Funding Agency:	Australian Dental Research Foundation Inc., Australia
	Amount:	$10,271
	Project Title:	Salivary diagnostics of HHV-8 and HPV in Port Moresby, Papua New Guinea: a controlled study of HIV positive and negative subjects.
	Investigators:	**Speicher DJ**, Amarasighe H, Johnson NW
2011 (Completed)	Funding Agency:	Australian Dental Research Foundation Inc., Australia
	Amount:	$5,500
	Project Title:	Saliva as a diagnostic fluid for Human Herpesvirus 8 carriage in man: a controlled study of HIV positive and negative subjects.
	Investigators:	**Speicher DJ**, Johnson NW
2011 (Completed)	Funding Agency:	Griffith Health Institute, Griffith University, Australia
	Amount:	$15,000
	Project Title:	Herpesviruses and human papillomavirus in oral fluids from HIV-positive patients in India.
	Investigators:	Johnson NW and **Speicher DJ**

Equipment Grants

2013	Funding Agency:	Griffith University, Australia
	Amount:	$32,000
	Equipment:	Taylor Wharton Vapour Phase Cryotank
	Investigators:	Hamlet S and **Speicher DJ**
2012	Funding Agency:	Griffith University, Australia
	Amount:	$55,930
	Equipment:	Bio-Rad Gel Doc Ezy, Tecan HydroSpeed Plate Washer, Infors Ecotron with cooling, Memmert Incubator INE550
	Investigators:	**Speicher DJ**
2011	Funding Agency:	Griffith University, Australia
	Amount:	$21,000
	Equipment:	Biometra TProfessional PCR Thermocyclers
	Investigators:	**Speicher DJ**
2010	Funding Agency:	Griffith University, Australia
	Amount:	$190,000
	Equipment:	Eppendorf EpMotion 5075 TMX, Roche LC480 Real-Time PCR machine
	Investigators:	Hamlet S and **Speicher DJ**

External Grant Reviews

2016 Project Grants, National Research Foundation, South Africa

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Lifetime Publications

Book Chapters

1. **Speicher DJ,** Nasir JA, Zhou P, Anderson DE (2021) Whole-Genome Sequencing of Pathogens in Saliva: A Target-Enrichment Approach for SARS-CoV-2. In: Adami G.R. (eds) The Oral Microbiome. Methods in Molecular Biology, vol 2327. Humana, New York, NY. https://doi.org/10.1007/978-1-0716-1518-8_8
2. **Speicher DJ,** Aziz RK (2021) Profiling the Human OralMycobiome in Tissue and Saliva Using ITS2 DNA Metabarcoding Compared to a Fungal-Specific Database. In: Adami G.R. (eds) The Oral Microbiome. Methods in Molecular Biology, vol 2327. Humana, New York, NY. https://doi.org/10.1007/978-1-0716-1518-8_15
3. Johnson NW, Gupta B, **Speicher DJ**, Ray CS, Shaikh MH, Al-Hebshi N, Gupta PC. Chapter 2. Etiology and risk factors. **In**: Shah JP, Johnson NW, editors. Oral and oropharyngeal cancer. 2nd ed. Boca Raton: CRC Press, Taylor & Francis Group; **2018**. p. 19–94.
4. **Speicher DJ,** Ali M, Smieja M. Respiratory Viruses. Manual of Molecular and Clinical Laboratory Immunology, Eighth Edition: American Society of Microbiology; **2016**. https://doi.org/10.1128/9781555818722.ch63.
5. **Speicher DJ,** Johnson NW: Improving the detection of human herpesvirus-8 in AIDS patients. In: Research priorities for meeting oral health goals in developing countries. edn. Edited by Rahmatulla M, Shah N. Hyderabad: Indian Academy for Advanced Dental Education; **2009**: 66-79.

Journal Articles (Published)

1. Ratnam S, Jang D, Alaghehbandan R, Gilbert L, Xu Y, Wang W, Andrews P, Green A, Speicher DJ, Chernesky M (2023) HPV genotype-specific distribution and attributable risk in cervical intraepithelial neoplasia in a referral population with a history of LSIL. Cancer Biomarkers.
2. **Speicher, DJ,** Fryk, JJ, Kashchuk, V, Faddy, HM, Johnson, NW (2022) Human Herpesvirus 8 in Australia: DNAemia and Cumulative Exposure in Blood Donors. Viruses 14, (10).
3. Knapp, JP, Kakish, JE, Bridle, BW, **Speicher, DJ** (2022) Tumor Temperature: Friend or Foe of Virus-Based Cancer Immunotherapy. Biomedicines 10, (8).
4. Wilson J, Rivers J, Anholt M, Onawola D, Lantos G, **Speicher DJ**, De Monte S, Kasab-Bachi H, Haines T, Noor S, Gillam W, Suganda E, Aramini J (2022) Veterinary leadership: Time for us to step into our own power. Can Vet J, 63: 647-648.
5. Jang, D., S. Ratnam, M. Smieja, **D. J. Speicher**, M. Arias, A. Clavio, D. Costescu, L. Elit, S. Huang, E. Herrero-Garcia, A. M. Joseph, H. Jiang, R. Needle and M. Chernesky (2021). "Comparison of Alinity m HPV and cobas HPV Assays on Cervical Specimens in Diverse Storage Media." Tumour Virus Res: 200224.
6. Shah A, Jang D, Martin I, **Speicher DJ**, Lidder R, Clavio A, Ratnam S, Smieja M, Chernesky M (2021) Workflow and throughput of commercial assays to detect Mycoplasma genitalium and macrolide resistance mediating mutations. Sexually Transmitted Diseases. doi:10.1097/olq.0000000000001360
7. Misra A, **Speicher DJ**, Luinstra K, Maciejewski J, Richard-Greenblatt M, Yu Y, Smieja M (2021) Self-collected oral flocked swabs to measure prevalence of Epstein-Barr Virus antibodies and DNA amongst university students. Diagnostic microbiology and infectious disease 100 (1):115295. doi:10.1016/j.diagmicrobio.2020.115295

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Journal Articles (Published) continued...

8. Chernesky M, Jang D, Martin I, **Speicher DJ**, Clavio A, Lidder R, Ratnam S, Smieja M, Arias M, Shah A (**2020**) Comparison of Assays for the Diagnosis of Mycoplasma genitalium and Macrolide Resistance Mutations in Self-Collected Vaginal Swabs and Urine. Sex Transm Dis 47 (10):705-711. doi:10.1097/OLQ.0000000000001226.

9. Bielska IA, Manis DR, Schumacher C, Moore E, Lewis K, Agarwal G, Mondoux S, Jewett L, **Speicher DJ**, Liu RH, Leyenaar M, McLeod B, Upadhye S (**2020**) Health Sector responses to the COVID-19 pandemic in Ontario, Canada – January to May 2020. Zdrowie Publiczne i Zarządzanie [Public Health and Management] 18(1):106-120. doi:10.4467/20842627oz.20.010.12664.

10. Bielska IA, Embrett M, Jewett L, Buote R, Manis DR, Parikh M, **Speicher DJ**, Agarwal G, Nartowski RO, Finnegan H, Bandara T, Hamilton CB, Moore E, Liu RH, Roher SIG, Lopatina E, Nguyen DTK, Lawrence L, Lukewich J (**2020**) Canada's multi-jurisdictional COVID-19 Public Health response January to May 2020. Zdrowie Publiczne i Zarządzanie [Public Health and Management] 18(1):88-105. doi:10.4467/20842627oz.20.009.12663.

11. Alcock BP, Raphenya AR, Lau TTY, Tsang KK, Bouchard M, Edalatmand A, Huynh W, Nguyen AV, Cheng AA, Liu S, Min SY, Miroshnichenko A, Tran HK, Werfalli RE, Nasir JA, Oloni M, **Speicher DJ**, Florescu A, Singh B, Faltyn M, Hernandez-Koutoucheva A, Sharma AN, Bordeleau E, Pawlowski AC, Zubyk HL, Dooley D, Griffiths E, Maguire F, Winsor GL, Beiko RG, Brinkman FSL, Hsiao WWL, Domselaar GV, McArthur AG (**2020**) CARD 2020: antibiotic resistome surveillance with the comprehensive antibiotic resistance database. Nucleic Acids Res 48 (D1):D517-D525. doi:10.1093/nar/gkz935.

12. **Speicher DJ**, Luinstra K, Smith EJ, Castriciano S, Smieja M (**2020**) Non-invasive detection of IgG antibodies from common pathogenic viruses using oral flocked swabs. Diagnostic microbiology and infectious disease 97 (3):115038. doi:10.1016/j.diagmicrobio.2020.115038

13. Jang D, Shah A, Arias M, Ratnam S, Smieja M, Chen X, Wang Y, **Speicher DJ**, Chernesky M (**2020**) Performance of AmpFire HPV assay on neck cervical lymph node aspirate and oropharyngeal samples. J Virol Methods 279:113840. doi:10.1016/j.jviromet.2020.113840.

14. Fernando S, Kumar S, Bakr M, **Speicher DJ**, Lea R, Scuffham PA, Johnson NW (**2019**) Children's untreated decay is positively associated with past caries experience and with current salivary loads of mutans Streptococci; negatively with self-reported maternal iron supplements during pregnancy: a multifactorial analysis. J Public Health Dent 79 (2):109-115. doi:10.1111/jphd.12301.

15. Perera M, Al-Hebshi NN, Perera I, Ipe D, Ulett GC, **Speicher DJ**, Chen T, Johnson NW (**2018**) Inflammatory Bacteriome and Oral Squamous Cell Carcinoma. Journal of dental research 97 (6):725-732. doi:10.1177/0022034518767118.

16. Perera M, Al-Hebshi NN, Perera I, Ipe D, Ulett GC, **Speicher DJ**, Chen T, Johnson NW (**2017**) A dysbiotic mycobiome dominated by Candida albicans is identified within oral squamous-cell carcinomas. Journal of oral microbiology 9 (1):1385369. doi:10.1080/20002297.2017.1385369.

17. **Speicher DJ**, Ramirez-Amador V, Dittmer DP, Webster-Cyriaque J, Goodman MT, Moscicki AB (**2016**) Viral infections associated with oral cancers and diseases in the context of HIV: a workshop report. Oral diseases 22 Suppl 1:181-192. doi:10.1111/odi.12418.

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Journal Articles (Published) continued...

18. Perera M, Al-Hebshi NN, **Speicher DJ**, Perera I, Johnson NW (**2016**) Emerging role of bacteria in oral carcinogenesis: a review with special reference to perio-pathogenic bacteria. Journal of oral microbiology 8:32762. doi:10.3402/jom.v8.32762.

19. Al-Hebshi NN, Nasher AT, **Speicher DJ**, Shaikh MH, Johnson NW (**2016**) Possible interaction between tobacco use and EBV in oral squamous cell carcinoma. Oral oncology 59:e4-e5. doi:10.1016/j.oraloncology.2016.06.005.

20. **Speicher DJ**, Wanzala P, D'Lima M, Njiru A, Chindia M, Dimba E, Johnson NW (**2015**) Diagnostic challenges of oral and cutaneous Kaposi's sarcoma in resource-constrained settings. Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology 44 (10):842-849. doi:10.1111/jop.12315.

21. **Speicher DJ**, Wanzala P, D'Lima M, Johnson KE, Johnson NW (**2015**) Detecting DNA viruses in oral fluids: evaluation of collection and storage methods. Diagnostic microbiology and infectious disease 82 (2):120-127. doi:10.1016/j.diagmicrobio.2015.02.013.

22. Fernando S, **Speicher DJ**, Bakr MM, Benton MC, Lea RA, Scuffham PA, Mihala G, Johnson NW (**2015**) Protocol for assessing maternal, environmental, and epigenetic risk factors for dental caries in children. BMC oral health 15 (1):167. doi:10.1186/s12903-015-0143-2.

23. **Speicher DJ**, Sehu MM, Mollee P, Shen L, Johnson NW, Faoagali JL (**2014**) Successful treatment of iatrogenic multicentric Castleman's disease arising due to recrudescence of HHV-8 in a liver transplant patient. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 14 (5):1207-1213. doi:10.1111/ajt.12693.

24. **Speicher DJ**, Johnson NW (**2014**) Comparison of salivary collection and processing methods for quantitative HHV-8 detection. Oral diseases 20 (7):720-728. doi:10.1111/odi.12196.

25. **Speicher DJ**, Sehu MM, Johnson NW, Shaw DR (**2013**) Successful treatment of an HIV-positive patient with unmasking Kaposi's sarcoma immune reconstitution inflammatory syndrome. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology 57 (3):282-285. doi:10.1016/j.jcv.2013.03.005.

26. **Speicher DJ**, Johnson NW (**2012**) Detection of human herpesvirus 8 by quantitative polymerase chain reaction: development and standardisation of methods. BMC infectious diseases 12:210. doi:10.1186/1471-2334-12-210.

27. Mackay IM, Arden KE, **Speicher DJ**, O'Neil NT, McErlean PK, Greer RM, Nissen MD, Sloots TP (**2012**) Co-circulation of four human coronaviruses (HCoVs) in Queensland children with acute respiratory tract illnesses in 2004. Viruses 4 (4):637-653. doi:10.3390/v4040637.

28. Patton LL, Ranganathan K, Naidoo S, Bhayat A, Balasundaram S, Adeyemi O, Taiwo O, **Speicher DJ**, Chandra L (**2011**) Oral lesions, HIV phenotypes, and management of HIV-related disease: Workshop 4A. Advances in dental research 23 (1):112-116. doi:10.1177/0022034511400079.

29. Johnson NW, Malamud D, Reznik D, **Speicher DJ**, Phelan J (**2011**) Mucosal fluids and biomarkers of clinical disease: workshop 3B. Advances in dental research 23 (1):137-141. doi:10.1177/0022034511400078.

30. **Speicher DJ**. Driving your research. Microbiology Australia. March **2009**: 30(1):46-47.

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Journal Articles (Published) continued...

31. Sloots TP, McErlean P, **Speicher DJ**, Arden KE, Nissen MD, Mackay IM (**2006**) Evidence of human coronavirus HKU1 and human bocavirus in Australian children. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology 35 (1):99-102. doi:10.1016/j.jcv.2005.09.008.

Journal Abstracts (published)

1. **Speicher DJ**, Luinstra K, Maciejewski J, Tsang KK, McArthur AG, Smieja. I03 Clostridioides difficile strain divergence over time. JAMMI **2019** Supplemental 4:P26.
2. Chernesky M, Jang D, Ratnam S, Shah A, Smieja M, **Speicher DJ**, Martin I, Arias M, Clavio A. P06 Comparison of two commercial amplification assays, SpeeDx Resistance Plus MG and Seeplex STD6 ACE detection, performed on self-obtained vaginal and urine specimens for the diagnosis of Mycoplasma genitalium infections. JAMMI **2019** Supplemental 4:P42.
3. Jang D, Shah A, Smieja M, **Speicher DJ**, Arias A, Clavio A, Ratnam S, Chernesky M. Mycoplasma genitalium and macrolide resistance mutations in vaginal swabs of Canadian women tested with commercial molecular assays. JAMMI **2019** Supplemental 4:P43.
4. Chernesky M, Jang D, Martin I, Shah A, Smieja M, **Speicher DJ**, Clavio A, Arias M. P597, Comparison of assays and specimen types for the diagnosis of mycoplasma genitalium and macrolide resistant mutations Sexually Transmitted Infections **2019**;95:A265.
5. Fernando S, Skelly E, Tadakamadla SK, Selway CA, Bakr M, **Speicher DJ**, Schuffham PA, Lalloo R, Kroon J, Weyrich L, Johnson NW (**2019**) The salivary microbiome associated with dental caries in Australian children Australian Dental Journal 64 (4).
6. Maciejewski J, Luinstra K, **Speicher DJ**, Jayaratne P, Smieja M. Detection of asymptomatic Clostridium difficile amongst hemodialysis patients. JAMMI **2018** Supplemental 3:P117.
7. **Speicher DJ**, Luinstra K, Smieja M. Bacteriophages associated with Clostridium difficile infection. JAMMI **2018** Supplemental 3:P122.
8. **Speicher DJ**, Luinstra K, Castriciano S, Smieja M. SP29 Detection of viral antibodies via dried oral swabs. JAMMI **2017** Supplemental 2:P57.
9. Al-hebshi N, Perera M, Perera I, Ipe D, Ulett G, **Speicher DJ**, Nasher A, Maryoud M, Homeida H, Idris AM, Chen T, Johnson N (**2017**) The bacteriome and mycobiome associated with oral squamous cell carcinoma: metagenomic analysis of samples from Yemeni and Sri Lankan cohorts. Journal of oral microbiology 9 (sup1):1325188. doi:10.1080/20002297.2017.1325188
10. **Speicher DJ**, Amarasinghe A, Johnson NW (**2016**) Detection of human herpes viruses and HIV in patients from Southeast India. Australian Dental Journal 61 (4).
11. Kashchuk V, **Speicher DJ**, Johnson N (**2014**) Prevalence of HHV-8 in an HIV-negative population on the Gold Coast, Australia. Australian Dental Journal 59 (4).
12. **Speicher DJ**, Saravanan S, Kumarasamy N, Ranganathan K, Johnson NW. Comparison of plasma and salivary HIV loads determined via a coupling of the Abbott HIV detection system with the DNA Genotek OMNIgene™ DISCOVER (OM-505) kits. BMC Infectious Diseases **2014** 14(Suppl 3):P80.

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Journal Abstracts continued...

13. Johnson NW, **Speicher DJ**. Oral Kaposi's sarcoma and the Global HHV-8 Story. Pathology 45: Supp 1, February **2013**, Abstract S11. RCPA Pathology Update 2013 IAP Australasian Division 37th Annual Scientific Meeting.
14. **Speicher DJ**, Wanzala P, D'Lima M, Dimba E, Nijiru A, Perera R, Chindia M, Johnson NW Diagnosis of oral and cutaneous Kaposi's sarcoma in Africa: Challenges involving histology and molecular detection. In, **2011**. http://hivaidsconference. com. au/Past-Conferences.

Preprints (BioRxiv, MedRxiv, and Preprints)

1. Speicher, David J., Jessica Rose, L. M. Gutschi, David M. Wiseman, PhD, and Kevin McKernan. (2023) DNA Fragments Detected in Monovalent and Bivalent Pfizer/biontech and Moderna Modrna COVID-19 Vaccines from Ontario, Canada: Exploratory Dose Response Relationship with Serious Adverse Events. OSF Preprints. October 19. doi:10.31219/osf.io/mjc97.
2. Khurshid Z, Zohaib S, Joshi C, Moin SF, Zafar MS, **Speicher DJ** (2020) Saliva as a non-invasive sample for the detection of SARS-CoV-2: a systematic review. medRxiv:2020.2005.2009.20096354. doi:10.1101/2020.05.09.20096354.
3. Nasir JA, **Speicher DJ**, Kozak RA, Poinar HN, Miller MS, McArthur AG (2020) Rapid Design of a Bait Capture Platform for Culture- and Amplification-Free Next-Generation Sequencing of SARS-CoV-2. Preprints doi:10.20944/preprints202002.0385.v1.
4. Tsang K; **Speicher DJ**; McArthur A. Pathogen Taxonomy Updates at the Comprehensive Antibiotic Resistance Database: Implications for Molecular Epidemiology. Preprints 2019, 2019070222 (doi: 10.20944/preprints201907.0222.v1).

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Presentations

*Presenter's name is underlined. My name and year are in **bold**.*

Oral Presentations

1. Wilson JB, Esfandiari N, Rivers J, **Speicher DJ**, Suganda E, Jauwena A, Haesler B, DeMonte S, Karrow K, Onawola D, Salman M. Community Network Integration: An Approach to Alignment of One Health Partners for Solutions to Antimicrobial Resistance. 11th International Conference on Antimicrobial Agents in Veterinary Medicine. September 11-14, 2022, Madrid, Spain.
2. **Speicher DJ**. Can dogs replace PCR for detecting COVID? Virology Journal Club. Public Health Ontario. June 24, **2022**.
3. **Speicher DJ**. SARS-CoV-2 RT-PCR: Do we really need the RT? Virology Journal Club. Public Health Ontario. February 28, **2022**.
4. **Speicher DJ**. SARS-CoV-2: Where have all the influenzas gone? Virology Journal Club. Public Health Ontario. February 12, **2021**.
5. **Speicher DJ**. Non-invasive detection and sequencing of SARS-CoV-2. 2nd Online Conference on Infectious Diseases – Coronaviruses". Virtual Conference. December 7, **2020**.
6. **Speicher DJ**. Detection of SARS-CoV-2 RNA and antibodies in saliva. Virology Journal Club. Public Health Ontario. October 30, **2020**.
7. **Speicher DJ**. Detection and surveillance of SARS-CoV-2. Virology Journal Club. Public Health Ontario. March 6, **2020**.
8. **Speicher DJ**. Faculty of Health Sciences Postdoctoral Association (FHS PDA) McMaster University. 2019 CAPS/ACSP Annual Meeting. Halifax, NS, Canada. November 3, 2019.
9. **Speicher DJ**. Phage Therapy: Two schools of thought. Which camp are you in? Virology Journal Club. Public Health Ontario. October 18, **2019**.
10. **Speicher DJ**. Coronavirus vaccines: Successes and failures from a mouse model. Virology Journal Club. Public Health Ontario. May 24, **2019**.
11. **Speicher DJ**, Luinstra K, Maciejewski J, Tsang KK, McArthur AG, Smieja. I03 Clostridioides difficile strain divergence over time. AMMI-CACMID Annual Conference. Ottawa, Canada. April 3-6, **2019**.
12. Mertz D and **Speicher DJ**. C. difficile: The role of colonization and phages. ID/IIDR Rounds. McMaster University. June 6, **2018**.
13. **Speicher DJ**. Target-enrichment for the in-depth analysis of viral genomes. Virology Journal Club. Public Health Ontario. February 8, **2019**.
14. **Speicher DJ**. CrAssphage: The most abundant virus in the human gut. Virology Journal Club. Public Health Ontario. September 29, **2018**.
15. **Speicher DJ**. The influence of bacteriophages on Clostridioides difficile toxigenicity. Virology Journal Club. Public Health Ontario. February 2, **2018**.
16. **Speicher DJ**. *Clostridium difficile*-associated Bacteriophage profiles in Faecal Microbiota Transplant Patients. 22nd Biennial Evergreen International Phage Meeting. Olympia, WA, USA. August 6-11, **2017**.

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Oral Presentations continued...

17. **Speicher DJ**. Control of multidrug-resistant bacteria via bacteriophages. Virology Journal Club. Public Health Ontario. May 13, **2017**.
18. **Speicher DJ**. Detection of viral antibodies via dried oral swabs. In-service seminar. St. Joseph's Healthcare Hamilton, Hamilton, Canada. April 20, **2017**.
19. **Speicher DJ**. Risk of transmitting HHV-8 by blood transfusions. Virology Journal Club. Public Health Ontario. March 24, **2017**.
20. **Speicher DJ**. Saliva as a diagnostic tool. Workshop. Sree Balarji Dental School, Barath University. September 9, **2016**.
21. Johnson NW and **Speicher DJ**. Epidemiology of HHV-8 in HIV infections. India. Invited Plenary. XXV Conference of the Indian Association of Oral and Maxillofacial Pathologists and the 18th International Congress of Oral Pathology. Chennai, India. September 8-16, **2016**.
22. **Speicher DJ**, Boobalan, Kausalya G, Saravanan S, Johnson NW. Potentially Infectious HIV and Herpesviruses are in saliva of HIV-positive individuals. IADR/AADR/CADR 93rd General Session, Boston, Massachusetts, USA. March **11-14, 2015.**
23. **Speicher DJ**. Saliva as a Diagnostic Tool: The usefulness of the OMNIgene●Discovery Kits. In-service seminar. DNA Genotek. May 15, **2015**.
24. **Speicher DJ**, Saravanan S, Kumarasamy N, Ranganathan K, and Johnson NW. Comparison of plasma and salivary HIV loads determined via a coupling of the Abbott HIV detection system with the DNA Genotek OMNIgene™•Discover (OM-505) kits. 2nd International Science Symposium on HIV and Infectious Disease (HIV SCIENCE 2014). Chennai, India. January 30 – February 1, **2014**.
25. Johnson NW and **Speicher DJ**. Oral Kaposi's sarcoma and the global HHV-8 story. Melbourne under the Microscope. Pathology Update 2013. Melbourne, Australia. February 22-24, **2013**.
26. **Speicher DJ**, Wanzala P, D'Lima M, Dimba E, Njiru A, Achila R, Bulimo W, Johnson NW. Histological and molecular diagnosis of Kaposi's Sarcoma in Kenya. 2nd Medical and Veterinary Viral Research Symposium, Mombasa, Kenya, October 18, **2012**.
27. **Speicher DJ**. Disseminating KS-IRIS in an HIV-positive patient lacking HHV-8 viraemia. Australian Society for Microbiology (ASM) Annual Scientific Meeting. Brisbane, Australia. July 1-4, **2012**.
28. **Speicher DJ**, Johnson NW. Evaluation of a new commercial kit for the detection of human herpesvirus 8 (HHV-8) in saliva. Gold Coast Health and Medical Research Conference. December 2-3, 2009.
29. **Speicher DJ**, Wanzala P, D'Lima M, Dimba E, Nijiru A, Perera R, Chindia ML, and Johnson NW. Diagnosis of oral and cutaneous Kaposi's sarcoma in Africa: Challenges involving histology and molecular detection. 23rd Annual conference of the Australasian Society for HIV Medicine (ASHM). Canberra, Australia. September 26-28, **2011**.
30. **Speicher DJ**, Sehu MM, Mollee P, Griffin A, Shen L, Noris D, Yarwood T, Playford EG, Faoagali JL. "Post liver transplant patient presenting with HHV-8 associated multicentric Castleman's disease: the role of qPCR." PA Week, Princess Alexandra Hospital, Brisbane, QLD. August 16-20, **2010**. http://www. health. qld. gov. au/pahospital/symposium/

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Oral Presentations continued...

31. **Speicher DJ**, Sehu MM, Mollee P, Faoagali JL. "Monitoring HHV-8 viremia in a post-transplant patient presenting with HHV-8 associated multicentric Castleman's disease." Australian Society for Microbiology Annual Scientific Meeting, Sydney Australia. July 4-8, **2010**.
32. **Speicher DJ**. HHV-8: The importance of this overlooked human herpesvirus. In-service seminar at the Royal Brisbane and Woman's Hospital, Brisbane, Australia. June 1, **2010**.
33. Sehu MM, **Speicher DJ**, Mollee P, Yarwood T, and Faoagali J. "Post liver transplant patient presenting with HHV-8 associated multicentric Castleman's disease." Pathology Update, Royal College of Pathologists of Australasia, Melbourne, Victoria. February 26-28, **2010**.
34. **Speicher DJ**. "Salivary diagnostics for oral complications of HIV" The Mouth & AIDS: 6th World Workshop on Oral Health and Disease. Beijing, China. April 21-24, **2009**.
35. **Speicher DJ**. "Role of healthcare workers in rapid diagnostic testing for HIV." The Mouth & AIDS: 6th World Workshop on Oral Health and Disease. Beijing, China. April 21-24, **2009**.
36. **Speicher DJ**. Determining HHV-8 subtypes in the Australian HIV-positive population. HIV & Sexual Health Research Forum, Brisbane May 21-22, **2009**.
37. **Speicher DJ**. Improving the detection of HHV-8 in AIDS patients. Oral Presentation. 'Research Priorities in Dental Science & Technology in Asia & Africa' hosted by the Indian Society for Dental Research. Hyderabad, India. December 1-3, **2007**.
38. Sloots, TP, McErlean P, **Speicher DJ**, Arden KE, Nissen MD, Mackay IM. **2006**. Evidence of Human Coronaviruses NL63, HKU1, and Human Bocavirus in Australian children with acute respiratory infection. ASM 2006, Gold Coast QLD, July 2-6, 2006.
39. Mackay IM, McErlean P, **Speicher DJ**, Arden KE, Nissen MD, Sloots TP. **2006**. The Significance of new Coronaviruses (HCoV-NL63 & HcoV-HKU1) in respiratory tract infections. ASID Annual Scientific Meeting, Wellington NZ, April 1-4, 2006.

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Poster Presentations

*Presenter's name is **underlined**. My name and year are in **bold**.*

1. Knapp JP, Van Vloten J, Mutsaers A, Meng B, **Speicher DJ**; Bridle BW. Exploring the heat sensitivity and heat-adaptation of oncolytic vesicular stomatitis virus for improved cancer immunotherapy. BioCanRx, Summit for Cancer Immunotherapy Conference. Ottawa, Canada, October 1-4, 2023.
2. **Speicher DJ**, Luinstra K, Maciejewski J, Tsang KK, Patel S, Allen V, McArthur AG, Smieja M. Clostridioides difficile strain divergence and prophages in Southern Ontario, Canada (2010-2018). BBS Research Symposium, McMaster University. Hamilton, Canada. March 12, **2020**.
3. **Speicher DJ**, Luinstra K, Maciejewski J, Tsang KK, Patel S, Allen V, McArthur AG, Smieja M. Clostridioides difficile strain divergence and prophages in Southern Ontario, Canada (2010-2018). IIDR Trainee Day, McMaster University. Hamilton, Canada. October 4, **2019**.
4. Chernesky M, Jang D, Ratnam S, Shah A, Smieja M, **Speicher DJ**, Martin I, Arias M, Clavio A. P06 Comparison of two commercial amplification assays, SpeDx Resistance Plus MG and Seeplex STD6 ACE detection, performed on self-obtained vaginal and urine specimens for the diagnosis of Mycoplasma genitalium infections. AMMI-CACMID Annual Conference. Ottawa, Canada. April 3-6, **2019**.
5. Jang D, Shah A, Smieja M, **Speicher DJ**, Arias A, Clavio A, Ratnam S, Chernesky M. Mycoplasma genitalium and macrolide resistance mutations in vaginal swabs of Canadian women tested with commercial molecular assays. AMMI-CACMID Annual Conference. Ottawa, Canada. April 3-6, **2019**.
6. Maciejewski J, Luinstra K, **Speicher DJ**, Jayaratne P, Smieja M. Detection of asymptomatic Clostridium difficile amongst hemodialysis patients. AMMI-CACMID Annual Conference. Vancouver, Canada. May 2-5, **2018**.
7. **Speicher DJ**, Luinstra K, Smieja M. Bacteriophages associated with Clostridium difficile infection. AMMI-CACMID Annual Conference. Vancouver, Canada. May 2-5, **2018**.
8. **Speicher DJ**, Luinstra K, Smieja M. Bacteriophages associated with Clostridium difficile infection. IIDR Trainee Day, McMaster University. Hamilton, Canada. October 26, **2017**.
9. Castriciano S, **Speicher DJ**, Luinstra K, Smieja M. Dried Oral FLOQSwabs™ for the Detection of Viral Antibodies. ASM Microbe. June 1-5, **2017**. New Orleans, USA.
10. **Speicher DJ**. Detection of viral antibodies via dried oral swabs. FHS Research Plenary **2017**. McMaster University. May 16-18, 2017. Hamilton, Canda.
11. Castriciano S, Luinstra K, **Speicher DJ**, Smieja M. Dried Oral FLOQSwabs™ for the Detection of Viral Antibodies. 11th European Symposium on Saliva. Netherlands. May 17-20, **2017**.
12. Castriciano S, **Speicher DJ**, Luinstra K, Smieja M. Oral Nylon FLOQSwabs™ Transported Dry for the Detection of Viral Antibodies. ASM Clinical Virology Symposium 2017. May 7-10, **2017**. Savannah, GA, USA.
13. **Speicher DJ**, Luinstra K, Castriciano S, Smith EJ, Smieja M. Detection of viral antibodies via dried oral swabs. AMMI-CACMID Annual Conference. Toronto, Canada. May 3-6, **2017**.
14. **Speicher DJ**, Luinstra K, Castriciano S, Smieja M. Dried Oral FLOQSwabs™ for the Detection of Viral Antibodies. 2016 North American Saliva Symposium. New York, USA. December 9-11, **2016**.

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Poster Presentations continued...

15. Fryk J, Johnson NW, Dieu A, Wilson K, Faddy H, Flower R, and **Speicher DJ**. HHV-8 in Australia: Exposure and carriage in healthy individuals. Australian Institute of Medical Science Tropical Division Conference. Townsville, QLD. June 5-7, **2015**. ***Awarded the best poster at the Conference.***

16. **Speicher DJ**, Nandagopal P, Saravanan S, Kumarasamy N, Ranganathan K, and Johnson NW. Detection of Human Herpesviruses in HIV-positive patients from Southeast India. 7th World Workshop on Oral Health & Disease in AIDS. Hyderabad, India. November 6-9, **2014.** ***Awarded the best poster at the WW7 Conference.***

17. Johnson NW, Saravanan S, Kumarasamy N, Boobalan, Ranganathan K & **Speicher DJ**. Comparison of plasma and salivary HIV loads with a new detection system: implications of prevention and patient care. 7th World Workshop on Oral Health & Disease in AIDS. Hyderabad, India. November 6-9, **2014**.

18. Fernando S, **Speicher DJ**, Scuffham P, Lea RA, Bakr M, Johnson NW. Assessing inherited and individual risk factors for dental caries. IADR - Australian/New Zealand Division. Brisbane, Australia. September 30 – October 1, **2014.**

19. **Speicher DJ**, McLean CA, Hoy J, and Johnson NW. Human herpesvirus 8 disease in Australia: Multicentric Castleman's Disease and Kaposi's sarcoma in the same lymph node; a model for disease evolution. International congress on oncogenic herpesviruses and associated diseases. Philadelphia, USA. August 1-4, **2012**.

20. **Speicher DJ**, McLean CA, Hoy J, and Johnson NW. Castleman's disease and Kaposi's sarcoma in the same lymph node: a model for disease progression. Australian Society for Microbiology (ASM) Annual Scientific Meeting. Brisbane, Australia. July 1-4, **2012**.

21. **Speicher DJ**, McLean CA, Hoy J, and Johnson NW. Kaposi's sarcoma and multicentric Castleman's disease in Australia: detection of HHV-8 by qPCR and Immunohistochemistry. Australian Society for Microbiology (ASM) Annual Scientific Meeting. Brisbane, Australia. July 1-4, **2012**.

22. **Speicher DJ** and Johnson NW. Evaluation of a new commercial kit for examining HHV-8 shedding and subtyping in saliva. Australian Society for Microbiology (ASM) Annual Scientific Meeting. Hobart, Australia. July 4-8, **2011**.

23. **Speicher DJ**, Johnson NW. "Evaluation of a new commercial kit for the salivary diagnosis of HHV-8 and other viruses." The Australian Health and Medical Research Congress. Melbourne, Australia. November 14-18, **2010**.

24. **Speicher DJ**, Lam A, McLean CA, Johnson NW. "Detection of human herpesvirus 8 in Queensland and Victoria in HIV-positive and HIV-negative patients." Australasian HIV/AIDS Conference 2010. 22nd Annual conference of the ASHM. Sydney, Australia. October 20-22, **2010**.

25. **Speicher DJ**, Lam A, Johnson NW. Detection of human herpesvirus 8 in Queensland HIV-positive patients. ASM Annual Scientific Meeting. Perth, Australia. July 6-10, **2009**.

26. **Speicher DJ**, Lam A, Johnson NW. Detection of human herpesvirus 8 subtype A in an HIV-negative Queensland patient. In, **2009**. http://www.griffith.edu.au/conference/gold-coast-health-medical-research-2009.

27. **Speicher DJ**, A Lam, and NW Johnson. Detection of human herpesvirus 8 subtype A in an HIV-negative Queensland patient. KSHV Workshop. Charleston, USA. September 13-16, **2009**.

David J. Speicher PhD, DTM dspeicher@redeemer.ca

Poster Presentations continued...

28. **Speicher DJ**, A Lam, and NW Johnson. Detection of human herpesvirus 8 subtype A in an HIV-negative Queensland patient. 6th World Workshop on Oral Health and Diseases in AIDS (WW6). Beijing, China. April 21-24, **2009**.
29. **Speicher DJ**, A Lam, and NW Johnson. Detection of human herpesvirus 8 subtype A in an HIV-negative Queensland patient. GIHMR Conference. Gold Coast, QLD. December 3-4, **2009**.
30. **Speicher DJ**, Mackay IM, McErlean P, Nissen MD, Sloots TP. **2006**. Detection of Human Coronavirus HKU1 in Queensland Children. RBWH Health Care Symposium, Brisbane QLD, October 16-20, **2006**.

News and Media

1. 'Health Canada hasn't considered the risk' of COVID vaccine DNA contamination issue, says citizen scientist. RebelNews. **October 25, 2023**. https://www.rebelnews.com/health_canada_hasnt_considered_the_risk_of_covid_vaccine_dna_contaminants
2. New study raises concerns over mRNA vaccine safety. Troy Media. **October 25, 2023.** https://troymedia.com/health/new-study-raises-concerns-over-mrna-vaccine-safety/
3. McMaster researchers developed 'fish hooks' to catch samples of coronavirus, CBC News; **February 28 2020** https://www.cbc.ca/news/canada/hamilton/mcmaster-coronavirus-sequencing-tool-1.5479663
4. McMaster develops tool for coronavirus battle; Lab+Life Scientist, **March 3 2020** https://www.labonline.com.au/content/life-scientist/news/mcmaster-develops-tool-for-coronavirus-battle-589425523
5. McMaster develops tool for coronavirus battle; **February 28 2020**. Science New Net https://sciencenewsnet.in/mcmaster-develops-tool-for-coronavirus-battle/
6. CFMU, Radio Interview; The AlmaMAC Episode 105 **(Feb. 14/19)**: Fun with Faeces with Dr. David Speicher; http://bit.ly/CFMU105
7. C. difficile: The Role of Colonization and Phages, Institute for Infectious Disease Research (IIDR), McMaster University, **July 2018**. https://iidr.mcmaster.ca/c-difficile-the-role-of-colonization-and-phages/
8. Tools for Drools: A general guide to collecting and processing saliva; **July 1 2015**; Leading scientists including Dr. Speicher provided technical advice. Interview by Kelly Rae Chi https://www.the-scientist.com/lab-tools/tools-for-drools-35231
9. DNA Genotek Inc. Announces Recipients of the DNA Genotek Grant Program, **May 3 2012**, https://www.prweb.com/releases/2012/5/prweb9469368.htm https://www.dnagenotek.com/ROW/company/news-events/press-releases/2012/2012-05-03.html
10. Seeing God's Hand at Work, Redeemer University; **November 11 2016** https://www.redeemer.ca/resound/seeing-gods-hand-at-work/
11. Redeemer Alumnus Awarded Post-Doc Fellowship; Redeemer University, **October 20 2016** https://www.redeemer.ca/resound/redeemer-alumnus-awarded-post-doc-fellowship/
12. Fighting a global pandemic. Alumni News. Redeemer University College. **May 2008.**

David J. Speicher PhD, DTM dspeicher@redeemer.ca

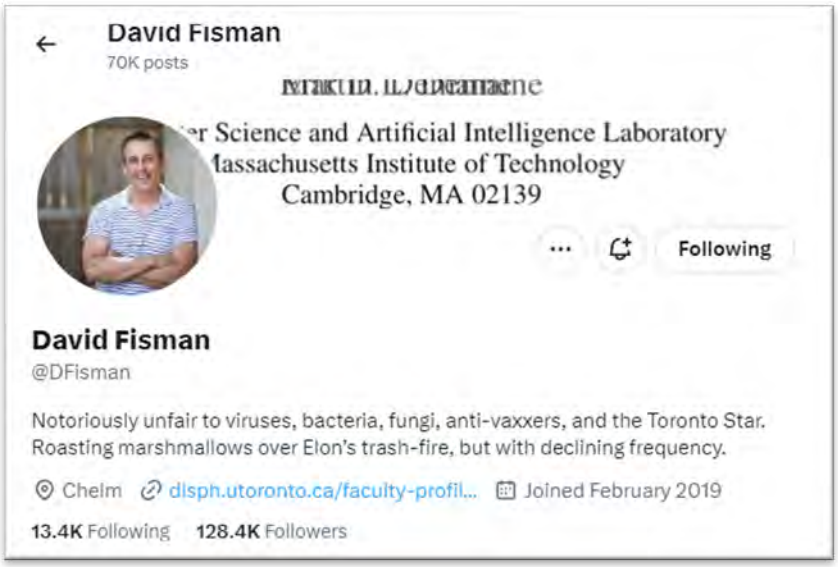
Community Engagement

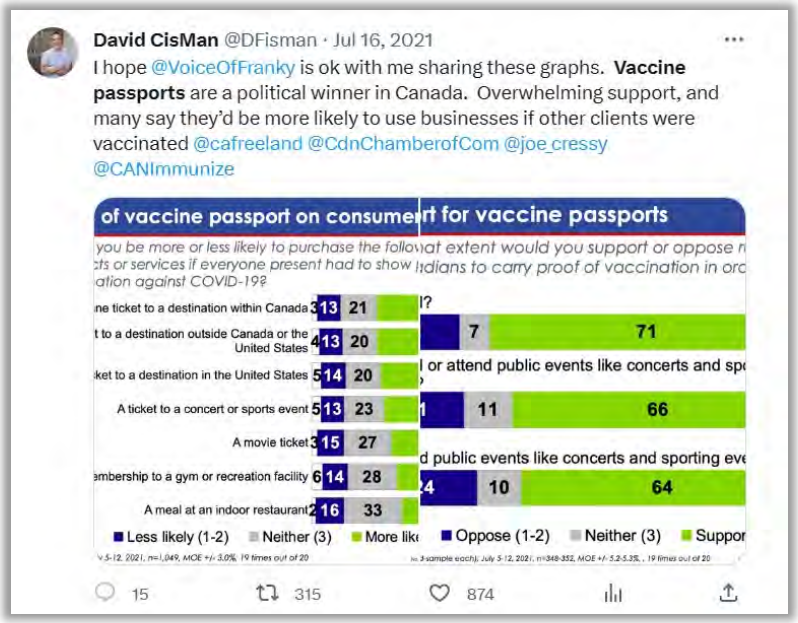
2023	Keynote Address, 2nd Annual Gala, State of our Nation Dinner and Dance, People's Party of Canada. December 16, 2023. Burlington, ON, Canada.
2020	"A Pandemic Plan for your Church to bring Hope and Help during Uncertain times" by Rev. Alex Douglas and Dr. David J. Speicher.
2018 – Present	Chapter Executive, Grand River Chapter, Delta Waterfowl
2019 – Present	Secretary, School Council, Highview Elementary School. Hamilton Wentworth District School Board. Hamilton, Canada

This is Exhibit "B" to the Affidavit of
Dr. David Speicher, sworn before me on
this 13th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

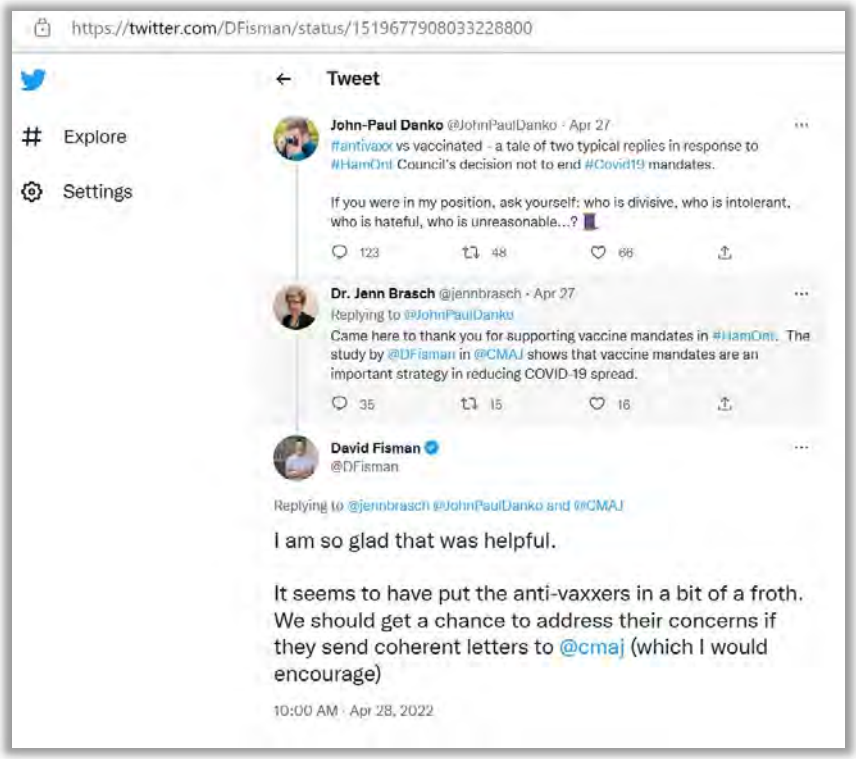
SAMPLE OF DAVID FISMAN'S TWEETS

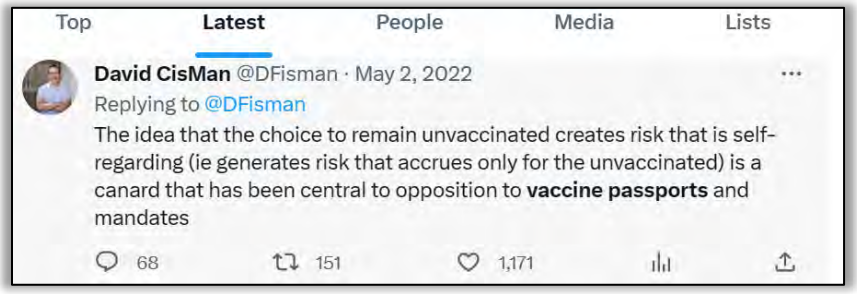


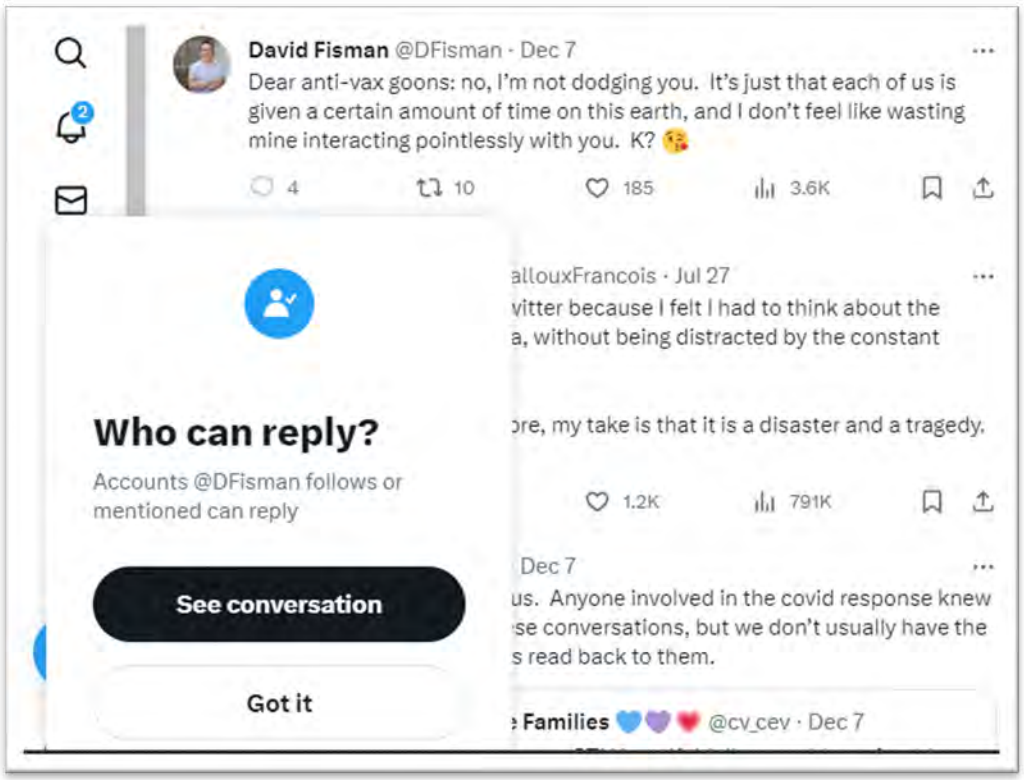

David CisMan @DFisman · Jul 16, 2021
I hope @VoiceOfFranky is ok with me sharing these graphs. Vaccine passports are a political winner in Canada. Overwhelming support, and many say they'd be more likely to use businesses if other clients were vaccinated @cafreeland @CdnChamberofCom @joe_cressy @CANImmunize
of vaccine passport on consume
rt for vaccine passports
you be more or less likely to purchase the follo
at extent would you support or oppose r
ts or services if everyone present had to show
dians to carry proof of vaccination in orc
ation against COVID-19?
ne ticket to a destination within Canada 3 13 21
t to a destination outside Canada or the United States 4 13 20
ket to a destination in the United States 5 14 20
A ticket to a concert or sports event 5 13 23
A movie ticket 3 15 27
embership to a gym or recreation facility 6 14 28
A meal at an indoor restaurant 2 16 33
Less likely (1-2)
Neither (3)
More lik
Oppose (1-2)
Neither (3)
Suppor
7 71
or attend public events like concerts and sp
11 66
d public events like concerts and sporting eve
4 10 64
15
315
874

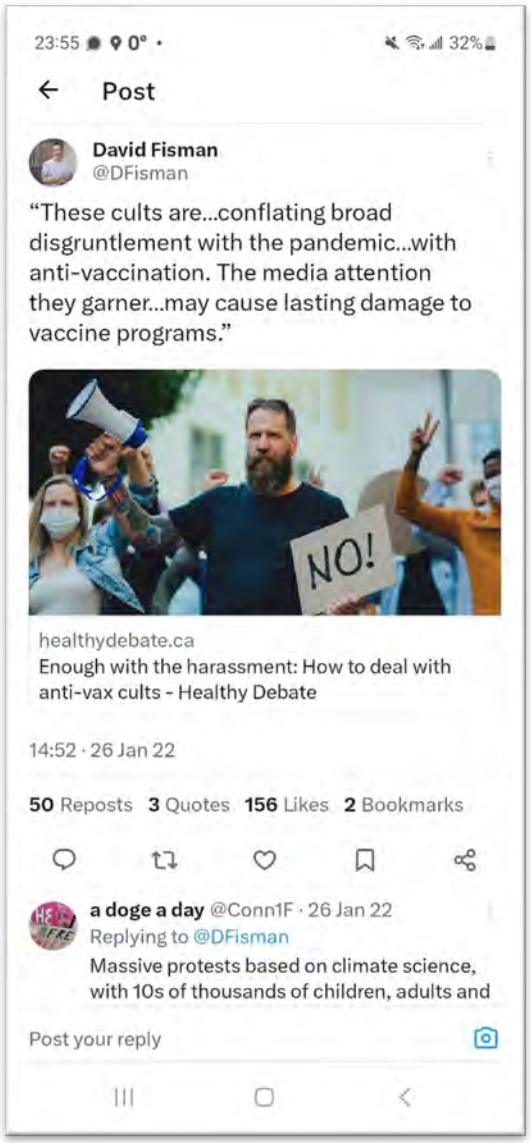

https://twitter.com/DFisman/status/1418175257177952259
Tweet
Explore
Settings
David Fisman
@DFisman
Time for the anti-vaxxers to stay home.
The rest of us deserve to get our lives back.
7:45 AM · Jul 22, 2021
696 Retweets 466 Quote Tweets 4,491 Likes

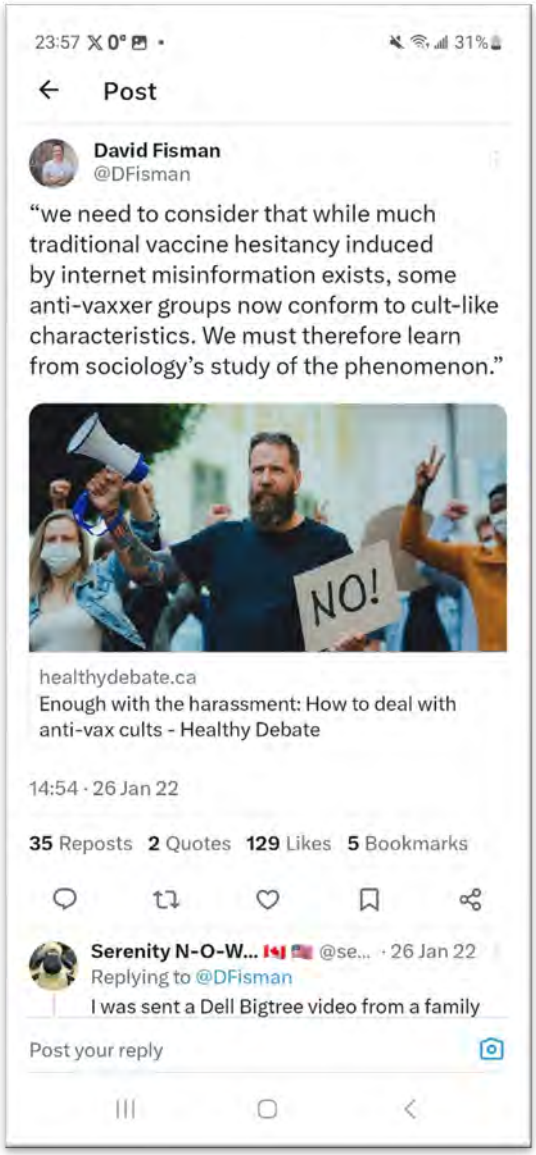

David CisMan
@DFisman
It's time for @uoft to lead on vaccinations. Of course we should have a vaccine mandate on campus. I know there are complexities with international students, but they can be managed.
Terezia Zorić @terezia_zoric · Aug 11, 2021
I and the rest of the @utfaculty sr. leadership support a vaccine mandate (w/ appropriate accommodations). I've called a special meeting of UTFA Council on Monday to vote on making it UTFA's official position + our excellent health & safety checklist. @DFisman @SalSpadafora1
Show this thread
11:14 AM · Aug 11, 2021
102 Retweets 10 Quotes 739 Likes 1 Bookmark

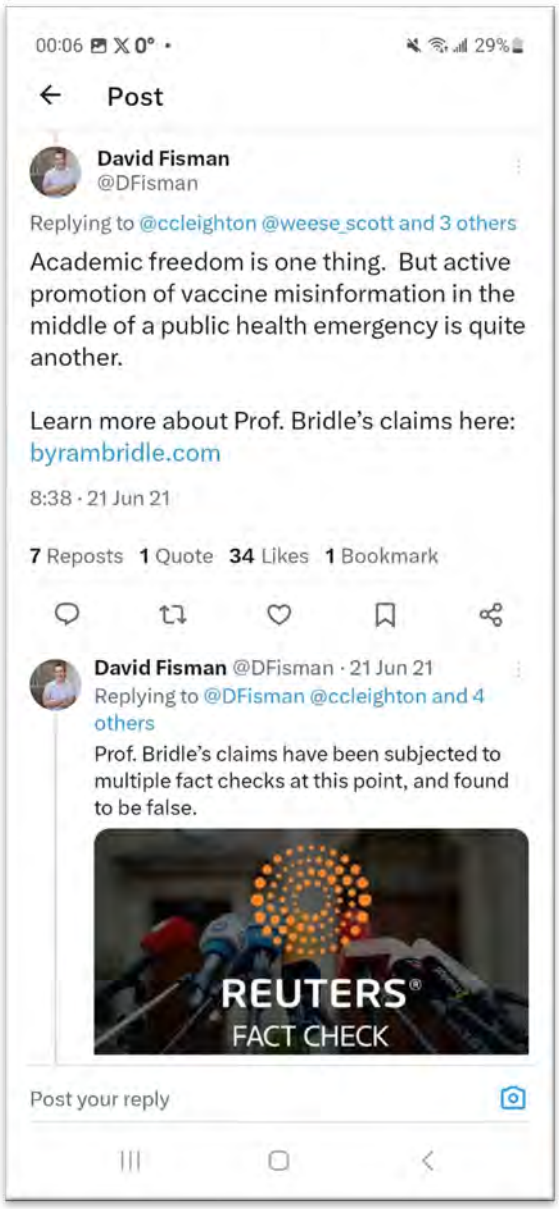

https://twitter.com/DFisman/status/1519677908033228800
Tweet
Explore
Settings
John-Paul Danko @JohnPaulDanko · Apr 27
#antivaxx vs vaccinated - a tale of two typical replies in response to #HamOnt Council's decision not to end #Covid19 mandates.
If you were in my position, ask yourself: who is divisive, who is intolerant, who is hateful, who is unreasonable...?
123
48
66
Dr. Jenn Brasch @jennbrasch · Apr 27
Replying to @JohnPaulDanko
Came here to thank you for supporting vaccine mandates in #HamOnt. The study by @DFisman in @CMAJ shows that vaccine mandates are an important strategy in reducing COVID-19 spread.
35
15
16
David Fisman
@DFisman
Replying to @jennbrasch @JohnPaulDanko and @CMAJ
I am so glad that was helpful.
It seems to have put the anti-vaxxers in a bit of a froth. We should get a chance to address their concerns if they send coherent letters to @cmaj (which I would encourage)
10:00 AM · Apr 28, 2022

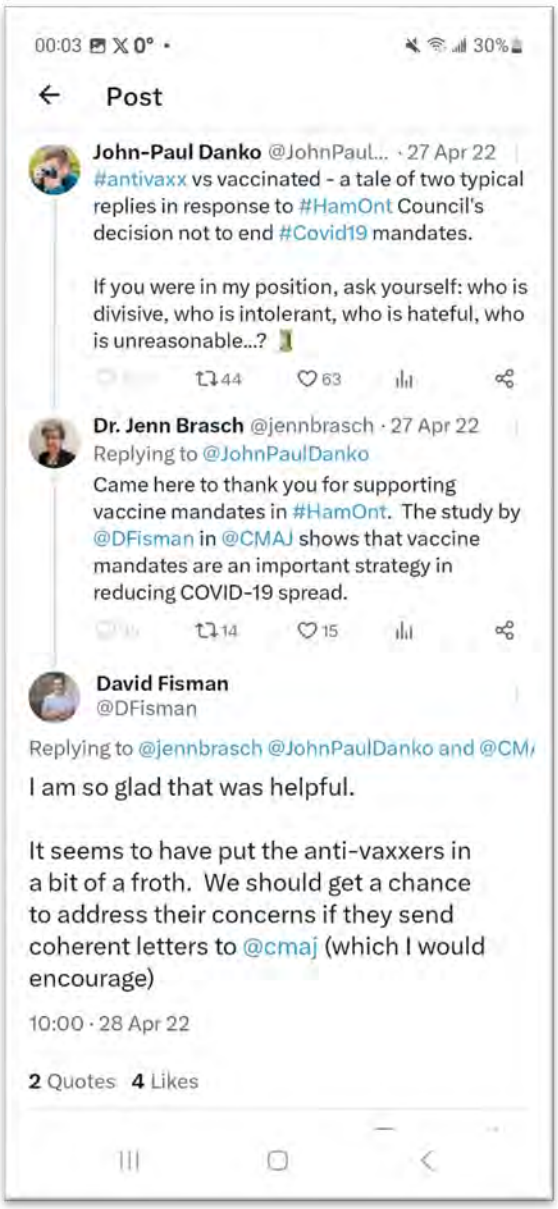

Top
Latest
People
Media
Lists
David CisMan @DFisman · May 2, 2022
Replying to @DFisman
The idea that the choice to remain unvaccinated creates risk that is self-regarding (ie generates risk that accrues only for the unvaccinated) is a canard that has been central to opposition to **vaccine passports** and mandates
68
151
1,171


David Fisman @DFisman · Dec 7
Dear anti-vax goons: no, I'm not dodging you. It's just that each of us is given a certain amount of time on this earth, and I don't feel like wasting mine interacting pointlessly with you. K?
4
10
185
3.6K
allouxFrancois · Jul 27
vitter because I felt I had to think about the
a, without being distracted by the constant
ore, my take is that it is a disaster and a tragedy.
1.2K
791K
Dec 7
us. Anyone involved in the covid response knew
se conversations, but we don't usually have the
s read back to them.
Families @cv_cev · Dec 7
Who can reply?
Accounts @DFisman follows or mentioned can reply
See conversation
Got it


23:55 0° 32%
Post
David Fisman
@DFisman
"These cults are...conflating broad disgruntlement with the pandemic...with anti-vaccination. The media attention they garner...may cause lasting damage to vaccine programs."
NO!
healthydebate.ca
Enough with the harassment: How to deal with anti-vax cults - Healthy Debate
14:52 · 26 Jan 22
50 Reposts 3 Quotes 156 Likes 2 Bookmarks
a doge a day @Conn1F · 26 Jan 22
Replying to @DFisman
Massive protests based on climate science, with 10s of thousands of children, adults and
Post your reply


23:57 0° 31%
Post
David Fisman
@DFisman
"we need to consider that while much traditional vaccine hesitancy induced by internet misinformation exists, some anti-vaxxer groups now conform to cult-like characteristics. We must therefore learn from sociology's study of the phenomenon."
NO!
healthydebate.ca
Enough with the harassment: How to deal with anti-vax cults - Healthy Debate
14:54 · 26 Jan 22
35 Reposts 2 Quotes 129 Likes 5 Bookmarks
Serenity N-O-W... @se... · 26 Jan 22
Replying to @DFisman
I was sent a Dell Bigtree video from a family
Post your reply


00:06
Post
David Fisman
@DFisman
Replying to @ccleighton @weese_scott and 3 others
Academic freedom is one thing. But active promotion of vaccine misinformation in the middle of a public health emergency is quite another.
Learn more about Prof. Bridle's claims here: byrambridle.com
8:38 · 21 Jun 21
7 Reposts 1 Quote 34 Likes 1 Bookmark
David Fisman @DFisman · 21 Jun 21
Replying to @DFisman @ccleighton and 4 others
Prof. Bridle's claims have been subjected to multiple fact checks at this point, and found to be false.
REUTERS
FACT CHECK
Post your reply


00:03
Post
John-Paul Danko @JohnPaul... · 27 Apr 22
#antivaxx vs vaccinated - a tale of two typical replies in response to #HamOnt Council's decision not to end #Covid19 mandates.
If you were in my position, ask yourself: who is divisive, who is intolerant, who is hateful, who is unreasonable...?
44 63
Dr. Jenn Brasch @jennbrasch · 27 Apr 22
Replying to @JohnPaulDanko
Came here to thank you for supporting vaccine mandates in #HamOnt. The study by @DFisman in @CMAJ shows that vaccine mandates are an important strategy in reducing COVID-19 spread.
14 15
David Fisman
@DFisman
Replying to @jennbrasch @JohnPaulDanko and @CM
I am so glad that was helpful.
It seems to have put the anti-vaxxers in a bit of a froth. We should get a chance to address their concerns if they send coherent letters to @cmaj (which I would encourage)
10:00 · 28 Apr 22
2 Quotes 4 Likes


23:59
31%
Post
David Fisman
@DFisman
I'm just going to read the text of Geoffrey's tweet the next time I make a toast with a glass of anti-vaxxer tears.
Geoffrey P. Johnston... · 22 Oct 21
Replying to @kristatee
The anti-vaccine online thugs are increasingly desperate. They have lost, & they know it. As a result, they are lashing out. If you protect your tweets, they win, because your important message only gets seen by your followers. I reco...
14:28 · 22 Oct 21
8 Reposts 68 Likes 1 Bookmark
Geoffrey P. Johnston... · 22 Oct 21
Replying to @DFisman
Post your reply

This is Exhibit "C" to the Affidavit of
Dr. David Speicher, sworn before me on
this 13th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

From: **Matthew Horwood** matthew.horwood@epochtimes.ca
Subject: Fwd: Health Canada - response
Date: July 29, 2023 at 1:35 AM
To: Noé Chartier noe.chartier@epochtimes.com

MH

---------- Forwarded message ---------
From: **Maddison, Anna (HC/SC)** <anna.maddison@hc-sc.gc.ca>
Date: Fri, Jul 28, 2023 at 2:36 PM
Subject: Health Canada - response
To: Matthew Horwood <matthew.horwood@epochtimes.ca>

Good afternoon Matthew,

Please find below the response to your follow up questions. My apologies for the delay in getting back to you.

Thanks and have a good afternoon,
Anna

Can Health Canada confirm that the Pfizer trial used a plasmid-free manufacturing method known as 'Process 1,' and then after the trial scaled up production with plasmids in a manufacturing process known as 'Process 2'?
If that is the case, how can Health Canada be assured the Pfizer vaccines are safe and effective if the trials didn't use plasmid-contaminated vaccines?

Pfizer's "process 1" uses PCR-amplified DNA to produce the COVID-19 vaccine. Although the PCR amplification reaction uses linearized plasmid DNA as template, not intact plasmid, Pfizer "process 1" derived clinical materials are not plasmid-free. The commercial batches of Pfizer's COVID-19 vaccine are produced using "process 2," which only uses linearized plasmid DNA (i.e., no PCR amplification) to produce the vaccine. Both "process 1" and "process 2" include a step to degrade the DNA template into fragments, followed by steps to reduce the quantity of DNA in the final product to below the approved limit. The approved limit for residual DNA is the same for "process 1" and "process 2," and is in line with the recommendation from the World Health Organization. The comparability of the vaccine produced by these two processes was demonstrated based on their biological, chemical and physical characteristics. Therefore, efficacy and safety demonstrated using clinical batches manufactured using "process 1" are also applicable to commercial batches produced using "process 2".

Can you point to the testing data analyzed by Health Canada on the issue? Is it public? Also, are the PCR primers and probes used to make this assessment public?

Testing data analyzed by Health Canada, as well as the PCR primers and probes used, are proprietary information of the vaccine manufacturer. They are not public information. However, the methods used for measuring residual DNA fragments were appropriately validated by the manufacturer and evaluated as fit for purpose by Health Canada. In addition, all Pfizer COVID-19 vaccine commercial batches released in Canada complied with the requirements approved by Health Canada, including the residual DNA.

McKernan asserts that the Pfizer vaccines contain an SV40 Enhancer sequence that is commonly used for gene therapy, but this sequence was not disclosed to the EMA. Do you have information on that matter?

Health Canada cannot comment on information provided to another regulatory authority. Health Canada expects sponsors to identify any biologically functional DNA sequences within a plasmid (such as an SV40 enhancer) at the time of submission. Although the full DNA sequence of the Pfizer plasmid was provided at the time of initial filing, the sponsor did not specifically identify SV40 sequence. When the presence of the SV40 enhancer was raised publicly by McKernan and Buckhaults, it was possible for Health Canada to confirm the presence of the enhancer based on the plasmid DNA sequence submitted by Pfizer against the published SV40 enhancer sequence.

As mentioned in response to the first question, the residual plasmid DNA is present in the final product as DNA fragments, due to the enzyme digestion step in the downstream process. As such, the original risk benefit analysis that supported the initial approval of the Pfizer vaccine continues to be valid.

Finally, information contained here indicates that plasmids are able to enter the nuclei of cells. Is it inaccurate?

https://www.urmc.rochester.edu/labs/dean/projects/nuclear-targeting-of-plasmids-and-protein-dna-comp.aspx

The information on the above website suggests that intact plasmids containing the SV40 enhancer sequence can translocate to the nucleus of cells in culture. However, this information has not been peer reviewed, hence its validity has not been verified. In addition, the DNA plasmid used for the Pfizer vaccine production is linearized, degraded, and reduced in quantity through additional steps. There is no peer reviewed evidence that linearized or fragmented DNA is capable of translocating to the nucleus of cells.

Also this paper discusses genomic integration and seems to contradict your statement about it not being of concern. Is it inaccurate?

https://www.nature.com/articles/s41434-021-00278-2

The paper cited provides evidence that adenovirus vectors have the potential to integrate into genomic DNA. The plasmid used to prepare the Pfizer vaccine does not contain adenovirus virus sequences. Furthermore, as noted in the response to the previous question, there is no evidence that fragmented DNA is capable of translocating to the nucleus of cells.-

---

Anna Maddison
She, her / elle

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Serving Health Canada and the Public Health Agency of Canada | Government of Canada
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- - -

Media | Média T: 613-957-2983 E/CE: hc.media.sc@canada.ca

--
-Matthew Horwood
Reporter, The Epoch Times
613-920-5409

From: **Maddison, Anna (HC/SC)** anna.maddison@hc-sc.gc.ca
Subject: Health Canada - response
Date: August 10, 2023 at 12:09 PM
To: Noé Chartier noe.chartier@epochtimes.com
Cc: Matthew Horwood matthew.horwood@epochtimes.ca

AM

Hi Noé and Matthew,

Please find below Health Canada's response to your follow up questions.

Thanks and take care,
Anna

PCR amplification of the plasmid materially alters the nature of the contaminant. PCR often amplifies molecules millions to billions of times. This would make the residual DNA being used for IVT to contain only the Spike sequence and the T7 promoter but eliminate the SV40 sequences and the rest of the 7810 base pair plasmid. While steps are in place to remove these dsDNA's, the documentation given to the EMA shows this step lacks validation and has high variance (815X across 10 vials). Has Health Canada produced any peer reviewed evidence or data regarding your monitoring of this step?

Health Canada cannot comment on information provided by sponsors to other regulatory authorities. The data generated to quantify the residual plasmid DNA was obtained using approved validated methods submitted to Health Canada by the sponsor. These data demonstrated that the residual DNA content in the final product was consistently below the limit approved by Health Canada. The limit for the residual DNA is controlled as not more than 10 ng/human dose, which is in line with the World Health Organization's recommendation concerning residual DNA in biological drugs.

How does Health Canada evaluate if a PCR assay is fit for purpose if the primers are proprietary? If the qPCR primers used to evaluate dsDNA contamination lie outside of the PCR amplification Pfizer is using to amplify their plasmid DNA, then these primers will report a false result. Given the Pfizer sequence is public and often mandated, why are qPCR primers used to evaluate the dsDNA contamination proprietary? Are any CT values for this dsDNA assessment available for public review?

Please note that the manufacturer does provide proprietary information and data to Health Canada for evaluation, which includes the type of methods, or details of the methods, used for manufacturing and control. The proprietary nature of the information indicates that this information is not disclosed publicly.

DNA-based vectors are very analogous to DNA adenovirus vectors. And there is evidence of SV40 virus integrating into genomes: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2913896/*. ***There is also ample evidence SV40 plasmids containing the same elements in the vaccines can integrate:*** *https://journals.asm.org/doi/10.1128/JVI.68.2.787-796.1994?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed*. ***Has Health Canada performed any work to assess if this genome integration is happening? Can Health Canada or manufacturers prove without the shadow of a doubt it isn't?***

The Pfizer DNA plasmid used to produce the COVID-19 vaccine is distinct from DNA adenovirus vectors in sequence and biological functions. Furthermore, the Pfizer plasmid does not contain sequences corresponding to SV40 proteins studied in the paper cited. Therefore, the integration mechanisms described are not applicable.

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anna.maddison@hc-sc.gc.ca | Mobile : 613-462-6617

Conseillère principale des relations avec les médias | Direction générale des affaires publiques et de communications
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anna.maddison@hc-sc.gc.ca | Mobile : 613-462-6617
- - -
Media | Média T: 613-957-2983 E/CE: media@hc-sc.gc.ca

From: Noé Chartier <noe.chartier@epochtimes.com>
Sent: Monday, July 31, 2023 6:21 PM
To: Maddison, Anna (HC/SC) <anna.maddison@hc-sc.gc.ca>
Cc: Matthew Horwood <matthew.horwood@epochtimes.ca>
Subject: Re: Health Canada - response

Hi Anna,

Thank you very much for the detailed response. My colleague Matthew is on vacation so I will send you what is hopefully one last round of questions. We are grateful for your time and that of the specialists going over this.

Your answer:
Pfizer's "process 1" uses PCR-amplified DNA to produce the COVID-19 vaccine. Although the PCR amplification reaction uses linearized plasmid DNA as template, not intact plasmid, Pfizer "process 1" derived clinical materials are not plasmid-free. The commercial batches of Pfizer's COVID-19 vaccine are produced using "process 2," which only uses linearized plasmid DNA (i.e., no PCR amplification) to produce the vaccine. Both "process 1" and "process 2" include a step to degrade the DNA template into fragments, followed by steps to reduce the quantity of DNA in the final product to below the approved limit. The approved limit for residual DNA is the same for "process 1" and "process 2," and is in line with the recommendation from the World Health Organization. The comparability of the vaccine produced by these two processes was demonstrated based on their biological, chemical and physical characteristics. Therefore, efficacy and safety demonstrated using clinical batches manufactured using "process 1" are also applicable to commercial batches produced using "process 2".

Follow-up question:
PCR amplification of the plasmid materially alters the nature of the contaminant. PCR often amplifies molecules millions to billions of times. This would make the residual DNA being used for IVT to contain only the Spike sequence and the T7 promoter but eliminate the SV40 sequences and the rest of the 7810 base pair plasmid. While steps are in place to remove these dsDNA's, the documentation given to the EMA shows this step lacks validation and has high variance (815X across 10 vials). Has Health Canada produced any peer reviewed evidence or data regarding your monitoring of this step?

Your answer:
Testing data analyzed by Health Canada, as well as the PCR primers and probes used, are proprietary information of the vaccine manufacturer. They are not public information. However, the methods used for measuring residual DNA fragments were appropriately validated by the manufacturer and evaluated as fit for purpose by Health Canada. In addition, all Pfizer COVID-19 vaccine commercial batches released in Canada complied with the requirements approved by Health Canada, including the residual

released in Canada complied with the requirements approved by Health Canada, including the residual DNA.

Follow-up question:
How does Health Canada evaluate if a PCR assay is fit for purpose if the primers are proprietary? If the qPCR primers used to evaluate dsDNA contamination lie outside of the PCR amplification Pfizer is using to amplify their plasmid DNA, then these primers will report a false result. Given the Pfizer sequence is public and often mandated, why are qPCR primers used to evaluate the dsDNA contamination proprietary? Are any CT values for this dsDNA assessment available for public review?

Your answer:
https://www.urmc.rochester.edu/labs/dean/projects/nuclear-targeting-of-plasmids-and-protein-dna-comp.aspx

The information on the above website suggests that intact plasmids containing the SV40 enhancer sequence can translocate to the nucleus of cells in culture. However, this information has not been peer reviewed, hence its validity has not been verified.

In addition, the DNA plasmid used for the Pfizer vaccine production is linearized, degraded, and reduced in quantity through additional steps. There is no peer reviewed evidence that linearized or fragmented DNA is capable of translocating to the nucleus of cells.

Follow-up comment:
The work of David Dean has been peer reviewed and published. The web link was just a general reference.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4152905/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4150867/
https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(16)30801-2
https://www.jbc.org/article/S0021-9258(20)38527-6/fulltext

Dean demonstrates that the 72bp SV40 enhancer is all that is required to recruit transcription factors that localize DNA to the nucleus.

Your answer:
https://www.nature.com/articles/s41434-021-00278-2

The paper cited provides evidence that adenovirus vectors have the potential to integrate into genomic DNA. The plasmid used to prepare the Pfizer vaccine does not contain adenovirus virus sequences. Furthermore, as noted in the response to the previous question, there is no evidence that fragmented DNA is capable of translocating to the nucleus of cells.-

Follow-up question:
DNA-based vectors are very analogous to DNA adenovirus vectors.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2913896/

There is also ample evidence SV40 plasmids containing the same elements in the vaccines can integrate:
https://journals.asm.org/doi/10.1128/JVI.68.2.787-796.1994?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

2008&rft_id=info:doi/10.1016/j.vaccine.2008.04.014&rft_dat=<rft_pub%20%20[pubmed

Has Health Canada performed any work to assess if this genome integration is happening? Can Health Canada or manufacturers prove without the shadow of a doubt it isn't?

Thank you and best regards,

Noé Chartier
Reporter
The Epoch Times
195 Allstate Parkway
Markham, ON, L3R 1P8
P 819-329-2211
E noe.chartier@epochtimes.com
www.TheEpochTimes.com

On Jul 29, 2023, at 1:34 AM, Matthew Horwood <matthew.horwood@epochtimes.ca> wrote:

---------- Forwarded message ---------
From: **Maddison, Anna (HC/SC)** <anna.maddison@hc-sc.gc.ca>
Date: Fri, Jul 28, 2023 at 2:36 PM
Subject: Health Canada - response
To: Matthew Horwood <matthew.horwood@epochtimes.ca>

Good afternoon Matthew,

Please find below the response to your follow up questions. My apologies for the delay in getting back to you.

Thanks and have a good afternoon,
Anna

Can Health Canada confirm that the Pfizer trial used a plasmid-free manufacturing method known as 'Process 1,' and then after the trial scaled up production with plasmids in a manufacturing process known as 'Process 2'?
If that is the case, how can Health Canada be assured the Pfizer vaccines are safe and effective if the trials didn't use plasmid-contaminated vaccines?

Pfizer's "process 1" uses PCR-amplified DNA to produce the COVID-19 vaccine. Although the PCR amplification reaction uses linearized plasmid DNA as template, not intact plasmid. Pfizer "process 1" derived clinical materials are not plasmid free. The

intact plasmid, Pfizer "process 1" derived clinical materials are not plasmid-free. The commercial batches of Pfizer's COVID-19 vaccine are produced using "process 2," which only uses linearized plasmid DNA (i.e., no PCR amplification) to produce the vaccine. Both "process 1" and "process 2" include a step to degrade the DNA template into fragments, followed by steps to reduce the quantity of DNA in the final product to below the approved limit. The approved limit for residual DNA is the same for "process 1" and "process 2," and is in line with the recommendation from the World Health Organization. The comparability of the vaccine produced by these two processes was demonstrated based on their biological, chemical and physical characteristics. Therefore, efficacy and safety demonstrated using clinical batches manufactured using "process 1" are also applicable to commercial batches produced using "process 2".

Can you point to the testing data analyzed by Health Canada on the issue? Is it public? Also, are the PCR primers and probes used to make this assessment public?

Testing data analyzed by Health Canada, as well as the PCR primers and probes used, are proprietary information of the vaccine manufacturer. They are not public information. However, the methods used for measuring residual DNA fragments were appropriately validated by the manufacturer and evaluated as fit for purpose by Health Canada. In addition, all Pfizer COVID-19 vaccine commercial batches released in Canada complied with the requirements approved by Health Canada, including the residual DNA.

McKernan asserts that the Pfizer vaccines contain an SV40 Enhancer sequence that is commonly used for gene therapy, but this sequence was not disclosed to the EMA. Do you have information on that matter?

Health Canada cannot comment on information provided to another regulatory authority. Health Canada expects sponsors to identify any biologically functional DNA sequences within a plasmid (such as an SV40 enhancer) at the time of submission. Although the full DNA sequence of the Pfizer plasmid was provided at the time of initial filing, the sponsor did not specifically identify SV40 sequence. When the presence of the SV40 enhancer was raised publicly by McKernan and Buckhaults, it was possible for Health Canada to confirm the presence of the enhancer based on the plasmid DNA sequence submitted by Pfizer against the published SV40 enhancer sequence.

As mentioned in response to the first question, the residual plasmid DNA is present in the final product as DNA fragments, due to the enzyme digestion step in the downstream process. As such, the original risk benefit analysis that supported the initial approval of the Pfizer vaccine continues to be valid.

Finally, information contained here indicates that plasmids are able to enter the nuclei of cells. Is it inaccurate?
https://www.urmc.rochester.edu/labs/dean/projects/nuclear-targeting-of-plasmids-and-protein-dna-comp.aspx

The information on the above website suggests that intact plasmids containing the SV40 enhancer sequence can translocate to the nucleus of cells in culture. However, this information has not been peer reviewed, hence its validity has not been verified. In addition, the DNA plasmid used for the Pfizer vaccine production is linearized, degraded, and reduced in quantity through additional steps. There is no peer reviewed evidence that linearized or fragmented DNA is capable of translocating to the nucleus of cells.

Also this paper discusses genomic integration and seems to contradict your statement about it not being of concern. Is it inaccurate?
https://www.nature.com/articles/s41434-021-00278-2

The paper cited provides evidence that adenovirus vectors have the potential to integrate into genomic DNA. The plasmid used to prepare the Pfizer vaccine does not contain adenovirus virus sequences. Furthermore, as noted in the response to the previous question, there is no evidence that fragmented DNA is capable of translocating to the nucleus of cells.-

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--

-Matthew Horwood
Reporter, The Epoch Times
613-920-5409

From: **Maddison, Anna (HC/SC)** anna.maddison@hc-sc.gc.ca
Subject: Health Canada - response
Date: August 18, 2023 at 2:42 PM
To: Noé Chartier noe.chartier@epochtimes.com

AM

Hi Noé,

Please find below Health Canada's response to your latest follow up questions.

Thank you,
Anna

Have you tried to independently verify other findings made by the scientists? Are you able to disprove Buckhaults' latest assertion, without relying on old assurances given by the manufacturer?

As noted previously, based on our evaluation of the data and scientific information for the vaccine, we have concluded that the risk/benefit profile continues to support the use of the Pfizer-BioNTech vaccine.

Health Canada does not rely on the conclusions provided by vaccine manufacturers. Health Canada conducts an in-depth independent review of the required evidence provided by the manufacturer to ensure that our high standards for safety, efficacy and quality are met. The Department works in close collaboration with international agencies including other regulators and the World Health Organization to ensure that vaccines available are safe and effective.

Are you currently assessing what would be the impact on the health of Canadians if Buckhaults is right about there being a genome modification?

As previously noted, the presence of residual plasmid DNA in the mRNA COVID-19 vaccines does not change Health Canada's assessments of the safety of these vaccines. In addition, scientists have been working to develop plasmid DNA based vaccines against infectious diseases since the 1990s. Although chromosomal integration of the plasmid DNA was initially a major theoretical concern, the data obtained to date do not support this concern.

Furthermore, the plasmid used to prepare the Pfizer-BioNTech vaccine does not contain adenovirus virus sequences, and there is no peer reviewed evidence that linearized or fragmented DNA is capable of translocating to the nucleus of cells.

- US FDA Guidance for Industry Considerations for Plasmid DNA Vaccines for Infectious Disease Indications
- WHO TRS N°1028, Annex2, Guidelines on the quality, safety and efficacy of plasmid DNA vaccines

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Anna Maddison
She, her / elle
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anna.maddison@hc-sc.gc.ca | Mobile : 613-462-6617

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anna.maddison@hc-sc.gc.ca | **Mobile : 613-462-6617**
- - -
Media | Média T: 613-957-2983 E/CE: media@hc-sc.gc.ca

From: Noé Chartier <noe.chartier@epochtimes.com>
Sent: Wednesday, August 16, 2023 12:27 PM
To: HEALTH MEDIA SANTÉ (HC/SC) <media@hc-sc.gc.ca>
Subject: Genome modification

Good day,

Scientist Dr. Buckhaults said yesterday "i guarantee you there has been genome modification" in reference to his latest findings surrounding covid vax contamination. https://twitter.com/P_J_Buckhaults/status/1691596093422006333

I know Health Canada's position on the matter, which you relayed to us in recent weeks. But you've also admitted having been unaware of the presence of SV40 in the vax, until McKernan and Buckhaults made the independent finding.

Have you tried to independently verify other findings made by the scientists?

Are you able to disprove Buckhaults' latest assertion, without relying on old assurances given by the manufacturer?

Are you currently assessing what would be the impact on the health of Canadians if Buckhaults is right about there being a genome modification?

Thank you and best regards,

Noé Chartier
Reporter
The Epoch Times
195 Allstate Parkway
Markham, ON, L3R 1P8
P 819-329-2211
E noe.chartier@epochtimes.com
www.TheEpochTimes.com

From: **Matthew Horwood** matthew.horwood@epochtimes.ca
Subject: Fwd: Health Canada - response
Date: July 19, 2023 at 2:03 PM
To: Noé Chartier noe.chartier@epochtimes.com

MH

---------- Forwarded message ---------
From: **Maddison, Anna (HC/SC)** <anna.maddison@hc-sc.gc.ca>
Date: Wed, Jul 19, 2023 at 2:01 PM
Subject: Health Canada - response
To: matthew.horwood@epochtimes.ca <matthew.horwood@epochtimes.ca>

Hi Matthew,

Thanks for your patience. Please find below Health Canada's response to your enquiry.

Thaks,

Anna

I was wondering if Health Canada/PHAC have checked COVID-19 vaccine vials for plasmid contamination if they are aware of this issue and are tracking it, and what the impacts on health and human DNA could be if the findings of McKernan and Buckhaults are correct.

Plasmids are an essential starting material for the production of mRNA vaccines. During the downstream process in mRNA vaccine manufacturing, the plasmid DNA is digested with enzymes to small fragments, and further removed to a level of not more than 10 ng/human dose, which is in line with the World Health Organization's recommendation concerning residual DNA in biological drugs. The DNA is digested with enzymes post-transcription.

Health Canada was aware of the presence of residual plasmid DNA as a process-related impurity during review and prior to the authorization of the mRNA COVID-19 vaccines. In addition, the release testing data for every COVID-19 vaccine lot released into the Canadian market were reviewed and deemed to meet the requirements approved by Health Canada. Furthermore, different assays assessing the same vaccine property, or even the same assay being performed in different laboratories, may generate different results.

It is important to assess the results using the authorized validated assays performed by the vaccine manufacturers to ensure that the quality of commercial vaccine lots are comparable to lots shown to be safe and efficacious in clinical studies.

We are aware HC has previously stated that the mRNA vaccines are not "gene altering therapies," but would DNA plasmid contamination on that reported scale change that assessment?

The presence of residual plasmid DNA in the mRNA COVID-19 vaccines does not change the safety assessment of these vaccines by Health Canada. In addition, scientists have been working to develop plasmid DNA based vaccines against infectious diseases since the 1990s. Although chromosomal integration of the plasmid DNA was initially a major theoretical concern, the data obtained to date do not support this concern. Additional details concerning the safety of plasmid DNA can be found in the following guidance documents:

- US FDA Guidance for Industry Considerations for Plasmid DNA Vaccines for Infectious Disease Indications
- WHO TRS N°1028, Annex2, Guidelines on the quality, safety and efficacy of plasmid DNA vaccines

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Anna Maddison
She, her / elle

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anna.maddison@canada.ca | Mobile : 613-462-6617

- - -

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--
-Matthew Horwood
Reporter, The Epoch Times
613-920-5409

This is Exhibit "D" to the Affidavit of
Dr. David Speicher, sworn before me on
this 13th day of December 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

improve. Please complete the survey at the end of the request process.

Government of Canada / Gouvernement du Canada

Access to Information and Personal Information Online Request Service

Summary of your request

Print | Previous

Request received

Date and time

November 28, 2023 1:39 PM

Request confirmation number

EA2023_0046482

Application fee

$5.00

Payment status

Approved

Moneris Order ID

17011967262f3l5eRLgaYdEAT

Request

Request type

Access to information request

Institution

Institution

Request details

Eligibility

Canadian citizen

Request label

Email exchange between Health Canada and Epoch Times

Request description

Any and all e-mail exchanges between Health Canada (e.g., Anna Maddison) and Epoch Times Canada (including, but not limited to Matthew Horwood and/or Noe Chartier) starting April 2023 to the present day regarding questions and responses to those questions which address the plasmid contamination, genomic integration,SV40, residual DNA and other related issues discovered by Kevin McKernan, Philip Buckhaults, David Speicher, and other scientists as well as any follow-up emails to further questions by either reporter.

Format of request

Electronic

Attached documents

Filename	Description

Contact information

Family name

SPEICHER

Given name

DAVID

Name of business or organization

250 Montmorency Dr

Apartment/ Suite/ Unit number

201

Country

Canada

Province

Ontario

City

HAMILTON

Postal code

L8K5H1

Phone

7057513898

Email

research@davidspeicher.com

Preferred language of communication

English

Preferred method of communication for correspondence

Email

Requester type

Academia

Previous

Version: 20231122 (b9ee5364)

TAB 7

Court File #: CV-22-0069-1880-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

AFFIDAVIT OF DR. HARVEY RISCH

I, Dr. Harvey Risch, of the Town of Fairfield, in the State of Connecticut, SOLEMNLY AFFIRM AND SAY:

1. I am a Professor Emeritus of Epidemiology at Yale School of Public Health, and as such, have knowledge of the matters contained in this Affidavit.

Professional, Academic and Research background as it relates to COVID 19 public health

2. I have a degree in medicine (MD) from the University of California San Diego and PhD, in mathematical modeling of infectious epidemics, from the University of Chicago. Attached and marked as "**Exhibit A**" is a copy of my CV.
3. In my medical training, a substantial fraction, perhaps 20-25%, was of infectious organisms, infectious diseases and their treatments. My PhD subject area was in mathematical modeling of infectious epidemics, and I published on this early in my academic career. Over the subsequent 40-plus years, as an appreciable part of my scientific research into the causes of various types of cancers, I studied the roles of infectious agents

and of their treatments. I also extensively studied the role of medications usage more generally with respect to cancer causation, and I have created and taught at Yale a graduate course covering pharmacoepidemiology, the epidemiologic study of drugs and their indications for use, to public health graduate students, law students and medical residents.

4. I am an elected member of the Connecticut Academy of Science and Engineering. Early during the Covid-19 pandemic, I was invited to participate in a scientific workshop panel of the Academy to provide advice to the Governor of Connecticut with respect to reopening the state after its lockdown. My role on the panel was to address possible outpatient Covid-19 treatments. From research that I did at that time, I published, on May 27, 2020, a long and detailed analysis of outpatient Covid-19 treatment efficacy and safety (https://academic.oup.com/aje/article/189/11/1218/5847586) that has now been viewed more than 166,000 times and downloaded more than 91,000 times. Subsequently, as further relevant Covid-19 outpatient treatment studies were published, I examined them and updated my summary analyses (https://earlycovidcare.org/wp-content/uploads/2021/09/Evidence-Brief-Risch-v6.pdf).

5. Additionally, I worked with medical and public health colleagues in Brazil to carry out a study of medications for outpatient Covid treatment and risk of hospitalization. This study was published (https://www.sciencedirect.com/science/article/pii/S1477893920304026).

6. I have continued over the course of the Covid-19 pandemic to study various aspects of the virus, vaccines, treatments, prevention, etc. In particular, I have collaborated with Dr. Peter McCullough and other medical researchers in the development and writing of two publications covering the medical management of outpatient Covid-19 illness in the pre-omicron era (https://www.imrpress.com/journal/RCM/21/4/10.31083/j.rcm.2020.04.264

and https://www.amjmed.com/article/S0002-9343(20)30673-2/fulltext), and have published on the evaluation of medical evidence during the Covid pandemic (https://onlinelibrary.wiley.com/doi/10.1111/ajes.12539). I have also written a number of lay essays on medical and scientific topics related to Covid pandemic management and policies. These essays have appeared in various newspapers and on the Brownstone Institute website (for example, https://brownstone.org/articles/covid-19-vaccine-mandates-fail-the-jacobson-test/).

7. More generally, I have been a professor of epidemiology for more than 40 years, first at the University of Toronto and then at Yale. I have been a fellow of the American College of Epidemiology since 1991. I have a research publication h-index of 111 (indicating high productivity and recognition) and have published more than 400 original peer-reviewed scientific research papers in the medical literature; those papers have been cited by other scientific publications more than 51,500 times. I have won honorary prizes for my epidemiologic research (for example, https://columbiasurgery.org/news/ruth-leff-siegel-award and https://aacrjournals.org/pages/h-a-risch-bio). I am an Associate Editor of the *Journal of the National Cancer Institute*, Editor of the *International Journal of Cancer*, and served for a six-year term as a Member of the Board of Editors of the *American Journal of Epidemiology*. Finally, I have taught coursework to MPH and PhD public health students on introductory epidemiologic methods, intermediate epidemiologic methods, and throughout my whole academic career, advanced epidemiologic methods.

Dr. Fisman is not qualified to opine on Dr. Bridle's area of expertise

8. I have read the affidavit of Dr. Fisman, filed in the within motion. I have written extensive observations and points about many of the items discussed by Dr. Fisman, wherein I attach as "**Exhibit B**". These observations and points are under solemn affirmation along with the body of my affidavit. I have also read Dr. Fisman's CMAJ modeling paper (https://www.cmaj.ca/content/194/16/E573) as well as Dr, Bridle's criticism of that paper (https://viralimmunologist.substack.com/p/fiction-disguised-as-science-to-promote). I have downloaded and explored Dr. Fisman's Excel version of his CMAJ publication model.
9. Dr. Fisman is an MD specializing in infectious disease and a professor of epidemiology. I am also an MD and PhD professor (now emeritus) of epidemiology. Dr. Bridle is a PhD associate professor of immunology and vaccinology. Neither I nor Dr. Fisman have the depth of expertise in viral vaccines and viral immunology possessed by Dr. Bridle.
10. Dr. Fisman claims that Dr. Bridle's expert opinions are not "data based". Such a statement is vague and non-scientific and requires specific examples in order to judge its veracity. Furthermore, scientific expertise can be subjective and narrowly tailored to the scientific questions at hand, and can reflect very different scientific worldviews between even closely related disciplines. Thus, what may be appropriate and consistent with scientific understandings and standards in one field may be devalued by scientists in other, even adjacent, fields. Dr. Fisman is not a viral vaccinologist or a viral immunologist and thus is not qualified to criticize Dr. Bridle on specific scientific opinions in those disciplines.

11. Epidemiologists and medical doctors, even those specializing in infectious diseases, do not have the depth of scientific expertise of viral immunologists researching and developing vaccines.

Expression of expert opinion does not undermine public health

12. Dr. Bridle is an expert on vaccines. Raising questions on the development and use of COVID-19 vaccines does not harm public health objectives.

13. Public health objectives must be based on accurate and timely scientific knowledge. Scientific knowledge is based on objective evidence, not on opinions of scientists. Objective scientific evidence is established by experts doing research studies and by asking and answering questions about the evidence, debating the evidence. Evidence must be interpreted, and interpretations can be subjective. Therefore, all evidence is open to discussion and criticism as part of the process by which it becomes scientifically established. Even during a declared public health emergency, the processes of science are not abrogated, and expert discussion and criticism of evidence and of policies derived from such evidence are de rigueur. If such expert open discussion and criticism is blocked or censored, that has the potential to undermine public health because accurate and objective evidence may not be established. This problem is compounded when public health agencies accumulate empirical evidence but do not release this evidence to experts for analysis or discussion.

False allegation of "Misinformation" is contrary to Public Interest

14. I am a professor (emeritus) at Yale University, which along with the University of Chicago (https://freeexpression.uchicago.edu/) and other universities has a long tradition of academic freedom of expression (https://yalecollege.yale.edu/get-know-yale-college/office-dean/reports/report-committee-freedom-expression-yale). Academic freedom means the ability to espouse dissenting scientific ideas publicly, without punishment. The amelioration of wrong scientific ideas occurs by the same academic freedom, to present countering correct scientific ideas, to allow independent and objective review in order to determine which of the ideas are more likely to be correct. Academic freedom certainly includes expert questioning and criticizing of public health and dominant government narratives.

15. Dr. Bridle is a faculty member at the University of Guelph. The University of Guelph has a policy supporting academic freedom of expression (https://www.uoguelph.ca/freedom-of-expression/policy).

16. Dr. Bridle is expert in the areas of vaccine development and vaccine performance, and in the immunology underlying such areas. As such, he is within the category of people appropriate to comment publicly on these topics.

17. The terms "misinformation" and "disinformation" are being misused as purported rationales for censorship of debate and dissenting views. This misuse of these labels creates a climate of intolerance to dissenting views and opinions. Additionally, these terms are irrelevant for public academic expression under legal free speech and university policies of freedom of expression.

18. Misuse of these terms has resulted in the abandonment of the academic and scientific value of debate and intellectual inquiry. This damages what would be the results of such debate and inquiry, the advancement of scientific knowledge, including knowledge about public health and public-health policies. These terms serve to censor academic and public speech, including by experts, without providing evidence of error in such speech. Censorship is not debate. If expert public or academic speech is in error, the counter to it is more speech not censorship. Employing the terms “misinformation” and “disinformation” thus is not in the public interest and harms the public interest.

Scholarly critique of publication is not "retaliatory" ad hominem attack on Dr. Fisman

19. I have read the paper co-authored by Dr. Fisman, Impact of population mixing between vaccinated and unvaccinated subpopulations on infectious disease dynamics: implications for SARS-CoV-2 transmission | CMAJ. I have also read Dr. Bridle's paper titled Fiction Disguised as Science to Promote Hatred- Article by Dr. Byram W. Bridle – Canadian Covid Care Alliance. As an epidemiologist, I can confirm that in his criticism, Dr. Bridle has accurately identified numerous serious flaws in the study by Fisman et al. I have explored the Excel model version made available by Dr. Fisman, and thank him for thinking to make his model generally available so that experts such as Dr. Bridle and I can evaluate its properties and performance. I note that this model is very similar to the epidemic model that I developed in my PhD dissertation (https://www.sciencedirect.com/science/article/abs/pii/0025556483900470).

20. The main problem that Dr. Bridle criticizes in the Fisman et al. paper and model is that the conclusions of the paper are exquisitely sensitive to the numerical values employed in the model, and that some of those numerical values are unrealistic, to the degree that realistic

values would result in conclusions opposite to those stated in the paper. There are a number of these issues here that I will illustrate in the next four paragraphs.

21. First, Dr. Fisman's model assumes parameter values taken from the initial waves of the Covid pandemic, through the delta variant. All of the parameter values save one in his paper Table 1 are supported by references published in 2021 or earlier; the one other was stated as assumption, i.e., without supporting citation. However, his paper was published on April 25, 2022, at a time when the delta variant was all but gone and omicron had widely replaced it. The omicron strain is known to be more infectious than delta (that's how it could replace delta), as well as substantially less virulent than delta and its predecessor strains. Thus, the applicability of the Fisman et al. model and its conclusions to the circulating omicron strain and subsequent omicron substrain variants was already doubtful at the time the paper was published.

22. Second, if the vaccine were to have zero efficacy against infection, then there would be no difference between the vaccinated and unvaccinated groups, and the tendency of the direction of infection between the groups should be balanced, i.e., that the ratio discussed by Dr. Bridle (column AI in the "Patch Model" worksheet of the Excel file, "Ratio of fraction of infections acquired from unvaccinated to fraction of contacts unvaccinated") should be 1.0. I examined this in the Excel model by inserting the value 0 (zero) in cell D11 (Vaccine Efficacy). For the initial time segment rows, this ratio is well below 1.0, but then climbs over longer time frames to greatly exceed 1.0. This suggests that the model itself or its assumed parameter values have an underlying problem which damages the credibility of the model.

23. Third, it was known by April 25, 2022, that the mRNA Covid vaccines were producing appreciable numbers of "breakthrough" infections, i.e., Covid infections after vaccination. It was thus observed that the initial 95% vaccine efficacy against Covid infection proclaimed in December 2020 or shortly thereafter did not last over time. However, the Fisman et al., paper states, "We did not model waning immunity." This is a major flaw of the model, because changing the vaccine efficacy parameter in cell D11 leads to major changes in the values of the Ratio in column AI.

24. Most importantly, the Fisman et al. model assumes a baseline immunity in unvaccinated people of 20% (Table 1 of the paper). There is no cited reference for this value. However, US seroprevalence studies in April-May 2022 (https://covid19serohub.nih.gov/) show that virus nucleocapsid seropositivity (i.e., seropositivity from the virus, not from vaccination) was about 75-85% in the general population and moving upward over time. Putting the value 80% (0.8) in cell D13 (Baseline immunity in unvaccinated) makes all of the Ratio values in column AI almost exactly 1.0, meaning no difference in transmission for vaccinated vs unvaccinated people. However, at values of 81% and greater, as the baseline immunity continued to increase, the Ratio values in column AI are all below 1.0, which indicates according to the model a bias in transmission coming more from the vaccinated, exactly opposite to the conclusions of the paper. This point was made by Dr. Bridle.

25. These four issues demonstrate that the conclusions of the Fisman et al. paper were completely unreliable and were determined by the inappropriate and unrealistic values of the parameters that the authors chose to use in their model. Dr. Bridle's criticism of the paper was therefore scientifically appropriate.

26. In Dr. Bridle's criticism of the Fisman et al. paper, he always refers to the authors as "Fisman et al." and he does not personally attack Dr. Fisman or impugn his reputation.

SOLEMNLY AFFIRMED BEFORE)
ME by Harvey Risch in the town of)
Fairfield, in the state of Connecticut,)
on this 11th day of December, 2023,)
in accordance with O. Reg. 431/20)
Administering Oath or Declaration)
Remotely)

Harvey Risch Digitally signed by Harvey Risch Date: 2023.12.11 12:05:21 -05'00'

A Commissioner for Taking Oaths
Rocco Galati B.A., LL.M., LL.B.

Dr. Harvey Risch

This is Exhibit "A" to the Affidavit of Harvey Risch, affirmed before me on this 11th day of December 2023

_____

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

EXHIBIT A: Curriculum Vitae for: HARVEY A. RISCH, M.D., PH.D.

Professor Emeritus of Epidemiology and Senior Research Scientist
Yale School of Public Health, Yale School of Medicine

Business Address: Yale School of Public Health
60 College Street
P.O. Box 208034, New Haven, CT 06520-8034
E-mail: harvey.risch@yale.edu

Education:

Date	*School*	*Degree, Major*
9/80-12/82	University of Washington	Postdoctoral Fellow, Epidemiology
9/76-8/80	University of Chicago	Ph.D., Biomathematics
9/72-6/76	UC San Diego School of Medicine	M.D., Medicine
9/67-6/72	California Institute of Technology	B.S. (Honors), Biology; Mathematics

Professional Appointments:

7/22-	Professor Emeritus of Epidemiology and Senior Research Scientist, Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale School of Medicine, New Haven, CT.
7/01-6/22	Professor of Epidemiology, Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale School of Medicine, New Haven, CT.
1/12-	Director, Molecular Cancer Epidemiology Laboratory and Shared Resource, Yale Comprehensive Cancer Center and Yale School of Public Health
9/06-8/07	Lady Davis Visiting Professor, Department of Community Medicine and Epidemiology, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
1/91-6/01	Associate Professor of Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine.
1/83-12/90	Epidemiologist-Biostatistician, Epidemiology Unit, National Cancer Institute of Canada, Toronto, Ontario.
7/90-12/90	Associate Professor, Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario (Concurrent Appointment).
1/83-6/90	Assistant Professor, Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario (Concurrent Appointment).
9/80-12/82	Postdoctoral Fellow, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Washington.
7/79-8/80	Postdoctoral Fellow, Department of Pathology, University of Chicago, Chicago, Illinois.

h-Index: 111. Publication citations: more than 51,500 research citations as of November 27, 2023.

Awards, Memberships, etc.:

NSF Undergraduate Research Fellowship, Department of Mathematics, California Institute of Technology, Pasadena (6/70-9/70)
General Medicine Stipended Externship, UC San Diego School of Medicine, La Jolla (6-9/73)
Theoretical Biology Predoctoral Traineeship, University of Chicago (9/76-6/79)
Pathobiology Postdoctoral Traineeship (GM 7190), University of Chicago (7/79-8/80)
Cancer Epidemiology Postdoctoral Traineeship (CA 9168), University of Washington (9/80-12/82)
Member, Society for Epidemiologic Research (1982-)
Member, American Society of Preventive Oncology (1984-)
Full Member, Sigma Xi (1986-)
Fellow, American College of Epidemiology (1991-); Member (1984-91)
Member, Yale Cancer Center (1992-), Sections: Cancer Prevention and Control; Gynecologic Oncology; Cancer Genetics
"Best of the AACR Journals" for "Aspirin Use and Reduced Risk of Pancreatic Cancer," one of the most highly cited *Cancer Epidemiology, Biomarkers & Prevention (CEBP)* articles published in 2016 (April 2018) (http://aacrjournals.org/h-a-risch-bio)
The Ruth Leff Siegel Award for Excellence in Pancreatic Cancer Research (2018), $50,000 (http://columbiasurgery.org/pancreas/ruth-leff-siegel-award)
Member, Connecticut Academy of Science and Engineering (2019-)
Highest attention paper ever published in the American Journal of Epidemiology (2020) (https://oxfordjournals.altmetric.com/details/82900954)

Consortia:

BEACON: Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (2005-)
OCAC: Ovarian Cancer Association Consortium (International Consortium of Case-Control Studies of Ovarian Cancer) (2005-)
PanC4: Pancreatic Cancer Case-Control Consortium (2006-); Elected Steering Committee Member (2008-2013, 2014-2017, 2018-2021)
Panscan: Pancreas Cancer Genome-wide Association Study Consortium (2008-)
CIMBA: Consortium of Investigators of Modifiers of BRCA1/2 (2017-)

Research Interests:

Cancer epidemiology and etiology—Pancreas, Ovary, Lung, Breast, Stomach, Bladder, etc.
Cancer genetic epidemiology: polymorphisms, major genes; Hormonal factors and cancer; Occupational/environmental exposures and cancer; Diet and cancer; *Helicobacter pylori* and cancer
Epidemiologic methods; Causal inference; Cancer registration, control and prevention

Teaching Experience:

Advanced Epidemiologic Research Methods (Yale University CDE 619a) (Course developer)
Litigational Epidemiology (Yale University CDE 550) (Course developer)
Fundamentals of Epidemiology (Yale University CDE/EMD 508) (Course co-developer)
Principles of Epidemiology II (Yale University CDE 516) (Course co-developer)
Research Methods in Epidemiology I (University of Toronto CHL 4102f) (Course co-developer)
Research Methods in Epidemiology II (University of Toronto CHL 4105s) (Course developer)
Cancer Epidemiology (University of Toronto CHL 4103f; Yale University CDE 532b)

Trainees

PhD: Advisor to five students; dissertation committee member for 11 students.
MPH or MSc: Advisor to 36 students.

Postdoctoral Fellows: Advisor to 16 fellows.
Visiting Faculty: Host to four visiting professors.

Service Activity:

Grant Review Panels:

Health Canada, National Health Research and Development Program: Epidemiology, Occupational Health and Chronic Disease Panel (1987-91)
NIH External Site Reviewer (1995)
NIH Study Section Regular Member: Epidemiology and Disease Control (EDC2) (1997)
US Army MRMC Ovarian Cancer Research Program Integration Panel Member (1997-2002)
American Cancer Society Extramural Grant Reviewer (1998)
Chair, Epidemiology Grant Review Panel, National Cancer Institute of Canada (2000-2)
Dutch Cancer Society Extramural Research Grant Reviewer (2000, 2001, 2008)
Cancer Council Australia Extramural Research Grant Reviewer (2004)
Pancreatic Cancer Action Network-AACR Career Development Awards Scientific Review Committee (2016-8)
NIH Study Section Member: Epidemiology and Disease Control (EDC2) (2000)
NIH Study Section Member: Epidemiology Special Emphasis Panel (ZRG4, 1998; ZRG1, 2001-3)
NIH Study Section Member: Pancreas SPORE Panel (ZCA1 GRB-V, 2002-3)
NIH Study Section Member: Small Grants Program for Cancer Epidemiology Panel (ZCA1 SRRB-Q, 2003)
NIH Study Section Member: Cancer Genetics Panel (CG) (2004, 2006)
NIH Study Section Member: Cancer Epidemiology, Prevention and Control (NCI-E X1) (2005)
NIH Study Section Member: Breast and Ovarian Cancer Genetics (ZRG1 ONC-U 03M) (2005)
NIH Study Section Member: Gene-Environment Interactions (ZHL1 CSR-D S1 R) (2007)
NIH Study Section Member: Epidemiology of Cancer Member Conflicts (ZRG1 HOP-Q, 2009; ZRG1 PSE-B, 2010)
NIH Study Section Member: Barrett's Esophagus Translational Research Network (ZCA1 SRLB-1 (O1) R, 2011)
NIH Study Section Member: Core Infrastructure and Methodological Research for Cancer Epidemiology Cohorts (ZCA1 SRLB-9 (M2) B, 2013; ZCA1 TCRB-9 (J2) R, 2014; ZCA1 SRBJ (O2) S, 2015)
NIH Study Section Member: Cancer Management, Epidemiology, and Health Behavior (ZCA1 SRLB-B (J1) S, 2013)
NIH Study Section Member: Population Science (U01) (ZCA1 RTRB-Z M1 R, 2016)
Medical Research Council UK External Reviewer (2019)

Journal Editor:

Associate Editor, *American Journal of Epidemiology* (1997-2014)
Editor pro tem, *American Journal of Epidemiology* (2002-2014)
Member, Board of Editors, *American Journal of Epidemiology* (2014-2020)
Associate Editor, *Journal of the National Cancer Institute* (2000-)
Editor, *International Journal of Cancer* (2008-)

Journal Referee:

Alimentary Pharmacology & Therapeutics (2015-)
American Journal of Epidemiology (1986-)
American Journal of Medical Genetics (2004-)
American Journal of Obstetrics and Gynecology (2015-)

American Journal of Preventive Medicine (1988-)
Annals of Epidemiology (1992-)
Annals of Oncology (2001-)
Annals of Surgical Oncology (2011-)
Biodemography and Social Biology (2018-)
Biometrics (1990-)
Blood Transfusion (2015-)
BMC Cancer (2007-)
BMC Public Health (2007-)
British Journal of Cancer (2003-)
Canadian Journal of Public Health (1987-)
Canadian Medical Association Journal (1983-)
Cancer (1996-)
Cancer Causes and Control (1992-)
Cancer Detection and Prevention (2003-2009)
Cancer Epidemiology (2009-)
Cancer Epidemiology, Biomarkers and Prevention (1995-)
Cancer Genetics (2012-)
Cancer Research (1988-)
Carcinogenesis (2008-)
Clinical Cancer Research (2015-)
Clinical Gastroenterology and Hepatology (2007-)
Current Pharmacogenomics (2007-)
DNA and Cell Biology (2019-)
Environmental Pollution (2018-)
Epidemiology (1989-)
European Journal of Cancer (2001-)
European Journal of Epidemiology (1995-)
European Journal of Human Genetics (2008-)
European Journal of Internal Medicine (2021-)
Gastroenterology (2007-)
Gynecologic Oncology (1997-)
International Journal of Cancer (1995-)
International Journal of Epidemiology (1995-)
JAMA (1990-)
Journal for Nurse Practitioners (2018-)
Journal of Clinical Epidemiology (2006-)
Journal of Clinical Gastroenterology (2010-)
Journal of Clinical Medicine (2019-)
Journal of Epidemiology (2016-)
Journal of Infectious Diseases (2002-)
Journal of Medical Virology (2022-)
Journal of the National Cancer Institute (1992-)
Menopause (2011-)
Molecular Carcinogenesis (2009-)
Nature Clinical Practice Oncology (2005-)
Nature Scientific Reports (2016-)
New England Journal of Medicine (2017-)

Oncology Research (2001-)
Oncotarget (2017-)
Preventive Medicine (1994-)
Reproductive Sciences (2008-)
Science (2004-)
Treatments in Endocrinology (2003-)
Tumor Biology (2015-)
World Journal of Gastroenterology (2013-)

Other Review and Service:

Society for Epidemiologic Research Student Prize Paper Review Committee (1987, 1994)
American Society for Clinical Oncology Cancer Prevention Curriculum (2006)
External Advisory Board Member, Multiple Myeloma Prevention Program Project, Washington University (2014-2015)
Mayo Clinic SPORE in Pancreatic Cancer External Advisory Committee (2018-2023)
Connecticut Academy of Science and Engineering (CASE) Advisory Committee on Covid-19 for Reopening Connecticut (2020)

Academic and Professional Standing Committees:

Yale School of Public Health:
Doctoral (Admissions and Progress; 1991-1999)
MPH (Academic Progress; 1991-1995)
Computer (1999-2001)
Medical Studies (2000-2005)
Chair, Genetics and Public Health Interest Group (2003-2006)
Chair, C.E.A. Winslow Medal Committee (2007-2010)
Chair, Hildreth Memorial Fund Committee (2007-2012)
The Honorable Tina Brozman Foundation Small Grant Proposal Review Committee (2010)
Chair, MPH Thesis Dean's Prize Committee (2010-2022)
Chair, Department of Chronic Disease Epidemiology, Epidemiology Competencies Committee (2015-2022)
Committee for Academic and Professional Integrity (2018-2022)
Education Committee (2019-2022)

Yale School of Medicine:
Program in Investigative Medicine Doctoral Committee (1999-2007)
Mentored Clinical Research Scholar Program Advisory Board (2003-2008)

Yale Cancer Center:
Rapid Case Ascertainment System Shared Resource (1995-2022)
American Cancer Society Institutional Research Award Review Committee (1996-2001)

American College of Epidemiology:
Education Committee (1996-2002)
Policy Committee (1997-2003)

Peer-Reviewed Research Publications:

2023

Risch HA. Plausibility, not science, has dominated public discussions of the COVID pandemic. Am J Econ Sociol 2023; http://doi.org/10.1111/ajes.12539. Online ahead of print.

Wang Z, Katsaros D, Wang J, Biglio N, Hernandez BY, Fei P, Lu L, **Risch H**, Yu H. Machine learning-based cluster analysis of immune cell subtypes and breast cancer survival. Nature Sci Rep 2023;13:18962. https://doi.org/10.1038/s41598-023-45932-4. Online ahead of print.

Frias-Gomez J, Alemany L, Benavente Y, Clarke MA, de Francisco J, De Vivo I, Du M, Goodman MT, Lacey J, Liao LM, Lipworth L, Lu L, Merritt MA, Michels KA, O'Connell K, Paytubi S, Pelegrina B, Peremiquel-Trillas P, Petruzella S, Ponce J, **Risch H**, Setiawan VW, Schouten LJ, Shu XO, Trabert B, Van den Brandt PA, Wentzensen N, Wilkens LR, Yu H, Costas L. Night shift work, sleep duration and endometrial cancer risk: A pooled analysis from the Epidemiology of Endometrial Cancer Consortium (E2C2). Sleep Med Rev. 2023;72:101848. doi: 10.1016/j.smrv.2023.101848. Online ahead of print.

Gersekowski K, Ibiebele TI, Doherty JA, Harris HR, Goodman MT, Terry KL, Wu AH, Bandera EV, Qin B, Ong JS, Tyrer JP, Dixon-Suen SC, Modugno F, **Risch HA**, Webb PM. Folate intake and ovarian cancer risk among women with endometriosis: a case-control study from the Ovarian Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev. 2023:EPI-23-0121. doi: 10.1158/1055-9965.EPI-23-0121. Online ahead of print

Lu L, Risch E, Halaban R, Zhen P, Bacchiocchi A, **Risch HA**. Dynamic changes of circulating soluble PD-1/PD-L1 and its association with patient survival in immune checkpoint blockade-treated melanoma. Int Immunopharmacol. 2023;118:110092. doi: 10.1016/j.intimp.2023.110092. Online ahead of print

Brasky TM, Hade EM, Cohn DE, Newton AM, Petruzella S, O'Connell K, Bertrand KA, Cook LS, De Vivo I, Du M, Freudenheim JL, Friedenreich CM, Goodman MT, Gorzelitz J, Ibiebele TI, Krogh V, Liao LM, Lipworth L, Lu L, McCann S, O'Mara TA, Palmer JR, Ponte J, Prizment A, **Risch H**, Sandin S, Schouten LJ, Setiawan VW, Shu XO, Trabert B, van den Brandt PA, Webb PM, Wentzensen N, Wilkens LR, Wolk A, Yu H, Neuhouser ML. Dietary omega-3 fatty acids and endometrial cancer risk in the Epidemiology of Endometrial Cancer Consortium: An individual-participant meta-analysis. Gynecol Oncol. 2023;169:137-146. doi: 10.1016/j.ygyno.2022.10.015. PMCID: PMC10025515

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Research Grants Held:

2021-2023 H Zhou (Principal Investigator), J Gelernter, B-Z Yang, V Vasiliou, **HA Risch**. *Genetic Causality of Alcohol Intake and Alcohol Use Disorder on Cancer Risk*. (National Cancer Institute, $257,125 total direct costs over 24 months)

2020-2025 AP Klein (Principal Investigator), G Petersen, D Li, **HA Risch**, P Bracci, S Gallinger, R Hung, M Meng, E Jacobs, J Manjer, M Sund, V Katzke, A Arslan, L Le Marchand, R Milne, R Stolzenberg-Solomon, C Kooperberg, S van den Eeden, J Genkinger, A Schwartz, J Brody, S Lynch, A Tjønneland, X-O Shu, L Amundadottir, K Visvanathan, B Wolpin. *Multi-Ancestry Mapping of Pancreatic Cancer Susceptibility Loci.* (National Cancer Institute, $112,843 total direct costs to Yale subcontract over 60 months)

2018-2020 CY Jeon (Principal Investigator), S Freedland, S Kim, NY Kyeong, TK Nuckols, SJ Pandol, **HA Risch**, B Spiegel. *Predicting the Diagnosis of Pancreatic Cancer by Leveraging Big Data*. (National Cancer Institute, $235,000 total direct costs over 24 months)

2018-2018 ML Irwin (Principal Investigator), L Lu, **H Risch**. *Impact of exercise and diet-induced weight loss on immunosuppression in breast cancer survivors*. (Cynthia Barnett Breast Cancer Foundation, $25,000 total costs over 12 months)

2017-2018 **HA Risch** (Principal Investigator), L Lu. *Feasibility of circulating exosomal proteins in ovarian cancer diagnos*is. (Brozman Ovarian Cancer Foundation, $25,000 total costs over 12 months)

2016-2021 AP Klein (Principal Investigator), P Bracci, S Cleary, S Gallinger, R Hung, D Li, R Neale, S Olson, G Petersen, **HA Risch,** G Scelo. *Validation and Fine-scale Mapping of Pancreatic Cancer Susceptibility Loci.* (National Cancer Institute, $220,000 total direct costs to Yale subcontract over 60 months)

2013-2017 Y Guan, X Ma (Principal Investigators), D Zimmerman, P Diggle, T Holford, **H Risch**, L Mueller, Y Zhang. *New Statistical Methods to Handle Spatial Uncertainty in Cancer Risk Estimation*. (National Cancer Institute, $1,100,000 total direct costs over 48 months)

2011-2016 R Kurman (Principal Investigator), H Berman, L Cope, T Diaz-Montes, M Gauthier, D Huso, D Levine, E Matloff, S Narod, V Parkash, **H Risch**, G Rosner, P Shaw, I-M Shih, R Soslow, R Vang, K Visvanathan, T-L Wang, et al. *Prevention of Ovarian High-Grade Serous Carcinoma by Elucidating Its Early Changes.* (Department of Defense USMRMC, $9,166,162 total direct costs, of which $199,000 total direct to Yale epidemiology subcontract, over 60 months).

2011-2015 AP Klein (Principal Investigator), P Bracci, P Brennan, E Duell, S Gallinger, D Li, R Neale, S Olson, G Petersen, **HA Risch**. *Validation and Fine-scale Mapping of*

Pancreatic Cancer Susceptibility Loci. (National Cancer Institute, $197,000 total direct costs to Yale subcontract over 48 months)

2011-2013 AP Klein, **HA Risch** (Co-Principal Investigators). *Validation and Fine-Scale Mapping of Pancreatic Cancer Susceptibility Loci*. (National Human Genome Research Institute, covers costs of large-scale high-throughput genotyping of collaborative multi-center pancreatic cancer study (see previous grant) at the Center for Inherited Disease Research (CIDR)).

2010-2016 H Yu (Principal Investigator), M Irwin, X Ma, S Mayne, **H Risch**, H Zhao, J Lim. *Epidemiologic Study of Hepatocellular Carcinoma in the US*. (National Cancer Institute, $5,385,000 total direct costs over 60 months)

2010-2014 T Sellers (Principal Investigator), A Berchuck, G Bloom, M Clyde, D Fenstermacher, B Fridley, S Gayther, W Ge, E Goode, E Iversen, H-Y Lin, S Mears, A Monteiro, T Moorman, L Pearce, P Pharoah, C Phelan, **H Risch**, MA Rossing, J Schildkraut, G Trench, Y-Y Tsai. *Follow-up of Ovarian Cancer Genetic Association and Interaction Studies (FOCI)*. (National Cancer Institute, $108,926 total direct costs to Yale subcontract 2012-2014)

2010-2013 CL Pearce (Principal Investigator), JA Doherty, S Gayther, VM McGuire, **H Risch**, MA Rossing, J Schildkraut, TA Sellers, W Sieh, D Stram, G Trench, P Webb, A Whittemore, A Wu. *Identifying Ovarian Cancer Susceptibility Alleles Using Genome-Wide Scan Data*. (National Cancer Institute, $22,500 total direct costs to Yale subcontract)

2009-2014 M Irwin (Principal Investigator), J Dziura, R McCorkle, G Mor, **H Risch**, P Schwartz, H Yu. *Impact of Exercise on Ovarian Cancer Prognosis*. (National Cancer Institute, $2,045,493 total direct costs over 59 months)

2009-2012 T Vaughan, D Whiteman (Principal Investigators), L Bernstein, D Corley, MD Gammon, L Hardie, N Hayward, G Liu, L Murray, O Nyrén, U Peters, B Reid, **HA Risch**, Y Romero, N Shaheen, D Stram, D Van Den Berg, B Weir, A Wu. *Barrett's and Esophageal Adenocarcinoma Consortium Genetic Susceptibility Study*. (National Cancer Institute, $3,750,000 total direct costs over 36 months)

2009-2010 M Goodman (Principal Investigator), A Berchuck, J Chang-Claude, D Cramer, CM Garcia, E Goode, S Krueger Kjaer, R Ness, P Pharoah, **HA Risch**, M Rossing, R Sutphen, K Terry, G Trench, A Whittemore. *Collaborative Genetic Study of Ovarian Cancer Risk*. (National Cancer Institute, $17,419 total direct costs over 12 months, to Yale subcontract)

2007-2014 **HA Risch** (Principal Investigator), Y-T Gao, MS Kidd, H Yu. *Case-Control Study of Pancreas Cancer in Shanghai, China*. (National Cancer Institute, $1,858,377 total direct costs over 75 months)

2007-2012 P Salovey (Principal Investigator), M Irwin, ST Mayne, **HA Risch**. *Promoting Cancer Prevention/Control with Message Framing: III. Extending Tailored Cancer Information Service-Delivered Messages Across the Cancer Continuum*. (National Cancer Institute: $1,525,215 total direct costs over 58 months)

2007-2012 R Neale (Principal Investigator), D Whiteman, J Young, L Fritschi, J Fawcett, P Webb, **H Risch**. *Case-Control Study of Genetic and Environmental Risk Factors for Pancreatic Carcinoma*. (National Health and Medical Research Council (Australia): AU$946,475 total nonacademic direct costs over 60 months)

2007-2011 T Sellers (Principal Investigator), D Ballinger, J Barnholtz-Sloan, ME Colter, Y Huang, E Iversen, J Lancaster, J McLaughlin, S Narod, VS Pankratz, **H Risch**, J Schildkraut, R Sutphen. *Haplotype-Based Genome Screen for Ovarian Cancer Loci*. (National Cancer Institute, $5,726,016 total direct costs over 60 months)

2006-2007 R Neale (Principal Investigator), D Whiteman, L Fritschi, J Young, J Fawcett, P Webb, **H Risch**. *A Case-Control Study of the Environmental and Genetic Causes of Pancreatic Carcinoma*. (Queensland Cancer Fund: AU$258,339 total nonacademic direct costs over 16 months)

2003-2012 **HA Risch** (Principal Investigator), FS Gorelick, D Jain, MS Kidd, ST Mayne, MD Topazian, H Yu. *Case-Control Study of Pancreas Cancer Etiologic Factors*. (National Cancer Institute: $2,578,672 total direct costs over 80 months, in NCE)

2003-2010 H Yu (Principal Investigator), **HA Risch**, ST Mayne, M Irwin, B Cartmel. *Role of Genetic and Lifestyle Interplay in Uterus Cancer*. (National Cancer Institute: $2,185,432 total direct costs over 60 months, in NCE)

2003-2006 SA Narod (Principal Investigator), B Rosen, JR McLaughlin, P Shaw, **HA Risch**. *The contribution of BRCA2 to ovarian cancer*. (National Cancer Institute of Canada: $375,000 total nonacademic direct costs over 36 months)

2002-2005 H Yu (Principal Investigator), **HA Risch**. *DNA Methylation, Aging, and Prostate Cancer Risk*. (National Cancer Institute: $600,000 total direct costs over 48 months)

2002-2006 JP Concato (Principal Investigator), W Li, P Peduzzi, **HA Risch**, D Jain. *Risk of Mortality in Prostate Cancer*. (USVA: $424,000 total direct costs over 48 months)

2001-2007 P Salovey (Principal Investigator), **HA Risch**, ST Mayne, M Morra. *Promoting Cancer Prevention/Control with Message Framing. II*. (National Cancer Institute: $1,324,481 total direct costs over 72 months)

1999-2005 **HA Risch** (Principal Investigator), AE Bale. *DNA Polymorphisms in Ovarian Cancer: Case-Control Study*. (National Cancer Institute: $325,168 total direct costs over 58 months)

1998-2002 JP Concato (Principal Investigator), W Li, P Peduzzi, S Flynn, C Howe, **HA Risch**, D Esrig. *Risk of Mortality in Prostate Cancer*. (USVA: $425,245 total direct costs over 48 months)

1997-2003 **HA Risch** (Principal Investigator), L DiPietro, AF Saftlas, A Duleba, ML Carcangiu. *Case-Control Study of Ovarian Cancer Hormonal Etiology*. (National Cancer Institute: $1,445,806 total direct costs over 70 months)

1997-2000 SA Narod (Principal Investigator), **HA Risch**. *Risk-Factor Analysis of BRCA1 and BRCA2 Carriers*. (National Cancer Institute: $1,228,000 total direct costs over 36 months)

1997-2001 P Salovey (Principal Investigator), **HA Risch**, M Morra. *Promoting Cancer Prevention/Control with Message Framing*. (National Cancer Institute: $498,295 total direct costs over 48 months)

1996-1999 P Salovey (Principal Investigator), **HA Risch**, M Morra. *Message Framing, Persuasion, and Cancer Prevention/Detection*. (American Cancer Society: $198,000 total direct costs over 24 months)

1994-2000 **HA Risch** (Principal Investigator), JR McLaughlin, SA Narod, NJ Risch, EJ Holowaty, BP Rosen, DEC Cole. *Genetic-Epidemiology Study of Epithelial Ovarian Tumors*.

(National Cancer Institute: $799,551 total direct costs over 69 months)

1994-1997 SA Narod (Principal Investigator), HT Lynch, **HA Risch**, DE Goldgar. *The Prevention of Hereditary Breast and Ovarian Cancer*. (National Cancer Institute: $356,875 total direct costs over 34 months)

1992-1996 **HA Risch** (Principal Investigator), ST Mayne, R Dubrow, AB West. *Epidemiologic Study of Esophageal/Gastric Adenocarcinoma*. (National Cancer Institute: $536,163 total direct costs over 43 months)

1991-1992 **HA Risch** (Principal Investigator). *Latency-Temporality Analysis in Case-Control Studies of Chronic Exposures*. (National Institutes of Health (BSRG): $19,000 total direct costs over 12 months)

1990-1991 **HA Risch** (Principal Investigator), GR Howe, R West, LM Strand. *A Record-Linkage Cohort Study of Menopausal Hormone Usage and Endometrial Cancer in Saskatchewan*. (National Health Research and Development Program, Health and Welfare Canada: $50,476 total nonacademic direct costs over 8 months)

1990-1994 JAJ Stolwijk (Principal Investigator), **HA Risch**, ST Mayne, R Dubrow, T Holford. *Cancer Prevention Research Unit for Connecticut at Yale*. (National Cancer Institute: $3,865,000 total direct costs over 60 months)

1989-1993 **HA Risch** (Principal Investigator), LD Marrett, GR Howe, M Jain. *A Case-Control Study of Dietary Factors and Epithelial Ovarian Cancer*. (National Health Research and Development Program, Health and Welfare Canada: $343,766 total nonacademic direct costs over 41 months)

1986-1990 GR Howe (Principal Investigator), **HA Risch**, M Jain, JD Burch, C Wall. *Research Project Support of the NCIC Epidemiology Unit*. (National Cancer Institute of Canada: total nonacademic direct costs $228,093 in 1986-7; $440,454 in 1987-8; $205,617 in 1988-9, etc.)

Selected Scholarly Presentations and Workshops:

11/23 "The Distortion of Evidence-Based Medicine." International Crisis Summit IV, Bucharest, Romania

5/23 "SARS-CoV-2 Vaccine Effectiveness." International Covid Summit III, Brussels, Belgium

10/22 "Plausibility but not Science has Dominated Public Discussions of the Covid Pandemic." Zoom seminar, The Lack of Scientific Freedom: Causes, Consequences & Cures Meeting, Copenhagen, Denmark

3/22 "Legal Considerations for the State of the Covid Emergency, and Why that Emergency No Longer Exists." Zoom seminar, IHU – Méditerranée Infection, Marseilles, France.

3/22 "Early Treatments for Covid-19 and the Trials to Suppress Them." Zoom seminar, PECC – The Israeli Public Emergency Council for the Covid19 Crisis, Tel Aviv, Israel.

1/22 "The War Against Early Covid Treatment." Testimony, US Senate, Washington, DC.

11/21 "Hydroxychloroquine and Other Outpatient Treatments for Covid-19, with Critique of Epidemiologic Methods." Zoom seminar, SIAM Texas-Louisiana Section, UTRGV, South Padre Island, TX

6/21 "Hydroxychloroquine and its Friends." Zoom seminar, IHU – Méditerranée Infection,

Marseilles, France.

11/20 "Randomized Controlled Trials, Hydroxychloroquine and Risk of Hospitalization and Mortality in Patients with Covid-19." Testimony, US Senate Committee on Homeland Security & Governmental Affairs, Washington, DC.

5/19 "Pancreatic Cancer and Diet." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.

3/19 "Reducing Mortality of What Will Be the #3 Cause of Cancer Death Two Years from Now." Virus and Other Infection-associated Cancers Research Seminar, Yale School of Medicine, New Haven, CT.

5/18 "New Concepts in Causation." Keynote speaker, Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.

2/18 "Risk Factors for Pancreatic Cancer." Yale Pancreas Symposium 2018: Multidisciplinary Management of Pancreatic Cancer. New Haven, CT.

4/17 "Reducing Mortality of what will be the #2 Cause of Cancer Death Four Years from Now." Gastroenterologic Oncology Service, Yale Cancer Center, New Haven, CT.

3/17 "Genomewide Association Study of Pancreatic Cancer in American Jews." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.

3/17 "New Markers and Approaches in Predicting Risk of Pancreatic Cancer." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.

12/16 "Genomewide Association Study of Pancreatic Cancer in American Jews." Pancreatic Cancer Case-Control Consortium (PanC4) GWAS Study Annual Meeting, Bethesda, MD.

10/16 "Reducing Mortality of Pancreatic Cancer in the International Context." Inaugural Global Oncology Seminar Series speaker, Yale Cancer Center, New Haven, CT.

6/16 "Prevention of Pancreatic Cancer." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Milan, Italy.

1/16 "Reducing Mortality of what will be the #2 Cause of Cancer Death Five Years from Now." Department of Therapeutic Radiation, Yale School of Medicine, New Haven, CT.

10/15 "Reducing Mortality of what will be the #2 Cause of Cancer Death Five Years from Now." Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Rockville, MD.

3/15 "Absolute Risk Models for Pancreatic Cancer." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.

12/12 Keynote Speaker, "From Cancer Registration to Cancer Etiology to Cancer Prevention." Cancer Registrars Association of New England Annual Meeting, Norwich, CT.

3/12 "Pancreatic Cancer Risk Models." Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Baltimore, MD.

3/12 Cancer Center Grand Rounds: "*Helicobacter pylori*, ABO Blood Group and the Etiology of Pancreatic Cancer in China and the US." Yale University School of Medicine, New Haven, CT.

9/11 "Etiology of Pancreatic Cancer: Theory and Evidence." Seminar, Division of Chronic Disease Epidemiology, Yale University School of Public Health, New Haven, CT.

3/11 "Genetic Effects and Modifiers of Radiotherapy and Chemotherapy on Survival in Pancreatic Cancer," Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, New York, NY.

1/11 Keynote Speaker, "Why is Pancreatic Cancer Less Frequent in Asia than in the US, in Spite of the Higher Prevalence of Risk Factors in Asia? Observations on the Etiology of Pancreatic Cancer." Japan Epidemiology Association National Meetings, Sapporo, Japan.

1/11 Department Seminar: "*BRCA1* and *BRCA2* Mutations: Population Frequencies and Associations with a Variety of Cancers." Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan.

1/11 Cancer Center Grand Rounds, "Why is Pancreatic Cancer Less Frequent in Asia than in the US, in Spite of the Higher Prevalence of Risk Factors in Asia? Observations on the Etiology of Pancreatic Cancer." Japan National Cancer Center, Tokyo, Japan.

11/10 Educational Session Seminar, "Gene, environment, and risk-factor interaction in pancreatic cancer." AACR Frontiers in Cancer Prevention Annual International Meeting, Philadelphia PA.

11/10 Workshop Presentation: "*KRAS* variation and risk of ovarian cancer." Biennial meeting of the Ovarian Cancer Association Consortium (OCAC), Bethesda, MD.

5/10 Cancer Center Retreat Seminar, "ABO blood group, *Helicobacter pylori* colonization and pancreatic cancer." Yale University School of Medicine, New Haven, CT.

3/10 "*Helicobacter pylori* colonization, ABO blood group and risk of pancreatic cancer," Pancreatic Cancer Case-Control Consortium (PanC4) Annual Meeting, Bethesda, MD.

7/09 Epidemiology Grand Rounds: "Pancreas Cancer and *Helicobacter pylori* in the U.S. and China." Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China.

3/09 Cancer Center Grand Rounds: "Inconsistencies in Pancreas-Cancer Risk Factors and Disease Incidence Between the U.S. and China: Observations on the Etiology of Pancreas Cancer." Yale University School of Medicine, New Haven, CT.

11/08 Workshop Participant, Defining the Public Health Research Agenda for Ovarian Cancer, Centers for Disease Control, Atlanta, GA.

7/08 Workshop Presentation: "*Helicobacter pylori* and pancreas cancer." Biological and Clinical Risks and Potential Benefits of *Helicobacter pylori* Colonization, Division of Microbiology and Infectious Diseases, NIAID, NIH, Bethesda, MD.

1/08 Research Seminar: "Smoking and lung cancer in women—yet again." Program in Cancer Prevention and Control, Yale Cancer Center, New Haven, CT.

11/07 Workshop Presentation: "*BRCA1* and *BRCA2* Mutations: Frequencies in the General Population of North America and Associations with Breast, Ovary, Stomach, Pancreas and Other Cancers." Nanjing International Symposium of New Frontiers in Cancer Research and Advanced Training Workshop of Cancer Molecular Epidemiology, Nanjing Medical University, Nanjing, China.

10/07 Workshop Presentation: "Why have epidemiology data and outcomes of clinical trials

not correlated?" Third Haifa Cancer Prevention Workshop. CHS National Cancer Control Center, Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel.

6/07 Workshop: "Advanced Statistical Methods for Epidemiologic Studies". Department of Community Medicine and Epidemiology, Technion Israel Institute of Technology Faculty of Medicine, Haifa, Israel.

3/07 Ruth and Bruce Rappaport Seminar: "Why Pancreas Cancer is Less Frequent in China than the US, in Spite of the Generally Higher Chinese Prevalence of Risk Factors: Insights on the Etiology of Pancreas Cancer." Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel.

2/07 Seminar: "Smoking and lung cancer in women—yet again." Department of Community Medicine and Epidemiology, Technion Israel Institute of Technology Faculty of Medicine, Haifa, Israel.

1/07 Seminar: "Etiologic theories for epithelial ovarian cancer." Department of Community Medicine and Epidemiology, Technion Israel Institute of Technology Faculty of Medicine, Haifa, Israel.

11/06 Seminar: "*BRCA1* and *BRCA2* Mutations: Frequencies in the General Population and Associations with Breast, Ovary, Stomach, Pancreas and Other Cancers." New York University Cancer Center, New York, NY.

2/06 Cancer Center Grand Rounds: "*BRCA1* and *BRCA2* Mutations: Their Frequencies in the General Population and Their Associations with Breast, Ovary, Stomach, Pancreas and Other Cancers," Yale University School of Medicine, New Haven, CT.

11/05 Symposium: "Why Pancreas Cancer is Less Frequent in China than the US, in spite of the Generally Higher Chinese Prevalence of Risk Factors: Insights on the Etiology of Pancreas Cancer." Clinical Oncological Society of Australia annual scientific meeting, Brisbane, Australia (Sponsored by the Queensland Cancer Fund).

11/05 Symposium: "Risks and penetrances of germline *BRCA1* and *BRCA2* mutations for ovarian, breast, stomach, pancreas and other cancers: updated results from the Ontario (Canada) ovarian cancer kin-cohort study." Clinical Oncological Society of Australia annual scientific meeting, Brisbane, Australia (Sponsored by the Queensland Cancer Fund).

6/05 Seminar: "Why Pancreas Cancer is Less Frequent in China than the US, in spite of the Generally Higher Chinese Prevalence of Risk Factors: Insights on the Etiology of Pancreas Cancer." Tumor Registrars Association of Connecticut Quarterly Meeting, Yale-New Haven Hospital, New Haven, CT.

5/05 Seminar: "Why Pancreas Cancer is Less Frequent in China than the US, in spite of the Higher Prevalence of Risk Factors There: Insights on the Etiology of Pancreas Cancer." Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL.

5/02 Symposium: "Genetic Epidemiology of Ovarian Cancer." Ovarian Cancer and High-Risk Women: Implications of Prevention, Screening and Early Detection. University of Pittsburgh, Pittsburgh, PA.

12/01 Seminar: "Prevalence and Penetrance of Germline *BRCA1* and *BRCA2* Mutations in Unselected Ovarian Cancer." Kaplan Cancer Center, NYU School of Medicine, New York, NY.

10/01 Research Seminar: "Prevalence and Penetrance of Germline *BRCA1* and *BRCA2* Mutations in Unselected Ovarian Cancer." Memorial Sloan Kettering Cancer Center, New York, NY.

6/01 Combined Monthly Research Seminar: "Prevalence and Penetrance of Germline *BRCA1* and *BRCA2* Mutations in Unselected Ovarian Cancer." Programs in Ovarian Cancer, Cancer Genetics and Cancer Prevention, Yale Cancer Center, New Haven, CT.

10/00 Departmental Seminar: "Etiology of Epithelial Ovarian Cancer." Department of Public Health Sciences, Fox Chase Cancer Center, Philadelphia, PA.

9/98 "Etiologic Mechanisms in Epithelial Ovarian Cancer," Third International Symposium on Hormonal Carcinogenesis, Seattle, WA.

5/98 Departmental Grand Rounds: "BRCA1 and BRCA2 Mutations in Unselected Ovarian Cancer," Department of Gynecologic Oncology, Yale University School of Medicine, New Haven, CT.

9/97 Departmental Seminar: "Etiologic Mechanisms in Epithelial Ovarian Cancer." Division of Epidemiology, Columbia University School of Public Health, New York, NY.

9/97 "Use of aspirin and other non-steroidal anti-inflammatory drugs and risk of esophageal and gastric cancer." American College of Epidemiology Annual Meetings, Cambridge, MA.

3/97 "Risk Factors for Familial and Hereditary Ovarian Cancer." American Cancer Society Science Writers Seminar, Reston, VA.

2/97 Departmental Grand Rounds: "Etiologic and Histologic Considerations in the Occurrence of Ovarian Cancer." Department of Pathology, Yale School of Medicine, New Haven, CT.

1/97 Departmental Seminar: "Ovarian Cancer Pathophysiology: Etiologic and Methodologic Issues." Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, NC.

6/96 "Risk factors for BRCA1-associated ovarian cancer." NCI Extramural Genetic Epidemiology PIs Second Biennial Meetings, Frederick, MD.

6/96 "Estrogen replacement therapy and the risk of epithelial ovarian cancer." Society for Epidemiologic Research Annual Meetings, Boston, MA.

6/95 "Pelvic inflammatory disease and the risk of epithelial ovarian cancer." Society for Epidemiologic Research Annual Meetings, Snowbird, UT.

6/94 "Dietary fat intake and the risk of epithelial ovarian cancer." Society for Epidemiologic Research Annual Meetings, Miami, FL.

6/93 "A cohort study of menopausal hormone usage and breast cancer in Saskatchewan." Society for Epidemiologic Research Annual Meetings, Keystone, CO.

2/93 "A cohort study of menopausal hormone usage and breast cancer in the province of Saskatchewan, Canada." International Epidemiology Association Regional European Meeting, Jerusalem.

9/92 "A record-linkage cohort study of menopausal hormone usage and breast cancer in Saskatchewan." American College of Epidemiology Annual Meetings, Bethesda, MD.

9/92 "Record-linkage cohort study of menopausal hormone usage and breast cancer."

Yale/Dana Farber Conference on Cancer Prevention and Control, Department of Epidemiology and Public Health, Yale University, New Haven, CT.

6/92 "Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type." Society for Epidemiologic Research Annual Meetings, Minneapolis, MN.

12/91 Departmental Seminar: "Some interesting results on lung cancer in women." Department of Epidemiology and Public Health, Yale University, New Haven, CT.

11/89 Departmental Seminar: "Occupational and dietary associations with bladder-cancer incidence." Department of Epidemiology and Public Health, Yale University, New Haven, CT.

8/89 "A demonstration of the GLIMP computer program for epidemiologic analysis." Canadian Epidemiology Research Conference Meetings, Ottawa.

4/89 "Nonlinear dose-response models with standard logistic regression." Upstate New York and Southern Ontario Epidemiology Group Meetings, Toronto.

6/88 "A unified framework for meta-analysis by maximum likelihood." Society for Epidemiologic Research Annual Meetings, Vancouver.

4/88 Departmental Seminar: "Occupational and dietary factors in the study of cancer of the bladder." Division of Epidemiology and Biostatistics, Graduate School of Public Health, San Diego State University, San Diego, CA.

3/88 Seminar: "Diet and occupation in the causation of bladder cancer." School of Public Health, New York State Department of Health, SUNY, Albany, NY.

12/87 Departmental Seminar: "Dietary and occupation factors in a case-control study of bladder cancer." Department of Epidemiology, Harvard School of Public Health, Boston, MA.

12/87 Departmental Seminar: "Risk factors for spontaneous abortion and its recurrence, and habitual abortion." Department of Medical Genetics, Hospital for Sick Children, Toronto.

11/87 Departmental Seminar: "Occupational and dietary factors in the causation of bladder cancer." Department of Social and Preventive Medicine, SUNY School of Medicine, Buffalo, NY.

11/87 Departmental Seminar: "Dietary and occupational factors in the study of bladder cancer." Department of Epidemiology and Biostatistics, University of Western Ontario, London.

9/87 Departmental Seminar: "Dietary and occupational factors in a case-control study of bladder cancer." Department of Epidemiology and Community Medicine, University of Ottawa.

11/86 Departmental Seminar: "Application of linear structural hypotheses in observational epidemiologic studies." Department of Environmental and Occupational Medicine, Mount Sinai School of Medicine, New York, NY.

9/86 Departmental Seminar: "Application of linear structural equations in observational epidemiologic studies." Department of Epidemiology and Public Health, Yale University, New Haven, CT.

6/86 "Measuring tumor induction period in case-control studies of chronic exposures."

Society for Epidemiologic Research Annual Meetings, Pittsburgh, PA.

8/84 "Nitrate and ascorbate in a study of gastric cancer." International Epidemiology Association Meetings, Vancouver.

5/84 "An improved method for obtaining confidence intervals of the odds ratio in logistic regression." Epidemiologic Methods Workshop, Upstate New York and Southern Ontario Epidemiology Group Meetings, Toronto.

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Toronto Superior Court of Justice / Cour supérieure de justice

Court File No.: **CV-22-0069-1880-0000**

Dr. BYRAM BRIDLE -and- David Fisman et al

Plaintiffs Defendants

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ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDING COMMENCED AT TORONTO

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This is Exhibit "B" to the Affidavit of Harvey Risch, affirmed before me on this 11th day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

EXHIBIT B: Risch Comments on the Fisman Affidavit

General observations. One could ask, after three years of observing the Covid pandemic following the large-scale vaccinations that were rolled out, how apparently honest scientists could arrive at almost completely contradictory opinions on the efficacy and safety of the Covid vaccines. In my understanding, this occurred because of different perceptions about what constitutes an appropriate public health management approach. I analogize this as follows. An engineer designs and builds a bridge across a major river. The bridge is 99.99% safe. From the engineer's point of view, achieving 99.99% is extraordinarily good. However, this bridge is on a major roadway and it carries across the river 100,000 cars per day. This means that 0.01% of those cars daily plunge into the river, 10 cars per day, 300 cars per month, 3,650 cars per year, year in and year out. Is that safe enough? Most people, reading media reports about the daily toll of deaths on the bridge, would say that the bridge is dangerous, at the same time that with knowledge of the low personal risk that they would actually face, would have little hesitation about driving across if they had a reason to do so. The point is that the Covid vaccines have not been entirely safe, but from the "engineering" public health viewpoint, have been claimed to be safe enough that they should be widely used. Further, in order to promote the large-scale vaccine uptake, the distinction between "safe enough" and "entirely safe" has been censored from public discussion so that only the latter claim has been promoted. Thus, with 677 million Covid vaccine doses administered as of December 5, 2023 to 270 million Americans, (https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-booster-percent-pop5), even the hypothetical one-in-a-thousand serious adverse event risk per dose, "99.99% safe," would have amassed 677,000 people who have had serious adverse reactions including death.

That said, previous vaccines have been withdrawn from general use after many fewer serious adverse events (https://www.cnn.com/2020/09/01/health/eua-coronavirus-vaccine-history/index.html). For example, "The CDC said the increased risk was about 1 additional case of Guillain-Barré for every 100,000 people who got the swine flu vaccine. Due to this small association, the government stopped the program to investigate." (https://academic.oup.com/aje/article-abstract/110/2/105/57614)

Additionally, serious vaccine adverse events are not temporally confined to the few days after vaccination but can occur weeks or months or even years later. However, proving that long-term adverse events have been caused by a vaccine can be evidentially challenging. Generally, observational epidemiologic studies provide evidence of such associations, and causal inference is required to draw conclusions of causation based on observed association. This allows proponents of vaccine safety to deny epidemiologic evidence of vaccine harm, by asserting that epidemiologic evidence is somehow not trustworthy or "gold-standard," and that, under the rubric of "evidence-based medicine," only double-blinded randomized controlled trials (RCTs) can be used to infer causation—when they know that such RCTs have not and will not be done because of their large costs as well as the motivation by the vaccine manufacturers and governments not to find evidence of the potential harms of their products.

This circumstance creates the situation where vaccine proponents can reasonably deny that the vaccines cause much harm, while at the same time, compilations of the numbers of individuals seriously harmed by the vaccines can reach into the hundreds of thousands, or maybe even larger numbers as follow-up time increases. In addition, it is easy to cherry-pick or deny evidence in order to artificially

strengthen claims of absolute safety or major harm. Objective science however requires honestly entertaining all relevant evidence (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1898525/), as messy and as subjective as that may be, in coming to conclusions about causation. I have argued extensively (https://onlinelibrary.wiley.com/doi/10.1111/ajes.12539) that RCT studies are not automatically good evidence and can be easily seriously flawed by design or execution, thus evidential reasoning requires evaluation of all relevant evidence, not reliance on RCT studies alone.

Individual Paragraphs in the Fisman Affidavit. Numbers refer to paragraph numbers in the affidavit.

6. "The World Health Organizations COVID-19 Dashboard states that, as of May 2023, there has been over 765,000,000 confirmed cases of COVID-19, and over 6,900,000 deaths. Deaths are believed to be under-reported globally by a factor of 3-4, such that the true death toll is likely over 20 million to date."

The statement about underreporting is unreferenced. On the contrary, deaths *from* Covid are many fewer than deaths *with* Covid, and the former has been what has largely been reported. Studies of adults and children indicate that roughly only half of deaths with Covid are from Covid, and among adults, only some 5% are in people who have no comorbidities that might be responsible for the deaths.

8. "A publication in the journal Lancet estimated that vaccination against COVID-19 had prevented approximately 20 million excess deaths worldwide as of December 2021."

This publication was seriously flawed by the use of inappropriate modeling parameter values.

13. "Dr. Bridle's interview with Ms. Pierson gained international attention because the claims he made were contrary to the overwhelming majority of scientific opinion at the time." ... "Associated Press News article titled "Spike Protein Produced by Vaccine Not Toxic" by Beatrice Dupuy dated June 9, 2021.

This statement has no supporting references about the beliefs of scientists. Further, it does not address evidence about the scientific validity of Dr. Bridle's claims, it cites a news article. Finally, as famously said by philosopher of science Karl Popper, "Studies of what scientists believe have no relation to studies of how nature behaves."

Additionally, the spike (S) protein is known to be toxic. See Moghaddar et al., https://www.mdpi.com/2076-2607/9/10/2167; Fernandes et al., https://www.sciencedirect.com/science/article/pii/S0048969721074222; Hulscher et al., https://www.cureus.com/articles/207654-clinical-approach-to-post-acute-sequelae-after-covid-19-infection-and-vaccination#!/, etc.

14. "Attached hereto as Exhibit "D" is an article from Reuters Fact Check titled "Fact Check No evidence spike proteins from COVID-19 vaccines are toxic" dated June 15, 2021."

See my comment to Paragraph 13. "Fact checks" are not scientific references. Dr. Fisman citing fact checks and news articles is not a serious scientific response.

15. "In my opinion, Dr. Bridle's comments had the potential to harm or halt Ontario's vaccine roll out. Late May and early June 2021 marked a crucial timeframe in the vaccine rollout. At this time efficacy of vaccines against Wuhan-variant COVID-19 as well as the emerging alpha variant remained high, and the

apparent reproduction number of COVID-19 remained low enough, in combination with high vaccine efficacy, that establishment of herd immunity was thought to be possible."

Dr. Fisman bases his assertion that Dr. Bridle's comments could have slowed or halted the Ontario Covid-19 vaccine roll-out on nothing. In reality, the roll-out was not affected by Dr. Bridle's comments. Furthermore, in late May and early June 2021, the US CDC was accumulating large numbers of reports of breakthrough infections (i.e., Covid-19 infections occurring after Covid-19 vaccination; https://data.cdc.gov/Public-Health-Surveillance/Rates-of-COVID-19-Cases-or-Deaths-by-Age-Group-and/3rge-nu2a), and the possibility of such breakthrough infection was generally recognized in public discussions. Because in May 2021, CDC stopped registering breakthrough infections that were not associated with hospitalization or death, the registered breakthrough infections from March through December 2021 were almost entirely serious cases, and the CDC data show that such serious breakthrough infections occurred to some 4.3% of all US vaccinated individuals. Though not officially registered by the CDC, breakthrough infections of lesser seriousness would have been occurring in much larger numbers than the 4.3%.

This means that (a) the Covid-19 vaccines in the time period cited by Dr. Fisman were not all that effective in blocking serious Covid infection, thus not substantially contributing to herd immunity; (b) the need for repeat booster vaccinations in fall 2021 and subsequently shows that herd immunity was not adequately achieved by the vaccine roll-out described by Dr. Fisman; (c) the SARS-CoV-2 Omicron strain sweeping the population from late fall 2021, with its increased infectivity and reduced virulence, infected much larger fractions of the population regardless of vaccination status and thus that wave of infection developed natural immunity and much better herd immunity than had occurred with large-scale vaccination over the previous pandemic period.

17. "Mortality from COVID-19 had declined dramatically in the face of high vaccine uptake by this time [December 2021]." Mortality did not drop because of vaccine uptake but because of the shift from delta to omicron viral strains that was occurring from November/December 2021, and the much lower virulence of the omicron strain.

17. "Ontario having had to establish field hospitals in March 2021 due to overflowing intensive care units."

Whether Ontario had to spend money to create more hospital space is irrelevant. This has no relation to anything that Dr. Bridle said. Furthermore, it was an artificial byproduct of government conspiracies at that time to suppress outpatient usage of hydroxychloroquine, which by mid-2021 was demonstrated to reduce Covid-19 mortality risk by some 75% when started outpatient use by symptom day 5 (https://earlycovidcare.org/wp-content/uploads/2021/09/Evidence-Brief-Risch-v6.pdf).

18. "It was my opinion at the time that COVID-19 vaccination represented an extremely important tool for the health and safety of the Canadian population in the face of a major health crisis."

This assertion has no supporting evidence. The overall case mortality risk of Covid-19 infection at this time was approximately 0.25%, one in 400. That risk would have been reduced by at least 75% by outpatient use of hydroxychloroquine (see previous point). The claim that the infection was a "major health crisis" was a fearmongering approach to the public health management. Further, this assertion

involves no recognition of the possible immediate and long-term health damages that the mass vaccination by a novel and inadequately tested vaccine could cause.

19. "Some claims [of Dr. Bridle's interview], however are not data based."

This is a negative and nonspecific assertion that is impossible to address because it does not specify which claims are in question. It therefore acts as a smear rather than as a statement about scientific evidence.

20. "My intention with this tweet was to warn against the spreading of misinformation to the public in regards to COVID-19 vaccines."

Dr. Fisman has facilely labeled Dr. Bridle's considered statements as "misinformation" without addressing the supposed inaccuracies in those statements. This constitutes a smear and an attempt at censorship rather than a scientific criticism of Dr. Bridle. I discuss the terms “misinformation” and “disinformation” and their use as censorship in my Affidavit.

21. The website Byrambridle.com.

It is beyond my bandwidth to examine all of the discussions posted on this website. I would note however that the anonymous authorship of this website does not rule out major conflicts of interest of its creator, or of malicious intent to damage Dr. Bridle's reputation or career. Dr. Fisman says that he directed "users" to this website, apparently without verifying the expertise of the website's author.

23. "The paper Byram cited doesn't support his claim." Twitter statement by a Dr. Pyle.

No discussion or references in support of this assertion.

24. "An excellent follow for good immune science from @UofGuelphOAC is Dr @glenpyle, who has addressed some of the misinformation in his own tweets."

Dr. Glen Pyle has a total of 55 publications in Pubmed, not a lot for a full professor, and his specialty appears to be cardiac pathophysiology. He does not appear to be a vaccinologist or an infectious diseases expert. Dr. Bridle on the other hand has published 86 peer-reviewed scientific papers and his academic expertise is specifically about vaccines and vaccine immunology.

25. "The purpose of my May 30, 2021 tweet was to direct the public to evidence-based information related to the COVID-19 vaccine."

This is another smear statement directed against Dr. Bridle. The implication that Dr. Fisman is pointing to "evidence-based information" is that Dr. Bridle was presenting information without evidence.

26. "The website debunking Dr. Bridle's Covid-19 vaccine claims has been updated with lots of peer-reviewed science that attests to the safety of vaccines."

I am unclear whether Dr. Fisman was referring in this tweet to all vaccines or to the Covid-19 vaccines. There is substantial evidence accumulating of the excess all-cause mortality associated with the Covid-19 genetic vaccines. At the time of this statement (May 31, 2021), the US VAERS database had already registered thousands of deaths occurring within a few days of Covid vaccination, thus providing evidence of short-term vaccine hazard. These reported deaths are likely to be an undercount of all such deaths occurring within a few days of Covid-19 vaccination.

27. "A friend indicates that Dr Bridle's interview caused his parents to cancel their vaccine appointments. This is not ok."

Dr. Fisman does not follow this comment with any information as to what subsequently happened to the parents. Many people chose not to take the Covid-19 genetic vaccines and did not suffer negative consequences from that choice, even those having gotten Covid. Dr. Fisman's statement here seems more like smear innuendo than statements about scientific evidence.

28 and 29. "The purpose of my May 31, 2021 Twitter thread was to direct members of the public to a website which contained peer-reviewed science-based information on the safety of vaccines."

From my perusal of the Byrambridle.com website, it is mostly innuendo and opinion about Dr. Bridle. There is a discussion of the Ogata et al., 2022 study that examined spike protein circulating in blood by successive days after Moderna mRNA vaccination. There is also a reference to the study by Lei et al., 2021 about effects of the SARS-CoV-2 spike protein on lung tissue cell function. Neither of these studies directly bears upon vaccine safety.

There are also numerous Fact Check citations about the spike protein issue, all denying any possible toxicity of the vaccine spike protein. However, contrary to all these statements, substantial evidence has emerged about the role of the vaccine spike protein in circulating to and causing pathology in various organs. This has been reviewed at length by Parry et al., 2023 (https://www.mdpi.com/2227-9059/11/8/2287).

Finally, mention is made on the Byrambridle.com website of Dr. Bridle's public statement about possible vaccine harm for fertility. The website does not provide scientific rebuttal, only a citation of the CDC webpage, "COVID-19 vaccination is recommended for everyone aged 6 months and older, including people who are pregnant, breastfeeding, trying to get pregnant now, or might become pregnant in the future. This recommendation includes getting boosters when it is time to get one." CDC provides no scientific evidence for this assertion, and the mRNA vaccine RCT studies did not include pregnant women, so Dr. Bridle's statement is not rebutted by any of this.

I find therefore Dr. Fisman's claim that he pointed members of the public to the Byrambridle.com website to provide information about vaccine safety not well justified.

41. "I felt the information Dr. Bridle was sharing could result in Canadians choosing not to get vaccinated for COVID-19. As the information was, and is, in my opinion, not scientifically sound, I wanted to ensure Canadians had access to evidence and data-based information so they could make informed decisions."

I think that Dr. Fisman is disingenuous here. In order for vaccine recipients to make informed choices, they would need thorough and accurate quantitative information on the short- and long-term risks of benefits and harms from taking each dose of the vaccine and of not taking the vaccine. Most of this information was not available to the public. Furthermore, pointing to an anonymous website as if it were an established scientific resource is improper. Finally, large numbers of people were subject to vaccine mandates that required them to accept the mRNA vaccines under threat of loss of employment, military status, etc., thus abrogating all claims to informed consent as part of the vaccination process.

42. "I believed in May and June 2021 that Dr. Bridle's speaking engagements, interviews and articles, posed a risk to the public. Given my professional responsibilities as a medical doctor and an advocate for public health measures on social media, I felt a moral and professional duty to respond to provide my own views and to direct the public to evidence and data-based resources."

Dr. Bridle appears to have asked Dr. Fisman to debate publicly their different scientific opinions in a civil fashion, but Dr. Fisman never responded. Dr. Fisman claims that he never received the emails. Dr. Fisman apparently never tried to engage with Dr. Bridle in such a public discussion either. I note that Dr. Bridle and Dr. Denis Rancourt publicly criticized a paper of Dr. Fisman published in the journal CMAJ (https://www.cmaj.ca/content/194/16/E573), and that the reporter Trish Wood invited Dr. Fisman to discuss his paper and the scientific criticisms, but Dr. Fisman did not respond to that either (https://twitter.com/WoodReporting/status/1520769440593453056).

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Plaintiffs Defendants

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ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDING COMMENCED AT TORONTO

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TAB 8

Court File #: CV-22-0069-1880-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

AFFIDAVIT OF DR. STEVEN PELECH

I, Dr. Steven Pelech, of the City of Richmond, in the Province of British Columbia, MAKE OATH AND SAY:

1. I am a professor of Neurology in the Department of Medicine at the University of British Columbia, and as such, have knowledge of the matters contained in this Affidavit.

Section A: Professional, Academic and Research Background as it Relates to COVID-19 Vaccines and Immunity

2. I am a full Professor in the Department of Medicine and Division of Neurology at the University of British Columbia (UBC), where I have been on faculty since 1988. I was one of the founding senior scientists of The Biomedical Research Centre at UBC in 1987. I hold B.Sc. Honours (1979) and Ph.D. (1982) degrees in Biochemistry from UBC. My post-doctoral training was at the University of Dundee with Sir Philip Cohen, and at the University of Washington in Seattle with Nobel laureate Dr. Edwin Krebs. Attached and marked as Exhibit A is a copy of my *curriculum vitae*.

3. I have previously completed several courses in microbiology, immunology and virology during my B.Sc. undergraduate training, and I was a founding and senior scientist for six years at The Biomedical Research Centre, which was an immunology focused institute located at UBC, where I have remained on faculty as a professor in the Department of Medicine for 35 years. Over a dozen of my scientific research articles have appeared in immunology specialty journals, including the *Journal of Immunology, Blood, Molecular Immunology, Immunology, Infectious Immunology, Cancer Immunology and Immunotherapy*, *International Journal of Vaccine Theory, Practice and Research* and *Vaccines*. These studies document some of my work to understand the molecular mechanisms by which different immune cells, including macrophages, T and B cells become activated. My lectures in formal graduate level courses include teaching in immunology, virology and bioinformatics at UBC. I have presented my research at over 100 national and international scientific conferences. My UBC lab and spin-out companies have been engaged in the production and testing of over 1600 antibodies for our internal research programs and for commercial sale for over 28 years. My independent research has routinely involved for over 35 years, the use of standard and novel immunological techniques developed in my lab, such as Western blotting, dot blotting, antibody microarrays, reverse lysate microarrays and epitope mapping for determination of where antibodies specifically bind their targets.

4. I have authored over 260 scientific publications in peer-reviewed journals and book chapters about cell communication systems important for cell survival and function and implicated in the pathology of cancer, diabetes, neurological and immunology-related diseases. Awards I have received include the 1993 Martin F. Hoffman Award for Research at UBC, and the 1993 Merck Frosst Canada Prize from the Canadian Society of Biochemistry and Molecular

Biology. I was the 2001 Distinguished Lecturer for the Faculty of Medicine at UBC for the Basic Sciences. I have served on grant review panels for the US National Institutes of Health, the Canadian Institutes for Health Research, the National Research Council of Canada, the Michael Smith Health Research Foundation, Genome Alberta, Genome Prairie, the Canadian National Cancer Institute, the Canadian Heart and Stroke Foundation and the American Heart Association, and I have acted as an external reviewer for 22 other agencies including the U.S. National Science Foundation and the Israel Science Foundation. I have also been an external reviewer for 28 different scientific journals, including those that are focused on immunology and vaccines.

5. I was the founder and president of Kinetek Pharmaceuticals Inc. from 1992 to 1998, and the founder, president and chief scientific officer of Kinexus Bioinformatics Corporation from 1999 to the present. Kinetek was engaged in the development of drugs that inhibit protein kinases, primarily for oncology application and diabetes. Kinexus has produced over 1600 antibody products against cell regulatory proteins, and employs these antibodies in novel, immunology-based, high throughput methods such as antibody microarrays to monitor cell communication systems in biological specimens from over 2000 academic and industrial clients in over 35 countries over the last 22 years. **These antibody products include those that specifically recognize parts of the SARS-CoV-2 virus, including its Spike, Nucleocapsid, Membrane and other Non-structural (NSP) proteins encoded by the genome of this virus.**

6. My expertise has been sought in over 14 court cases in Canada and South Africa as an expert witness specifically with respect to understanding the immunological mechanisms by which a natural immune response is elicited by SARS-CoV-2, the causative agent of COVID-19, and

the immunity afforded by the lipid nanoparticle Spike RNA- and adenovirus Spike DNA-based COVID-19 vaccines. This has been informed, in part, by clinical studies undertaken in the last three (3) and a half years at my company Kinexus in which we have investigated the nature and production of antibodies against the 28 different proteins that constitute the SARS-CoV-2 virus particle, by examination of blood samples from over 4500 participants from across Canada. In this independent ethics review board approved clinical study, I am the lead investigator, and I have been in direct communication with all of the participants. Some of our preliminary findings have already been published in *JCI Insights*, which is the flagship journal of the American Society for Clinical Investigation in 2021.[1] Additional manuscripts that document our SARS-CoV-2 antibody testing study are currently in preparation, and we recently finished a second antibody testing study to determine the extent of immunity against the Omicron variants and the duration and effectiveness of the COVID-19 vaccines.

7. I have also been investigating the use of drugs to inhibit the replication of the SARS-CoV-2 virus in infected host cells. My expertise on enzymes known as protein kinases has permitted me to predict and then verify that compounds that inhibit a protein kinase known as GSK3-beta can block the production of the Spike of the virus, and assembly of SARS-CoV-2 virus particles. A provisional patent based on this work has already been filed with the University of British Columbia (UBC) and manuscript that describes this work has been published.[2] Presently, I have been involved in the development of a short peptide that binds with high

[1] Majdoubi, A., Michalski, C., O'Connell, S.E., Dada, S., Narpala, S. *et al*. (2021) A majority of uninfected adults show pre-existing antibody reactivity against SARS-CoV-2. *JCI Insight* 6(8): e14631. https://doi.org/10.1172/jci.insight.146316

[2] Shapira, T., Rens, C., Pichler, V., Rees, W., Steiner, T., Jean, F., Winkler, D.F.H., Sarai, I., Pelech, S., Av-Gay, Y. (2022) Inhibition of glycogen synthase kinase-3-beta (GSK3β) blocks nucleocapsid phosphorylation and SARS-CoV-2 replication. *Molecular Biomedicine* 3, 43. https://doi.org/10.1186/s43556-022-00111-1

affinity to the NSP15 protein of SARS-CoV-2, which may block the replication of this virus and also serve as a therapeutic for treatment of COVID-19. I have also spearheaded the development commercial antibodies against many of the SARS-CoV-2 proteins and verified their utility in another published scientific article in the peer-reviewed journal Microbial Factories.[3]

8. In addition to the direct study of the SARS-CoV-2 and immune responses to this virus in people, I am also a co-founder and vice president of the Canadian Covid Care Alliance (CCCA) and very active within this organization. The CCCA's membership include over 600 biomedical scientists, medical doctors and other health practitioners, and the CCCA examines the scientific literature and data from public health authorities to ascertain the threat of COVID-19 and the various strategies available to mitigate its effects. In my capacity as the co-chair of the Scientific and Medical Advisory Committee (SMAC) of the CCCA, I oversee the activities of a panel of over 30 scientists and medical doctors that seeks to provide a scientific evidence-based and balanced, independent, but critical assessment of health care policies related to COVID-19. This Committee has met weekly over the last two (2) and half years by Zoom, but typically has daily correspondences by e-mails. The fruits of our efforts are published on the CCCA website (www.canadiancovidcarealliance.org) and in peer-reviewed scientific journals. In particular, I was a coauthor on a CCCA report that critiqued the original 6-months clinical study performed by Pfizer/BioNTech on their BNT162b2 RNA vaccine,[4] a published review about COVID-19 vaccines and pregnancy in the peer-reviewed

[3] McGuire, B.E., Mela, J.E., Thompson, V.C., Cucksey, L.R., Stevens, C.E., McWhinnie, R.L., Winkler, D.F.H., Pelech, S., Nano, F.E. (2022) *Escherichia coli* recombinant expression of SARS-CoV-2 protein fragments. *Microbial Cell Factories*. 21:21. https//doi.org/10.1186/s12934-022-01753-0. *bioRxiv* pre-print. https://doi.org/10.1101/2021.06.22.449540)

[4] Bridle, B.W., Martins, I., Mallard, B.A., Karrow, N.A., Speicher, D.J., Chaufan, C., Northey, J.G.B., Pelech, S., Shaw, C.A., Halgas, O. (2021) Concerns regarding the efficacy and safety for BNT162b2

journal *Vaccines*,[5] and another manuscript published in the peer-reviewed journal *International Journal of Vaccine Theory, Practice and Research*.[6] In addition, I am a coauthor on several other publications that have been posted on the CCCA website that relate to the manufacturing and quality issues associated with the BNT162b2 mRNA COVID-19 vaccine,[7] the efficacy and safety of the BNT162b2 mRNA COVID-19 vaccine based on phase III trial results,[8] and the vaccination of children with COVID-19 vaccines.[9] I am the senior editor of an upcoming book "Down the COVID-19 Rabbit Hole: Independent Scientists and Physicians Unmask the Pandemic." In addition to co-editing the book with Dr. Christopher Shaw (another professor at UBC), I have personally written about half of the chapters in this 700-page manuscript with over 1800 references, along with 24 other authors.

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mRNA coronavirus disease (COVID-19) vaccine through six months. www.CanadianCovidCareAlliance.org (January 10, 2022) 1-10 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/01/Final-CCCA-Critique-Thomas-COVID-19-Vaccines-6-months-NEJM-Jan-10-22.pdf

5 Karrow, N.A., Shandilya, U.K., Pelech, S., Wagter-Lesperance, L., McLeod, D., Bridle, B, Mallard, B.A. (2021) COVID-19 vaccination and potential impact on fetal and neonatal development. *Vaccines* **2021**, *9*, x. https://doi.org/10.3390/xxxxx

6 McLeod, D., Martins, I., Pelech, S., Beck, C., Shaw. C.A. (2022) Dispelling the myth of a pandemic of the unvaccinated. *Int. J. Vaccine Theory Practice Res.* 2(1):267-286.

7 Gutchi, M., Speicher, D. J., Natsheh, S., Oldfield, P., Britz-McKibbon, P., Palmer, M., Karrow, N., Massie, B., Mallard, B., Chan, G. Pelech, S. (2022) An independent analysis of the manufacturing and quality control issues of the BNT162b BioNTech/Pfizer vaccine identified by the European Medicine Agency. www.Canadian Covid Care Alliance.org (Octiober 29, 2022) 1-5 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/11/22OC29_EMA-Analysis-of-BNT162b-Manufacture.pdf

8 Bridle, B.W., Martins, I., Mallard, B.A., Karrow, N.A., Speicher, D.J., Chaufan, C., Northey, J.G.B., Pelech, S., Shaw, C.A., Halgas, O. (2021) Concerns regarding the efficacy and safety for BNT162b2 mRNA coronavirus disease (COVID-19) vaccine through six months. www.CanadianCovidCareAlliance.org (January 10, 2022) 1-10 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/01/Final-CCCA-Critique-Thomas-COVID-19-Vaccines-6-months-NEJM-Jan-10-22.pdf

9 Payne, E., Rennebohm, R., Bridle, B., Mallard, B., Karrow, N., Massie, B., Northey, K., Shoemaker, C., Pelech, S., Chaufan C., McLeod, D., Hardie, J., Pinto, C., Britz-McKibbin, P., Shaw, C. (2022) Request to halt vaccinations of children. www.CanadianCovidCareAlliance.org (July 14, 2022) 1-28 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/07/CCCA-Halt-vaccination-of-children-Officials-Letter-Jul-14-22.pdf

9. It is in my capacity as the co-chair of the CCCA Scientific and Medical Advisory Committee that I have come to know Dr. Bridle professionally as a member of our committee. I have not interacted with Dr. Bridle socially, and I have not met him in person, but only by Zoom meetings. I have also seen and heard him speak on podcast videos. I have remained highly impressed by his tireless and ongoing commitment to apply his excellent critical thinking skills, and his deep knowledge of immunology, vaccinology and virology, to the handling of the COVID-19 pandemic in our committee discussions and to the general public. I have never witnessed any occasion during this time when I was concerned that he might be spreading "misinformation." Like all of the members of the Scientific and Medical Advisory Committee, he is a strong proponent of vaccination to reduce the spread of infectious diseases. However, like the rest of the committee, including myself, he has genuine concerns about the production, testing, efficacy and safety of COVID-19 genetic vaccines, such as the lipid nanoparticle/RNA COVID-19 vaccines from Pfizer/BioNTech (BNT162b2; Comirnaty) and Moderna (mRNA-1273; Spikvax), and the adenovirus COVID-19 vaccines from AstraZeneca (Vaxzevria) and Johnson & Johnson (Jcovden).

Section B. Scope of Opinion

11. For the preparation of this affidavit, I have listened to Dr. Bridle's interview with Ms. Alex Pierson, on her Global News radio show on May 28th, 2021. I have further reviewed the May 26, 2023, affidavit of Dr. David Fisman, filed in this motion. In my affidavit, I specifically and scientifically address:

    a. Whether what Dr. Bridle stated in the Global News interview with Ms. Alex Pierson on her radio show on May 28th, 2021 was scientifically accurate.

b. Whether Dr. Fisman's statement that Dr. Bridle's statements were "misinformation", are true or tenable?

c. Whether Dr. Fisman, based on his qualifications and expertise, was appropriately qualified to determine that Dr. Bridle's statements could be construed as "misinformation?"

d. The (potential) impact of Dr. Fisman's behaviour/conduct to Dr. Bridle's research funding and career?

Section C. Dr. Bridle's Claims were Not Misinformation

12. In the Alex Pierson interview, Dr. Bridle made the following specific claims:

a. The lipid nanoparticles of the Pfizer.BioNTech COVID-19 travel from the site of injection in the deltoid muscle of the arm to organs throughout the body, including the spleen, bone marrow, liver, adrenals and ovaries. This is accurate and was evident in a Pfizer study that was submitted to the Japan Regulatory Agency.[10]

b. In a study by Ogata *et al*. (2021),[11] it was shown that in a study of 13 young health care workers following injection of the Moderna COVID-19 vaccine, there was detection Spike protein in many of their blood samples.

c. The Spike protein produced from inoculation of the COVID-19 genetic vaccines was a toxin that caused blood clotting and abnormal bleeding.

[10] "SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048) 2.6.4 薬物動態試験の概要文 (translation: "Summary of pharmacokinetic study")" https://pandemictimeline.com/wp-content/uploads/2021/07/Pfizer-report_Japanese-government.pdf

[11] Ogata, A.F., Cheng, C.A., Desjardins, M., Senussi, Y., Sherman, A.C., *et al.* (2022) Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccine antigen detected in the plasma of mRNA-1273 vaccine recipients. Clin Infect Dis. 74(4):715-718. doi:10.1093/cid/ciab465

d. The COVID-19 mRNA vaccines are able to transfer into breast milk following vaccination of lactating mothers.

e. The Canadian Blood Services uses blood from recently COVID-19 vaccinated individuals, which might permit the transfer of the vaccine lipid nanoparticles and/or Spike protein to recipients.

f. The possibility exists, since the COVID-19 mRNA vaccine lipid nanoparticles concentrate in the ovaries following inoculation, that this might lead to infertility.

13. All of Dr. Bridle's assertions and concerns at the interview were scientifically grounded, accurate, and supported by the scientific evidence and not "misinformation" nor "disinformation." I will address each of these claims below.

- **Biodistribution of COVID-19 RNA/Lipid Nanoparticle Vaccines**

14. The specific document that Dr. Bridle referred to in the Alex Pierson interview was translated from Japanese to English in a report submitted to the Japanese government by Pfizer that outlined the results of a 48 hour-post inoculation study performed with rats that were injected with the same lipid nanoparticles used in their COVID-19 vaccine formulation, but was missing the Spike-encoding RNA.[10] Within 48 hours of injection, 76% of the lipid nanoparticles had left the site of injection, and especially concentrated in the liver, spleen, adrenal glands and ovaries, although much wider distribution was documented. The data could also be retrieved from a response (see page 47) from the European Medicine Agencies to what appears to be exactly the same biodistribution study that was submitted to the Japan Regulatory Agency.[12] Di *et al*. (2022) have also noted the wide-spread distribution of COVID-

[12] Comirnaty European Public Assessment Report. Dec. 21, 2020. European Medicines Agency. Retrieved from https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

19 RNA vaccine lipid nanoparticle following their injection of mice.[13] This study also demonstrated that the surrogate luciferase gene that replaced the Spike RNA in the lipid nanoparticles was clearly being produced in these other organs. Such studies have not been performed in humans for ethical reasons.

15. Nevertheless, there are numerous reports of the presence of vaccine Spike mRNA and protein that are detectable for weeks and even months in the blood and lymph nodes of vaccinated individuals.[14] [15] [16] [17] Vaccine mRNA encoding Spike protein was found circulating in plasma of patients 15-28 days after administration of the Moderna and Pfizer-BioNTech vaccines.[11] [14] [18] [19] Both vaccine mRNA and Spike protein were detected in lymph nodes 60 days post vaccination,[15] and Spike protein persisted in circulating exosomes isolated from patients 4 months after vaccination.[17]

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[13] Di, J., Du, Z., Wu, K., Jin, S., Wang, X., Li, T., Xu, Y. (2022) Biodistribution and non-linear gene expression of mRNA LNPs affected by delivery route and particle size. Pharm Res. 39(1):105-114. doi: 10.1007/s11095-022-03166-5

[14] Fertig, T.E., Chitoiu, L., Marta, D.S., Ionescu, V.S., Cismasiu, V.B., *et al.* (2022) Vaccine mRNA Can be detected in blood at 15 Days post-vaccination. Biomedicines. 10(7:1538. doi:10.3390/biomedicines10071538

[15] Röltgen, K., Nielsen, S.C.A., Silva, O., Younes, S.F., Zaslavsky, M., *et al.* (2022). Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. Cell. 185(6):1025-1040.e14. doi:10.1016/j.cell.2022.01.018

[16] Castruita, J.A.S., Schneider, U.V., Mollerup, S., Leineweber, T.D., Weis, N., *et al.* (2023) SARS-CoV-2 spike mRNA vaccine sequences circulate in blood up to 28 days after COVID-19 vaccination. APMIS. 131(3):128-132. doi:10.1111/apm.13294

[17] Bansal, S., Perincheri, S., Fleming, T., Poulson, C., Tiffany, B., *et al.* (2021) Cutting edge: Circulating exosomes with COVID Spike protein are induced by BNT162b2 (Pfizer-BioNTech) vaccination prior to development of antibodies: A novel mechanism for immune activation by mRNA vaccines. J Immunol. 207(10):2405-2410. doi:10.4049/jimmunol.2100637

[18] Appelbaum, J., Arnold, D.M., Kelton, J.G., Gernsheimer, T., Jevtic, S.D., *et al.* (2022).SARS-CoV-2 spike-dependent platelet activation in COVID-19 vaccine-induced thrombocytopenia. Blood Adv, 6(7):2250-2253. doi:10.1182/bloodadvances.2021005050

[19] Yonker, L.M, Swank, Z., Bartsch, Y.C., Burns, M.D., Kane, A., *et al.* (2023) Circulating Spike protein detected in post-COVID-19 mRNA vaccine myocarditis. Circulation. 147(11):867-876. doi:10.1161/CIRCULATIONAHA.122.061025

16. The expression of the Spike protein in diverse organs and tissues following autopsy of people who died following COVID-19 vaccination has also been revealed by immunohistochemical examinations. This became first apparent in the scientific literature from immunohistochemistry studies performed by German pathologist Dr. Michael Mörz on a deceased male, 76-years-old Parkinson's patient who died within 3 weeks of receiving his third inoculation with the BNT162b2 mRNA.[20] Using specific antibodies to detect either the Spike or Nucleocapsid proteins of SARS-CoV-2 in tissue slices, only the Spike protein was detected within the foci of inflammation in both the brain and the heart, particularly in the endothelial cells of small blood vessels. No Nucleocapsid protein could be detected at these sites, which ruled out an actual SARS-CoV-2 infection to account for the Spike protein detection. From inspection of the foci of Spike protein detected in the brain and heart slices, it was evident that the Spike protein has been locally produced, almost certainly from the spread of the lipid nanoparticles in the COVID-19 vaccines.

17. Even more extensive analyses of 75 people in the Reutlingen area that had died following COVID-19 vaccinations were performed by another German pathologist Professor Arne Burkhardt and his international team of nine other pathologists, coroners, biologists and chemists. These deceased individuals (40 men and 35 women with a median age at death of 65.7 years) had died one day to ten months after their last COVID-19 vaccination, most commonly with the BNT162b2 vaccine. The cause of death for 68 of them was previously ruled as "natural" or "uncertain" by pathologists or coroners at the time of death (only 7 were said to be possibly linked to COVID-19 vaccination), and 19 of these cases were examples of

[20] Mörz, M. (2022) Case report: Multifocal necrotizing encephalitis and myocarditis after BNT162b2 mRNA vaccination against COVID-19. Vaccines (Basel). 10(10):1651. doi: 10.3390/vaccines10101651

unexpected Sudden Adult Death Syndrome. Dr. Burkhardt's team subsequently determined that 77% of these deaths (21 beyond reasonable doubt and 37 probably) were caused by their COVID-19 vaccination. The CCCA Scientific and Medical Advisory Committee was privileged to review many of Professor Burkhardt's findings with him, and a video copy of his presentation is posted on the CCCA website.[21] In the immunohistochemistry images of the various tissues retrieved from the deceased individuals that Dr. Burkardt's team analyzed, it was apparent that the Spike protein was widely and highly expressed in many of the tissue samples, in the absence of any detectable Nucleocapsid protein from an active SARS-CoV-2 infection. Furthermore, in these images it was clear that there was infiltration of immune cells and clear tissue pathology. This included, as observed by Dr. Matthew Mörz with the deceased Parkinson's patient, Spike protein expression, immune cell presence and cellular damage in the heart muscle. These findings are in line with the expected inflammatory responses that would arise from the expression of Spike protein on the surface of cells. Significantly, the detection of Spike protein was evident in deceased that had been vaccinated even 10 months after their last inoculation before death, and the Spike protein production was concentrated in the tissue images at the sites of destruction. This means that the detected Spike protein was not simply produced at the site of injection in the muscle and released from the muscle cells into the circulation, but rather the lipid nanoparticles or adenoviruses in the vaccines traveled throughout the body and produced the Spike protein locally.

18. Collectively, these studies fully support Dr. Bridle's original assertion that the COVID-19 RNA vaccine lipid nanoparticles do not remain at the site of injection, but rather travel

[21] Burkhardt, A. (2023) The underlying pathology of Spike protein biodistribution in people that died post COVID-19 vaccination. Canadian Covid Care Alliance. Retrieved from https://www.canadiancovidcarealliance.org/all/professor-arne-burkhardt-video/

throughout the body. In paragraphs 13 and 14 of Dr. Fisman's affidavit, he simply refers to website reports posted by "facts checkers" to discredit Dr. Bridle's claims. In particular, he cited an Associated Press News article by Beatrice Dupuy,[22] and by Reuters.[23] However, none of these actually dispute the fact that the vaccine lipid nanoparticles distribute throughout the body within a day of injection and permit the wide-spread production of Spike protein.

19. In retrospect, this widespread distribution was entirely predictable, as the lipid nanoparticles were originally designed to pass through the blood brain barrier.[24] The intramuscular injection of COVID-19 vaccines is well known to release at least a small proportion (2% or more) of the lipid nanoparticles directly into the blood stream. A standard protocol of 'aspiration' during intramuscular injection of COVID-19 vaccines was generally abandoned, since it slightly increases the less of pain during administration.[25] While this might seem to be a small proportion of the vaccine that gets directly into the blood stream, it is important to recognize that the standard dose of the Moderna COVID-19 vaccine contains 100 micrograms of RNA. This corresponds to tens of trillions of individual nanoparticles per injection. Each nanoparticle contains 5 to 10 copies of Spike RNA molecules that have been genetically modified to be highly stable. Each RNA molecule can be used to generate a hundred or more copies of Spike protein, which ultimately gets deposited on the surface of cells that take up

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[22] Dupuy, B. (2021) CLAIM: Covid-19 vaccines make people produce a spike protein that is a toxin and can spread to other parts of the body and damaged organs. Associated Press. Retrieved from https://apnews.com/article/fact-checking-377989296609

[23] Reuters Fact Check (2021) No evidence spike proteins from COVID-19 vaccines are toxic. Reuters. Retrieved from https://www.reuters.com/article/factcheck-vaccine-safe/fact-check-no-evidence-spike-proteins-from-covid-19-vaccines-are-toxic-idUSL2N2NX1J6/

[24] Satapathy, M.K., Yen, T.L., Jan, J.S., Tang, R.D., Wang, J.Y., et al. (2021) Solid lipid nanoparticles (SLNs): An advanced drug delivery system targeting brain through BBB. Pharmaceutics. 13(8):1183. doi:10.3390/pharmaceutics13081183

[25] Rzymski, P., Fal, A. (2022) To aspirate or not to aspirate? Considerations for the COVID-19 vaccines. Pharmacol Rep. 74(6):1223-1227. doi:10.1007/s43440-022-00361-4

the lipid nanoparticles. Since the lipid nanoparticles have no targeting structures on their surfaces, they will fuse and deliver their RNA contents into any cell that they happen to pass by. The consequence of this is that the cells of the immune system will attack any of the body's cells that expresses the Spike protein on their surface, often killing these cells. In the cases of neurons in the brain and spinal cord, and heart muscle cells, these are not replaceable by generation of new neurons or heart muscle cells.

- **Detection of Spike Protein in Blood Samples**

20. In his radio conversation with Alex Pierson, Dr. Bridle referred to the study of 13 young health care workers by Ogata *et al*. (2021),[11] in which was detected the presence of Spike protein in blood samples retrieved from several of the participants. To understand this study, it is important to know a few facts about the structure of the Spike protein produced by the COVID-19 RNA and adenovirus vaccines. The resultant Spike protein is cleaved into two subunits, S1 and S2, following the production of the protein inside of transfected cells. The S1 subunit features the Angiotensin Converting Enzyme 2 (ACE2) binding portion of the Spike protein. ACE2 acts as the main receptor for the SARS-CoV-2 virus binding and entry as it is expressed on the surface of host cells. The S2 subunit contains a transmembrane domain region and a palmitic fatty acid modification near the backend of the protein. These anchor the Spike protein to the surface lipid membrane of the cell in a complex of three S1 and three S2 subunits that are highly intertwined. However, if a portion of the RNA in the COVID-19 vaccines is incomplete, this may result in truncated versions of Spike protein that are not full-length and can be missing the membrane anchoring portion. Such incomplete Spike protein complexes can be easily released from cells into the lymphatic and blood systems. Since these truncated Spike proteins still retain the ACE2 binding domain of the S1 subunit, they may still

bind and engaged ACE2 and other receptors that the Spike protein can also recognize (such as Neuropilin[26]) and have functional consequences.

21. In the Ogata *et al*. (2021) study,[11] 3 of the 13 Moderna COVID-19 vaccinated individuals had detectable full length Spike protein in their blood plasma with their first injection and 11 of them had detectable S1 subunit protein. While the S1 protein was detectable in the plasma within the first day of injection, peak levels were detectable 5 days after the first inoculation. Thereafter, the detectable Spike and S1 levels declined, which was attributed to the production of antibodies against these target proteins that quickly cleared them from the circulation. Due to such antibodies, the presence of these proteins was not detectable after the second dose of the vaccine. In the cited Associated Press News article by Beatrice Dupuy,[22] and by the article by the Reuters' facts checkers,[23] the presence of the Spike and S1 proteins in the plasma samples was dismissed, since a very sensitive assay was needed for their protection. However, it should be appreciated that typical blood volume in the circulation alone is over 4 litres, so a high degree of dilution is expected of released Spike and S1 proteins into the plasma, especially since the vast majority of the Spike protein is supposed to remain anchored to cells. In principle, there should never have been any Spike protein evident in the plasma samples from blood. As such, Dr. Bridle accurately reported the findings of this study, which are corroborated by the other studies cited in paragraph 16 earlier in my affidavit.

[26] Cantutu-Castelvetri, L., Ojha, R., Pedro, L.D., Djannatian, M., Franz, J., *et al.* (2020) Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science. 370(6518):856-860. doi:10.1126/science.abd298

- **Spike Protein is a Toxin that caused Blood Clotting and Abnormal Bleeding**

22. Apart from contaminating DNA[27], double-stranded RNA[28] and endotoxin[29] along with other undesirable ingredients[30] [31] in the COVID-19 RNA vaccines, the Spike protein produced from the modified RNA can be toxic itself. This was evident in a study by Rong *et al.* (2023),[32] in which recombinant Spike protein was injected into the tail vein of mice. The S1 the subunit of the Spike protein was localized to virtually every organ, including prefrontal cortex and in narrow niches of the brain, where Spike protein persisted for 28 days, causing cell death and neuronal injury.

23. As discussed above in paragraph 21, impurities in the RNA vaccines that result in truncated Spike protein may be released more readily into the circulation from vaccine transfected cells if they are missing the transmembrane domain region and the palmitic fatty acid modification. At the time of conditional approval of the vaccines, the allowable limits for fragmented mRNA

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[27] Speicher, D.J., Rose, J., Gutschi, L.M., Wiseman, D.M., McKernan, K. (2023) DNA fragments detected in monovalent and Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada: Exploratory dose response relationship with serious adverse events. OSF Preprints. Retrieved from https://osf.io/mjc97/

[28] Milano, G., Gal, J., Creisson, A., Chamorey, E. (2021) Myocarditis and COVID-19 mRNA vaccines: A mechanistic hypothesis involving dsRNA. Future Virol. 10.2217/fvl-2021-0280 doi:10.2217/fvl-2021-0280

[29] Whitley, J., Zwolinski, C., Denis, C., Maughan, M., Hayles, L., *et al.* (2022) Development of mRNA manufacturing for vaccines and therapeutics: mRNA platform requirements and development of a scalable production process to support early phase clinical trials. Transl Res. 242:38-55. doi:10.1016/j.trsl.2021.11.009

[30] Blackwell, T. (2021) More than half Canada's AstraZeneca vaccine came from U.S. plant accused of quality-control problems. National Post. Retrieved from https://nationalpost.com/news/canada/more-than-half-canadas-astrazeneca-vaccine-came-from-u-s-plant-accused-by-fda-of-quality-control-problems

[31] Chooi, W.H., Ng, P.W., Hussain, Z., Ming, L.C., Ibrahim, B., Koh, D. (2022) Vaccine contamination: Causes and control. Vaccine. 40(12):1699-1701. doi:10.1016/j.vaccine.2022.02.034

[32] Rong, Z., Mai, H., Kapoor, S., Puelles, V.G, Czogalla, J., *et al.* (2023) SARS-CoV-2 Spike protein accumulation in the skull-meninges-brain axis: Potential implications for long-term neurological complications in post-COVID-19. bioRxiv [Preprint]. doi:10.1101/2023.04.04.535604

were up to 45% in the final product.[33] Despite alteration of the sequence in the Spike protein with two serine residues replaced by proline residues from mutation of mRNA sequence, which locks the Spike protein in a prefusion state, the Spike protein should still be able to engage angiotensin-converting enzyme 2 (ACE2) and other Spike receptors that are expressed on cells of the body. ACE2 is important for reducing blood pressure through its ability to degrade the hormone angiotensin 2. The Spike protein binding to ACE2,[34] TMEM16F,[35] and CD42b receptors on platelets and stimulate their activation and aggregation,[36] and contribute to thrombosis (blood clotting) and thrombocytopenia (reduction of production of platelets), which are known risks associated with COVID-19 vaccines.[38]

24. Due to issues of blood clotting and vaccine-induced immune thrombotic thrombocytopenia (VIIT) following injection with the AstraZeneca COVID-19 adenovirus vaccine, the National Advisory Committee on Immunization (NACI) in Canada recommended a pause for using this vaccine in people under 55 years of age.[39] Later, Ontario Public Health suspended offering the AstraZeneca vaccine on May 11, 2021 out of caution due to the increased risk of blood

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[33] Josephson, F. (2020) Rapporteur's Rolling Review assessment report. Committee for Medicinal Products for Human Use. EMEA/H/C/005735/RR. Retrieved from https://covidvaccinereactions.com/ema-pfizer-leak/

[34] Zhang, S., Liu, Y., Wang, X., Yang, L., Li, H., Wang, Y., *et al.* (2020) SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol. 13(1):120. doi: 10.1186/s13045-020-00954-7

[35] Cappelletto, A., Allan, H.E., Cresente, M., Schneider, E., Bussani, R. *et al.* (2021) SARS-CoV-2 Spike protein activates TMEM16F-mediated platelet pro-coagulant activity. Biorxiv. doi: 10.1101/2021.12.14.472668

[36] Li, T., Y.Y., Li, Y., Wang, Z., Ma, F., Luo, R*., et al.* (2020) Platelets mediate inflammatory monocyte activation by SARS-CoV-2 spike protein. J Clin Invest. 132(4):e150101. doi:10.1172/JCI150101

[38] Cox, D. (2021) Targeting SARS-CoV-2-platelet interactions in COVID-19 and vaccine-related thrombosis. Front. Pharmacol. 12:708665. doi: 10.3389/fphar.2021.708665

[39] Cochrane, D., Tasker, P. (2021) Suspend AstraZeneca use for people under 55, vaccine committee recommends. Canada Broadcasting Corporation News. Retrieve from https://www.cbc.ca/news/politics/astrazeneca-under-55-1.5968128

clots of 1 in 55,000 that were vaccinated.[40] In the Canada Adverse Events Following Immunization System (CAEFIS), the two major safety signals for COVID-19 vaccines that were acknowledged as confirmed were thrombosis (blood clotting) with thrombocytopenia syndrome (low platelet count in blood) and myocarditis/myopericarditis.[41]

25. It should be appreciated that the COVID-19 RNA vaccines have also been linked with elevated D-dimer and VITT as exemplified in cases studies of individuals that were vaccinated with either the Pfizer/BioNTech or Moderna vaccines for COVID-19.[42] [43] In a systematic review of the literature, Tan *et al.* (2023)[44] reported:

> *"Studies included in this review included 10 cohort studies and 57 case report or case series. A total of over 24,000 thrombotic events have been reported, the majority of which have been associated with adenoviral vector-based vaccine, particularly AstraZeneca (5 in 100,000 up to 6 in 1000), followed by Janssen (8–30 in 1,000,000 doses), Pfizer (6 in 1,000,000 up to 1 in 1000 doses) and Moderna (4 in 10,000,000)."*

26. Soon after the COVID-19 genetic vaccines were introduced into the general population, there were many anecdotal reports that vaccinated women were experiencing prolonged menstrual

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[40] Draaisma, M. (2021) Ontario will no longer give AstraZeneca COVID-19 vaccine as 1st dose due to blood clot risk. Canada Broadcasting Corporation News. Retrieve from https://www.cbc.ca/news/canada/toronto/ontario-update-astrazeneca-vaccine-1.6022545

[41] (2023) Reported side effects following COVID-19 vaccination in Canada. Public Health Canada. Retrieved from https://health-infobase.canada.ca/covid-19/vaccine-safety/

[42] Kaimori, R., Nishida, H., Uchida, T., Tamura, M., Kuroki, K., *et al.* (2022) Histopathologically TMA-like distribution of multiple organ thromboses following the initial dose of the BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech): an autopsy case report. Thromb J. 20(1):61. doi:10.1186/s12959-022-00418-7

[43] Bekal, S., Husari, G., Okura, M., Huang, C.A., Bukari, M.S. (2023) Thrombosis development after mRNA COVID-19 vaccine administration: A case series. Cureus15(7):e41371. doi:10.7759/cureus.41371

[44] Tan, L.J., Koh, C.P., Lai, S.K., Poh, W.C., Othman, M.S., Hussin, H. (2022) A systemic review and recommendation for an autopsy approach to death followed the COVID 19 vaccination. Forensic Sci Int. 340:111469. doi:10.1016/j.forsciint.2022.111469

cycles and heavier menstrual bleeding, even including in some post-menopausal women.[44] [] A Facebook group featured over 20,000 testimonials regarding abnormalities in menstrual cycles before it was deleted in an act of censorship. Since then, other organizations such as My Cycle Story have emerged to record such experiences.[45] Initially, these claims were largely dismissed by health officials. However, this has been investigated in several prospective studies, almost all of which support the finding of abnormal menstrual periods with COVID-19 vaccination, although to different degrees of severity.

27. In the Pregnancy Study Online (PRESTO) with 1,137 participants from the US and Canada, who were trying to conceive without fertility treatment, it was noted that the women "had [a] 1.1 day longer menstrual cycles after receiving the first dose of COVID-19 vaccine and 1.3 day longer cycles after receiving the second dose."[46] The authors "*did not observe strong associations between COVID-19 vaccination and cycle regularity, bleed length, heaviness of bleed, or menstrual pain*." The participants were followed over 5 menstrual cycles and of the 437 that were vaccinated at least once, 93% of them received a COVID-19 RNA vaccine (60% Pfizer/BioNTech vaccine and 32.9% Moderna vaccine). Another larger US prospective study with 3,959 participants also noted a slight increase in the length of the menstrual cycle, but no change in the duration of the menses period.[47]

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[44] Mercola, J. (2022) COVID Jabs impact both male and female fertility. Substack. Retrieved from https://takecontrol.substack.com/p/covid-vaccine-fertility-issues

[45] (2023) My Cycle Story Group. Retrieved from https://mycyclestory.com/

[46] Wesselink, A.K., Lovett, S.M., Weinberg, J., Geller, R.J., Wang, T.R., *et al.* (2023) COVID-19 vaccination and menstrual cycle characteristics: A prospective cohort study. Vaccine. 41(29):4327-4334. doi:10.1016/j.vaccine.2023.06.012

[47] Edelman, A., Boniface, E.R., Benhar, E., Han, L., Matteson, K.A., *et al.* (2022) Association between menstrual cycle length and Coronavirus Disease 2019 (COVID-19) vaccination: A U.S. Cohort. Obstet Gynecol. 139(4):481-489. doi:10.1097/AOG.0000000000004695

28. Another prospective study, the Nurses' Health Study 3, with 3858 premenopausal American and Canadian female nurses that were not taking hormonal contraceptive medications, similarly found a change to longer menstrual cycles within the first 6 months after COVID-19 vaccination.[48] This was particularly evident among women who took the COVID-19 adenovirus vaccines, and whose cycles were short, long, or irregular before vaccination; by contrast SARS-CoV-2 infection did not produce any changes in menstrual cycle characteristics.[48]

29. The delay in menstrual periods in recently vaccinated women was found to be reduced if they were taking hormonal contraceptive medications in a study with 1273 British and French women, and the study authors speculated "*that menstrual changes following vaccination may be mediated by perturbations to ovarian hormones*."[49] In this study, for participants with "progesterone-only contraceptions", their periods post-vaccination were significantly heavier than usual. Heavier menstrual bleed was also more evident in older women following vaccination.[49]

30. Other studies have also described heavier and/or more prolonged bleeding during menses in woman after COVID-19 vaccination. A Norwegian study of 3972 women between 18 to 30 years of age found that while menstrual disturbances were common regardless of vaccination status, "increased risks of prolonged bleeding, shorter interval between menstruations, and stronger pain during menstruation were also observed after both doses" of COVID-19

[48] Wang, S., Mortazavi, J., Hart, J.E., Hankins, J.A., Katuska, L.M., *et al.* (2022) A prospective study of the association between SARS-CoV-2 infection and COVID-19 vaccination with changes in usual menstrual cycle characteristics. Am J Obstet Gynecol. 227(5):739.e1-739.e11. doi:10.1016/j.ajog.2022.07.003

[49] Alvergne, A., Woon, E.V., Male, V. (2022) Effect of COVID-19 vaccination on the timing and flow of menstrual periods in two cohorts. Front Reprod Health. 4:952976. doi: 10.3389/frph.2022.952976

vaccines.[50] This research group also tracked unexpected vaginal bleeding and COVID-19 vaccination in non-menstruating women both 3 months before and then after SARS-CoV-2 mRNA BNT162b2 vaccination.[51] The authors noted:

> "*Among 7725 postmenopausal women, 7148 perimenopausal women, and 7052 premenopausal women, 3.3, 14.1, and 13.1% experienced unexpected vaginal bleeding during a period of 8 to 9 months, respectively. In postmenopausal women, the risk of unexpected vaginal bleeding (i.e., postmenopausal bleeding) in the 4 weeks after COVID-19 vaccination was increased two- to threefold, compared to a prevaccination period. The corresponding risk of unexpected vaginal bleeding after vaccination was increased three- to fivefold in both nonmenstruating peri- and premenopausal women*."[51]

31. Another study included women aged 18-50 years without known gynecologic comorbidities who regularly monitor their menstruation through electronic calendars.[52] A total of 219 women in this study met the inclusion criteria. Of these, 51 (23.3%) experienced irregular bleeding following the vaccine. Almost 40% (n = 83) of study participants reported a menstrual change following vaccination with the BNT162b2 SARS-CoV-2 mRNA vaccine.

32. Likewise, in a cross-sectional European study with 14,153 women, who were double COVID-19 vaccinated at least three months before, 78% of them (many of them older or smokers)

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[50] Trogstad, L., Laake, I., Robertson, A.H., Mjaaland, S., Caspersen, I.H., *et al.* (2023) Heavy bleeding and other menstrual disturbances in young women after COVID-19 vaccination. Vaccine. 41(36):5271-5282. doi:10.1016/j.vaccine.2023.06.088

[51] Blix, K., Laake, I., Juvet, L., Robertson, A.H., Caspersen, I.H., *et al.* (2023) Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. *Science Advances*. 9(38):eadg1391. doi:10.1126/sciadv.adg1391

[52] Lessans, N., Rottenstreich, A., Stern, S., Saar, T.D., Porat, S., Dior, U.P. (2023) The effect of BNT162b2 SARS-CoV-2 mRNA vaccine on menstrual cycle symptoms in healthy women. Int J Gynecol Obstet. 160(1):313-318. doi: 10.1002/ijgo.14356

reported premenstrual symptoms including "increased fatigue (43%), abdominal bloating (37%), irritability (29%), sadness (28%), and headaches (28%)" and the predominant changes were "more menstrual bleeding (43%), more menstrual pain (41%), delayed menstruation (38%), fewer days of menstrual bleeding (34.5%), and shorter cycle length (32%)."[53]

33. In a large US study with 39,129 participants that were followed for 3 months after receiving two doses of a COVID-19 vaccine and had not contracted COVID-19, the authors reported:[54]

> *"42% of people with regular menstrual cycles bled more heavily than usual, while 44% reported no change after being vaccinated. Among respondents who typically do not menstruate, 71% of people on long-acting reversible contraceptives, 39% of people on gender-affirming hormones, and 66% of postmenopausal people reported breakthrough bleeding. We found that increased/breakthrough bleeding was significantly associated with age, systemic vaccine side effects (fever and/or fatigue), history of pregnancy or birth, and ethnicity."*

34. As mentioned earlier, hormonal changes induced by the COVID-19 vaccines appeared to partly underlie the menstrual changes observed with vaccination. Since the Pfizer COVID-19 vaccine lipid nanoparticles have been shown to accumulate in the ovaries, it is possible that this might contribute to the abnormal menstrual cycles in some fertile women following vaccination. The hypothalamus and pituitary glands in the brain and the ovaries hormonally

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[53] Baena-García, L., Aparicio, V.A., Molina-López, A., Aranda, P., Cámara-Roca, L., Ocón-Hernández, O. (2022) Premenstrual and menstrual changes reported after COVID-19 vaccination: The EVA project. Womens Health (Lond). 18:17455057221112237. doi:10.1177/17455057221112237

[54] Lee, K.M.N., Eleanor J., Junkins, E.J., Luo, C., Fatima, U.A., Cox, M.L., Clancy, K.B.H. (2022) Investigating trends in those who experience menstrual bleeding changes after SARS-CoV-2 vaccination. Science Advances. 8(28):1-15. doi:10.1126/sciadv.abm7201

control the menstrual cycle, so damage to the ovaries from an inflammatory attack might contribute to this effect, as well as platelet depletion following blood clotting induced by the COVID-19 vaccines.

35. It is important to appreciate that a female is born with all of the oocytes that she will have in her lifetime, and once she is fertile after puberty, she will have approximately 400 periods in which one (and sometimes more) oocyte is converted to a fertilizable egg by the process of meiosis. The vast majority of oocytes die off without undergoing meiosis during a woman's fertile life. Menopause occurs in women when they deplete their supply of oocytes. Inflammatory damage to the ovaries can endanger the overall supply of oocytes, and could lead to an earlier onset of menopause. In working women, there is a trend to delay having children, so if the ovaries are damaged by COVID-19 vaccine injury, there could possibly be a much shorter window in which they will be able to conceive. While this is a hypothetical risk, it is serious enough to warrant caution when weighing the risks and the benefits of the COVID-19 genetic vaccines.

- **Transfer of COVID-19 Vaccines into Breast Milk Following Vaccination of Lactating Mothers**

36. A small scale study of 11 lactating women by Hanna *et al.* (2022) found after inoculation with either the Pfizer/BioNTech or Moderna RNA COVID-19 vaccines that trace levels of the Spike RNA were detectable in the breast milk of 5 of the participants in the first 45 hours post-administration.[55] In other studies, 2 of 9 breast milk samples in one study (collected 1 to. 3

[55] Hanna, N., Heffes-Doon, A., Lin, X., De Mejia, C.D., Botros, B., *et al.* (2022) Detection of messenger RNA COVID-19 vaccines in human breast milk. JAMA Pediatr. 176(12):1268-1270. doi:10.1001/jamapediatrics.2022.3581

days after first vaccination),[56] and breast milk samples from 4 of 31 mothers in another study,[57] also confirmed the transfer of Spike RNA from the vaccine into milk. In the later study,[57] a total of 10/16 and 10/25 mothers had detectable vaccine RNA in their serum 1-3 days of their first vaccination and 7-10 days, respectively, after their second dose of the COVID-19 RNA vaccine. However, the presence of the RNA in the serum of their breast-fed infants has not been reported.

37. These studies confirm Dr. Bridle's claim that COVID-19 mRNA vaccines are able to transfer into breast milk following vaccination of lactating mothers.

38. With respect to the effects of recent COVID-19 vaccination on breast feeding from lactating women, there are limited studies, for which the work of Kachikis *et al.* (2022), among the most representative.[58] Some of the possible adverse effects reported included: 355 of 10,278 (3.5%) lactating women reported a decrease in breast milk supply. Further, all signs and symptoms were recorded during the first 24 hours post-vaccination and from a given list of options. When asked about other signs symptoms post-vaccination, the participants were instructed to record them only if they thought they were related to vaccination, which makes the data collection subjective to the participants' own biases.

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[56] Low, J.M., Gu, Y., Ng, M.S.F., Amin, Z., Lee, L.Y., *et al*. (2021) Codominant IgG and IgA expression with minimal vaccine mRNA in milk of BNT162b2 vaccinees. NPJ Vaccines. 6(1):105. doi:10.1038/s41541-021-00370-z

[57] Yeo, K.T., Chia, W.N., Tan, C.W., Ong, C., Yeo, J.G., *et al.* (2022) Neutralizing activity and SARS-CoV-2 vaccine mRNA persistence in serum and breastmilk after BNT162b2 vaccination in lactating women. Front Immunol. 12:783975. doi:10.3389/fimmu.2021.783975

[58] Kachikis, A., Englund, J.A., Covelli, I., Frank, Y., Haghighi, C., *et al.* (2022) Analysis of vaccine reactions after COVID-19 vaccine booster doses among pregnant and lactating individuals. JAMA Netw Open. 5(9):e2230495. doi:10.1001/jamanetworkopen.2022.30495

39. In a Pfizer post-marketing report,[59] the authors considered 133 reports of the vaccinated mother breast feeding. Of these, 116 were taken to be normal; of the 17 cases with adverse events listed, 3 were considered "serious" and 14 "non-serious." The symptoms in the infants included: pyrexia (fever), rash, irritability, vomiting, diarrhea, insomnia, poor feeding, lethargy, abdominal discomfort, allergy to vaccine, increased appetite, anxiety, crying, poor sleep quality, eructation (belching), agitation, pain and uticaria (hives).

40. Fu *et al.* (2022)[60] conducted a meta-analysis of 23 studies that examined the immune response in pregnant and lactating individuals to COVID-19 vaccination. They noted that these individuals experienced vaccine-related reactions at a similar rate to the general population. With respect to whether the levels of IgA anti-Spike in breast milk was higher following vaccination against COVID-19 or if it was higher in lactating individuals that had previously been infected with SARS-CoV-2, the authors noted that the findings in the literature were conflicting.

- **Canadian Blood Services uses Blood from Recently COVID-19 Vaccinated Individuals**

41. Dr. Bridle noted in his interview with Alex Pierson that the Canadian Blood Services uses blood from recently vaccinated individuals for transfusions. This is true. As stated on the Canadian Blood Services website,[61] "*Consistent with our eligibility criteria for other non-live*

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[59] (2021) Cumulative analysis of post-authorization adverse event reports of PF-07302048 (BNT162B2) received through 28-FEB-2021. World-wide Safety Pfizer. Retrieved from https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf

[60] Fu, W., Sivajohan, B., McClymont, E., Albert, A., Elwood, C., *et al.* (2022) Systematic review of the safety, immunogenicity, and effectiveness of COVID-19 vaccines in pregnant and lactating individuals and their infants. Int J Gynaecol Obstet. 156(3):406-417. doi:10.1002/ijgo.14008

[61] (2023) COVD-19 vaccines and blood donation. Canadian Blood Services. Retrieved from https://www.blood.ca/en/covid19/vaccines-and-blood-donation.

vaccines, Canadian Blood Services accepts donations from otherwise eligible donors who have received a Health Canada-authorized COVID-19 vaccine, with no required deferral period following vaccination." It is further stated, "*Canadian Blood Services does not reflect vaccination status for any COVID-19 or other vaccines on the labels of products derived from blood donations."*

42. I do not think that the transfer of blood from a COVID-19 vaccinated person to a non-vaccinated individual is likely to cause significant injury, except in one particular scenario. In a person that has been recently vaccinated, the vaccine lipid nanoparticles are likely quickly taken up by the cells of the body, so there should be relatively low concentrations of the free vaccine lipid nanoparticles in the sampled blood. Moreover, during the temporary storage of the blood, the erythrocytes are likely to take up any of the remaining lipid nanoparticles. However, in the first few weeks after COVID-19 vaccination, especially with the second and subsequently doses, there will be high titres of anti-Spike antibodies. If the individual that receives the blood sample receives a COVID-19 vaccination within a few days prior to the transfusion, then there is a high prospect that the anti-Spike antibodies from the donor blood sample will induce a strong inflammatory reaction against the cells in the recipient that took up the lipid nanoparticles. Since the health of the blood recipient may already be compromised, and especially if the SARS-CoV-2 virus is in the environment and the risk of exposure is high, the distraction of the innate immune system to fight what is perceived as an active SARS-CoV-2 infection in the rest of the body could result in an easier infection of the upper respiratory system. Most of the response of intramuscular injection of COVID-19 vaccines is production of the IgG class of antibodies, which are in much lower concentrations in the nasopharyngeal passages and upper lungs, where mucosal antibodies of the IgM and

IgA classes predominate. Ironically, the COVID-19 vaccination of the blood recipient would increase the prospect that they will be infected by SARS-CoV-2 with the possibility of more severe and contagious COVID-19.

- **Concentration of COVID-19 mRNA vaccine lipid nanoparticles in Ovaries and Risk of Infertility**

43. As pointed out in paragraph 15, from biodistribution studies carried out in rats, the lipid nanoparticles used in the Pfizer/BioNTech COVID-19 vaccine (which are very similar to those used in the Moderna COVID-19 vaccine) are known to concentrate in ovaries within 48 hours.10 12 At the last time point in the biodistribution studies, only 24.6% of the lipid nanoparticles were still at the site of injection, and the ovaries were the fourth major site with an uptake of about 0.1% of the total lipid nanoparticles injected. However, due to the small size of the ovaries, the concentration of lipid nanoparticle was high at 10 micrograms of lipid equivalent per gram of tissue) The concentrations of the other major organs that accumulated the lipid nanoparticles were liver at 24.3, spleen at 23.4, adrenal glands at 18.2, and bone marrow at 3.77 μg/g.[10]

44. As noted in paragraphs 27-34, the COVID-19 RNA vaccines affect menstrual cycles in many women following their inoculation, and this is normally controlled by hormones produced by the hypothalamus and pituitary gland in the brain and the ovaries. It is also noteworthy that the COVID-19 RNA vaccine have also been correlated with a temporary reduction in sperm

counts and motility in males.[62] [63] [64] However, other studies were unable to detect COVID-19 RNA vaccine induced reduction of sperm counts or motility.[65] Unlike continuous new sperm production in males through to old age, in females, all of the oocytes that will ever be produced are already present at the time of birth as described in paragraph 36. Therefore, an inflammatory attack by immune cells against the Spike protein expressed in ovarian cells could result in damage to the ovaries and the oocytes stored therein. This is similar to the mechanism that is proposed to underlie COVID-19-vaccine induced myocarditis.[28] [66] [67]

45. The question is whether there has been indeed a reduction in female fertility rates in Canada since the introduction of the COVID-19 vaccines. From 2019 to 2020, the Canadian fertility rate declined by 4.1% from 1.47 children per woman in 2019 to 1.41.[68] In 2021, it slightly increased by 2.1% to 1.44 children per woman, but then dropped by 7.6% to 1.33 in 2022.[69] The highest decline in birthrate was in women 20 to 24 years with a 37.5% decline, followed by 34% in 15- to 19-year-olds, 17% in 25- to 29-year-olds, then dropping to 7.6% in 30- to

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[62] Wolf, Dr. N., Kelly, A. (2022) Report 37: Pfizer, FDA, CDC hid proven harms to male sperm quality, testes function, from mRNA vaccine ingredients. Retrieved from https://dailyclout.io/pfizer-fda-cdc-hid-proven-harms-to-male-sperm-quality-testes-function-from-mrna-vaccine-ingredients/

[63] Gat, I., Kedem, A., Dviri, M., Umanski, A., Levi, M., Hourvitz, A., Baum, M. (2022) COVID-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count among semen donors. Andrology. 10:1016–1022. doi: 10.1111/andr.13209

[64] Abd, Z.H., Muter, S.A., Saeed, R.A.M., Ammar, O. (2022) Effects of CCOVID-19 vaccination on different semen parameters. Basic Clin Androl. 32(1):13. doi:10.1186/s12610-022-00163-x

[65] Ma, Y.-C., Chao, C., Chi, Y., Xiang, L.-Y., Wen, J., Xi, J. (2023) The effect of COVID-19 vaccines on sperm parameters: a systematic review and meta-analysis. Asian J. Andrology. 25(4):468-473. doi:10.4103/aja2022100

[66] Barmada, A., Klein, J., Ramaswamy, A., Brodsky, N.N., Jaycox, J.R., et al. (2023) Cytokinopathy with aberrant cytotoxic lymphocytes and profibrotic myeloid response in SARS-CoV-2 mRNA vaccine-associated myocarditis. Sci Immunol. 8(83):eadh3455. doi:10.1126/sciimmunol.adh3455

[67] Mörz, M. (2022) Case report: Multifocal necrotizing encephalitis and myocarditis after BNT162b2 mRNA vaccination against COVID-19. Vaccines (Basel). 10(10):1651. doi: 10.3390/vaccines10101651

[68] (2022) Fewer babies born as Canada's fertility rate hit a record low in 2020. Statistics Canada. Retrieved from https://www.statcan.gc.ca/o1/en/plus/960-fewer-babies-born-canadas-fertility-rate-hits-record-low-2020

[69] (2023) Fertility indicators, provinces and territories: Interactive dashboard. Statistics Canada. Retrieved from https://www150.statcan.gc.ca/n1/pub/71-607-x/71-607-x2022003- eng.htm

34-year-olds, and leveling off after that for 35- to 49-year-olds.[70] From 2019 to 2022 in Canada, the crude birth rate decline was 8.6%; total fertility rate decline was 12%.

46. Worldwide, the steady decline during the pandemic period of 2019 to 2023 in fertility continued, but includes both countries with high mRNA vaccine uptake, as well as those with very low rates. It should be appreciated that birthrates have declined yearly by approximately 4% per annum since the 1950s in most nations.[71]

47. The reduction in birthrates from the beginning of the COVID-19 pandemic, to the later introduction of mRNA and other COVID-19 vaccines may be due to a number of possibilities such as: the influence of COVID-19 or the COVID-19 genetic vaccines on lowered birthrates, the overall decline in male sperm levels, increased economic hardship and social impacts of the pandemic, as well as concerns about having children given the current world situation. In Canada, conscious decisions not to have children during the current uncertain period and the lack of available housing in addition to these other factors, have contributed to the lower birth rate during the COVID-19 crisis.[72] Thus, while it may be tempting to attribute the decline in birthrates at least in part to COVID-19 vaccines, it is premature to make this a solid conclusion. **However, Dr. Bridle was right, and professionally diligent, when he posited the query, in his interview, of whether we should look deeper into this potential issue.**

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[70] (2023) Crude birth rate, age-specific fertility rates and total fertility rate (live births). Statistics Canada. Retrieved from https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310041801

[71] (2023) World fertility rate 1950-2023. MacroTrends. Retrieved from https://www.macrotrends.net/countries/wld/world/fertility-rate

[72] Hopper, T. (2023) First Reading: Canada's birth rate has dropped off a cliff (and it's likely because nobody can afford housing). National Post. Retrieved from https://nationalpost.com/opinion/canadas-birth-rate-has-dropped-off-a-cliff-and-its-because-nobody-can-afford-housing

Section D. Dr. Fisman Qualifications to Opine on Dr. Bridle's Expertise

48. In Dr. Fisman's affidavit, he identified himself as a physician that specializes in infectious disease and as a professor of epidemiology at the Dala Lana School of Public Health at the University of Toronto. From his Wikipedia profile,[73] he completed his M.D. at University of Western Ontario and obtained a Masters of Public Health at Harvard School of Public Health. He did his internal medicine residency training at McGill University and Brown University. He did further training at Beth Israel Deaconess Medical Center and Harvard School of Public Health.

49. From my reading through the titles of 260 publications available on PubMed that Dr. Fisman is listed as a sole or coauthor, and reading through a large sampling of these publications, it is evident that his work focuses on mathematical modeling of primarily infectious diseases and meta-analysis of data from other scientific reports. What is apparent from his training and written works is a lack of depth when it comes to the molecular and cellular mechanisms of immunology, microbiology, virology and vaccinology, which are the domains in which Dr. Bridle researches and publishes.

50. In his criticisms of Dr. Bridle's claims, Dr. Fisman has relied primarily on "fact checkers" who have limited expertise on their own to evaluate their validity.[22] [23] In my reading these articles, selected experts are usually quoted with little critical review of the published work that supports their opinions. While science can be controversial by nature, this is usually exercised by civil debate backed up by peer-reviewed evidence that can be critically analyzed. Someone who is truly an expert in their field would have little trouble finding primary references in the scientific literature rather than turn to websites where journalists write

[73] (2023) David Fisman. Wikipedia. Retrieved from https://en.wikipedia.org/wiki/David_Fisman

opinion pieces that generally push a particular narrative. While Dr. Fisman offers a limited number of scientific publications that support his viewpoint, these are few and far in his affidavit and in some cases are questionable in their own right. For example, Dr. Fisman cites the mathematical modeling study of Davies *et al.* (2021) as supportive of his opinion that early adoption of COVID-19 vaccination could have permitted herd immunity and saved lives from this disease.[74] However, such mathematic models are only as good as the assumptions used to drive such approximations. For example, the Davies *et al.* (2021) publication, it is assumed that COVID-19 vaccination reduced the occurrence of COVID-19 disease by 95%, which was based on relative risk reduction rather than absolute risk reduction, waning efficacy of the vaccines was not accounted for, and it seems to be assumed that those that were vaccinated and got COVID-19 would not be particularly transmissible for the SARS-CoV-2 virus. As I will explain later, these are some of the same pitfalls that Dr. Fisman has made in his own modelling of the impacts of COVID-19 vaccination on the outcomes of the COVID-19 pandemic in Canada.

51. I would also point out that other modeling groups in the UK, such as led by Dr. Neil Ferguson at the Imperial College London, projected COVID-19 deaths that were out by more than an order of magnitude.[75] Dr. Ferguson's models recklessly projected exaggerated COVID-19 deaths during the February to May 4, 2020, period in the absence of lockdowns and his prescribed non-pharmaceutical interventions to be in the range of 400,000 to 610,000 in the

[74] Davies, N.G., Abbott, S., Barnard, R.C., Jarvis, C.I., Kucharski, A.J., *et al.* (2021) Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 372(6538):eabg3055. doi:10.1126/science.abg3055

[75] Magness, P.W. (2021) The failure of Imperial College modeling is far worse than we knew. American Insitute for Economic Research. Retrieved from https://www.aier.org/article/the-failure-of-imperial-college-modeling-is-far-worse-than-we-knew/

UK, when the actual number of deaths was 28,734.[76] For almost all of the first year of the COVID-19 pandemic, there were no COVID-19 vaccines for the public. Dr. Ferguson and his colleagues forecasted 7 billion SARS-CoV-2 infections and around 40 million deaths world-wide by the end of 2020 if drastic measures were not implemented and the virus was left unchecked. [77] These estimates of morbidity were wildly over-estimated. As of October 15, 2023, over 3 and a half years into the COVID-19 pandemic, there has been some 771 million confirmed COVID-19 cases, although the actual number of SARS-CoV-2 infections is probably closer to 7 billion, and the cumulative deaths with COVID-19 were reported to be just under 7 million.[78] While the serological prevalence of SARS-CoV-2 infections in Canada[79] and in many other countries around the world is over 80%, the death toll has been vastly smaller than predicted by the Fergusson model. Unfortunately, such estimates were initially treated as near-factual representations and used to guide public policy in the UK and abroad.

52. Unfortunately, Dr. Fisman seems to be Canada's counterpart to Dr. Ferguson as a purveyor of doom and gloom with projected COVID-19 casualties without enforcement of strict public health measures and mandates. His own flawed COVID-19 pandemic modeling was reported in the Canadian Medical Association Journal article entitled "Impact of population mixing

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[76] Flaxman, S., Mishra, S., Gandy, A., Unwin, H.J.T., Mellan, T.A., *et al.*; Imperial College COVID-19 Response Team. (2020) Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. Nature. 584(7820):257-261. doi:10.1038/s41586-020-2405-7

[77] Walker, P.G.T., Whittaker, C., Watson, O.J., Baguelin, M., Winskill, P., *et al.* (2020) The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries. Science. 369(6502):413-422. doi: 10.1126/science.abc0035

[78] (2023) WHO Coronavirus (COVID-19) Dashboard. World Health Organization. Retrieved from https://covid19.who.int/

[79] Murphy, T.J., Swail, H., Jain, J., Anderson, M., Awadalla, P., *et al.* (2023) The evolution of SARS-CoV-2 seroprevalence in Canada: a time-series study, 2020-2023. CMAJ. 195(31):E1030-E1037. doi: 10.1503/cmaj.230249

between vaccinated and unvaccinated subpopulations on infectious disease dynamics: implications for SARS-CoV-2 transmission."[80] The publication promoted the concept that the spread of SARS-CoV-2 was primarily from the unvaccinated to the COVID-19 vaccinated, which was widely disseminated in the popular press. This article also received widespread critical commentary, including many calls for retraction of the article directly to the journal, which is the way that academics normally criticize each other works. [81] [82] [83] A whole book has been written about the problems associated with Dr. Fisman's work.[84]

53. Some of the major issues with his modeling included:

    a. Using relative risk reduction rather than absolute risk reduction with the COVID-19 vaccines;

    b. Over-inflating the effectiveness of COVID-19 vaccines and ignoring evidence of negative efficacy with booster shots;[85] [86]

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[80] Fisman, D.N., Amoako, A., Tuite, A.R. (2022) Impact of population mixing between vaccinated and unvaccinated subpopulations on infectious disease dynamics: implications for SARS-CoV-2 transmission. CMAJ. 194(16):E573-E580. doi:10.1503/cmaj.212105

[81] Bridle, B. (2022) Fiction disguised as science to promote hatred. COVID Chronicles substack. Retrieved from https://viralimmunologist.substack.com/p/fiction-disguised-as-science-to-promote?s=r

[82] Rancourt, D., Hickey, J. (2022) OCLA statement on CMAJ Fisman *et al.* article claiming disproportionate infection risk from unvaccinated population, and on negligent media reporting. Ontario Civil Liberties Association. Retrieved from https://ocla.ca/ocla-statement-on-cmaj-fisman-et-al/

[83] Rose, J. (2022) Call for retraction of paper entitled: "Impact of population mixing between vaccinated and unvaccinated subpopulations on infectious adisease dynamics: implications for SARS-CoV-2 transmission."] Unacceptable Jessica substack. Retrieved from https://jessicar.substack.com/p/call-for-retraction-of-paper-entitled?s=r

[84] Watteel, R.N. (2023) Fisman's fraud: The rise of Canadian hate science. Rainsong Books

[85] Andrews, N., Stowe, J., Kirsebom, F., Toffa, S., Rickeard, T., *et al.* (2022) COVID-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med. 386(16):1532-1546. doi:10.1056/NEJMoa2119451

[86] Hansen, C.H., Schelde, A.B., Moustsen-Helm, I.R., Emborg, H.-D., Krause, T.G. *et al.* (2021) Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study. medRxiv. doi:10.1101/2021.12.20.21267966

c. Falsely assuming that the protection from COVID-19 vaccination did not wane;

d. Falsely assuming that vaccinated people do not get infected, do not get sick, and do not transmit SARS-CoV-2. Real-world data shown on the Ontario Public Health website on March 31, 2022 showed that 70% of hospitalized COVID-19 cases at the time were fully vaccinated for COVID-19.[87] There are no data that support the notion that vaccinated individuals with COVID-19 do not transmit SARS-CoV-2 with viral loads that are different from unvaccinated individuals;

e. Underestimating the percentage of the population that has been infected with SARS-CoV-2 as under 20% even after the Delta and Omicron waves of the virus sweeping through Canada. This should have been more like 80% or higher,[88] and which if used as a parameter instead of 20% would have completely flipped the conclusions of the model, *i.e.*, the unvaccinated were protecting the vaccinated from spread of COVID-19;

f. Almost completely ignoring the protection conferred by natural immunity;

g. Ignoring any safety issues related to COVID-19 vaccination such as for example, thrombosis, Gullian-Barré syndrome, myocarditis and myopericarditis; and

h. It does not help that Dr. Fisman was highly conflicted as a consultant on advisory boards related to influenza and SARS-CoV-2 vaccines for Pfizer, AstraZeneca, Seqirus and Sanofi-Pasteur.

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[87] (2022) COVID-19 vaccination data. Ontario Public Health. Retrieved from https://web.archive.org/web/20220401023423/https://covid-19.ontario.ca/data

[88] Clarke, K.E.N., Jones, J.M., Deng, Y., Nycz, E., Lee, A., *et al.* (2022) Seroprevalence of infection-induced SARS-CoV-2 antibodies - United States, September 2021-February 2022. MMWR Morb Mortal Wkly Rep. 71(17):606-608. doi:10.15585/mmwr.mm7117e3

54. Prior to his resignation as an active member of its modeling group, Dr. Fisman also played a key role in the Ontario Science Table, which prominently advised the Ontario provincial government on policy during COVID-19 pandemic.[89] In the end, even Dr. Fisman *et al.* (2022) stated that "*the simplicity of our model is …. a weakness, because it does not precisely simulate a real-world pandemic process in all its complexity.*" [80] So while they concluded, "*we found that the choices made by people who forgo vaccination contribute disproportionately to risk among those who do get vaccinated*," this is clearly conjecture since no real-world observations with people were used to test their study. Thus, although the title of the publication implied that there was actual mixing of populations in the study, this did not actually transpire.

55. Regretfully, Dr. Fisman's dubious COVID-19 pandemic modeling is not unique in Canada. Modeling performed by the Public Health Agency of Canada (PHAC) has also been roundly criticized for being overly simplistic, relying on outdated assumptions and flawed reasoning.[90] Secrecy should have no place in this context. If models are used to guide society's actions and potentially impose risks, complete transparency is essential, and the entire model must be subject to critical discussion. Unlike his earlier modeling work, including with the Ontario Science Table, at least Dr. Fisman made his more recent COVID-19 pandemic modeling more open to analysis, which exposed many of its problems as outlined above.[80]

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[89] Lilley, B. (2022) Lilley: Take Ontario Science Table COVID advice with a grain of salt. Toronto Sun. Retrieved from https://torontosun.com/opinion/columnists/lilley-science-table-advice-needs-to-be-taken-with-a-grain-of-salt-given-their-track-record

[90] Vickers, D.M., Hardie, J., Eberspaecher, S., Chaufan C., Pelech, S. (2023) Counterfactuals of effects of vaccination and public health measures on COVID-19 cases in Canada: what could have happened? Frontiers. 11:2023. doi:10.3389/fpubh.2023.1173673

56. Modeling, like science, is an iterative process that thrives on evaluation and correction. An authoritarian approach to science is inherently flawed. Throughout the pandemic, numerous examples emerged where insightful individuals from disparate fields, such as or physics and geology, identified problems within the domain of epidemiology missed by others.[91] [92] Ethical considerations aside, allowing open discourse is the only way to prevent echo chambers from leading society into catastrophic scenarios. For this, transparency is indispensable.

57. Academic freedom as a university professor affords the opportunity for Dr. Fisman to express his opinions in a scholarly manner on matters in which he had demonstrated expertise. However, it is unfitting for a professor of his stature to make public statements about another biomedical research scientist in a different discipline when he does not appear to have the requisite specialized knowledge to claim in his affidavit that Dr. Bridle's interpretations, analyses and opinions are:

    a. "contrary to the overwhelming majority of scientific opinion" (para. 13)
    b. "have the potential to harm or halt Ontario's vaccine rollout" (para.15)
    c. "spreading misinformation regarding COVID-19 vaccines" (para. 20)
    d. "misinformation on the efficacy of vaccines" (para. 28)
    e. "Dr. Bridle's claims are implausible and not data based" (para.30)
    f. Dr. Bridle's information is "not scientifically sound" (para. 41)

[91] Rancourt, D.G., Baudin, M., Mercier, J. (2021) Analysis of all-cause mortality by week in Canada 2010-2021, by province, age and sex: There was no COVID-19 pandemic, and there is strong evidence of response-caused deaths in the most elderly and in young males. ResearchGate. doi: 10.13140/RG.2.2.14929.45921

[92] Ruechel, J. (2021) Autopsy of a pandemic: The lies, the gamble, and the Covid-zero con. Independently published

g. "Dr. Bridle's speaking engagements, interviews and articles posed a risk to the public" (para. 42).

58. On the one hand, as I have explained earlier on in paragraphs 15 to 48, there is strong support in the scientific literature to support Dr. Bridle's statements and concerns. It is therefore not in the public interest to not have scientists with highly specialized expertise and their expert opinions labelled as "misinformation." On the other hand, I think the published modeling work on the COVID-19 pandemic by Dr. Fisman, who suggested that the unvaccinated were driving the COVID-19 pandemic in the vaccinated, does qualify as "misinformation" as exemplified in paragraph 53 to 55 above.

Section E. The Changing Response of Public Health Authorities Abroad to COVID-19 Vaccination

59. While most Canadian public health authorities still remain gung-ho about the COVID-19 vaccines, public health authorities in Quebec[93] and many other countries are much less enthusiastic. In fact, the COVID-19 adenovirus vaccines and Medicago, while initially approved by Health Canada, have all since been discontinued in 2023.

61. In view of the mounting and disturbing data about the limited efficacy and serious safety issues associated with the COVID-19 genetic vaccines, health regulatory agencies around the world have begun one after another to discourage or ban the use of these vaccines, especially in younger people. Denmark was the first nation in Europe to invoke this step by stopping

[93] Rigs, A. (2023) COVID-19: Quebec drops recommendation that all should get booster vaccine. Montreal Gazette. Retrieved from https://montrealgazette.com/news/local-news/quebec-covid-vaccine-recommendation-hybrid-immunity

vaccination invitations on May 14, 2022.[94] By autumn 2022, Denmark recommended vaccination only to those over 50 years old and some vulnerable populations.[95]

62. Many other European countries, as well as Australia and some US states such as Florida, have stopped recommending vaccinations for COVID-19 to anyone under 40, 50 or 60 years of age and especially children. Even in 2021, France and Scandinavian countries did not recommend the Moderna vaccine for people under 30 years of age.[96] [97] The United Kingdom Joint Committee on Vaccination and Immunisation (JCVI) no longer recommends vaccination of healthy individuals under 50 years of age in the UK except for those in clinical risk groups or those attending to such individuals.[98] The Federal Office of Public Health in Switzerland also no longer recommends COVID-19 vaccination for healthy people in all age groups, and will not pay for COVID-19 vaccination for anyone, unless medically indicated by a physician for an individual patient with a clear risk-benefit analysis.[99] The Australian government has advised that a booster dose is **not recommended** as of February 2023 for children and

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94 Ellyatt, H. (2022) Denmark becomes the first country to halt its COVID vaccination Program. CNBC News. Retrieved from https://www.cnbc.com/2022/04/28/denmark-the-first-country-to-halt-its-covid-vaccination-program.html

95 Goldenberg, J. (2022) Denmark halts COVID vaccinations for low-risk people under 50. The Suburban. Retrieved from https:/www.thesuburban.com/news/city_news/denmark-halts-covid-vaccinations-for-low-risk-people-under-50/article_1e0264ec-dea3-59e0-bf3e-db59eee4378d.html

96 (2021) France advices against Moderna for under-30s over rare heart risk. France 24. Retrieved from https://www.france24.com/en/live-news/20211109-france-advises-against-moderna-for-under-30s-over-rare-heart-risk

97 Lehto, E. (2021) Finland joins Sweden and Denmark in limiting Moderna's COVID-19 vaccine. Retrieved from https://www.reuters.com/world/europe/finland-pauses-use-moderna-covid-19-vaccine-young-men2021-10-07/

98 (2023) JCVI statement on the COVID-19 vaccination programme for 2023:8 November 2022. Updated 27 January 2023. UK Department of Health and Social Care. Retrieved from https://www.gov.uk/government/publications/covid-19-vaccination-programme-for-2023-jcvi-interim-advice-8-november-2022/jcvi-statement-on-the-covid-19-vaccination-programme-for-2023-8-november-2022

99 (2023) COVID-19: Vaccination. Federal Office of Public Health FOPH. Retrieved from https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/impfen.html#21889874

adolescents up to 18 years who do not have any risk factors for severe COVID-19, and only for those 18-64 years of age who have undergone a risk-benefit analysis with their healthcare provider.[100] The German Federation of Hospitals (DKG) called for the mandatory vaccination obligation of healthcare personnel to be revoked after the German Ministry of Health admitted that 1 in 5,000 COVID-19 vaccination shots led to serious side-effects.[101]

63. In April 2023, the European Medicine Agency and the European Parliament finally recognized that at least 11,448 deaths in the EU occurred following COVID-19 vaccination, and that there were 50,648 deaths attributed to these vaccines in the Eudravigilance database as of April 10, 2023.[102] It would appear that health regulatory agencies in Europe and elsewhere have come to realize the clear and present dangers of the COVID-19 genetic vaccines.

64. It seems that the populations of Canada and the US have also finally come to recognize the efficacy and safety issues of the COVID-19 vaccines, despite the heavy messaging from public health officials to the contrary. For example, only about 16% of those 6 months or older in Ontario within the past year had received a COVID-19 vaccination by September 14, 2023.[103] In the US, only about 5.4% of children and 14.8% of adults 18 years and older

[100] (2023) COVID-19. Australian Immunisation Handbook. Australian Government Department of Health and Aged Care. Retrieved from https://www.health.gov.au/our-work/covid-19-vaccines/advice-for-providers/clinical- guidance/clinical-recommendations

[101] Mek, A. (2022) German Hospital Federation demands withdrawl of vaccination mandate after massive side effects revealed. RAIR Foundation USA. Retrieved from https://rairfoundation.com/german-hospital-federation-demands-withdrawal-of-vaccination-mandate-after-massive-side-effects-revealed/

[102] Joro, V. (2023) European Parliament: How many deaths have been caused by 'COVID vaccines'? Question for written answer E-001201/2023. Retrieved from https://www.europarl.europa.eu/doceo/document/E-9-2023-001201_EN.html

[103] (2023) COVID-19 vaccine uptake in Ontario: December 14, 2020 to November 5, 2023. Public Health Ontario. Retrieved from https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-vaccine-uptake-ontario-epi-summary.pdf?la=en

received the updated XBB1.5 COVID-19 vaccines by November 17, 2023, whereas 35.1% of children and 36.3% of adults opted to be vaccinated against influenza.[104]

65. It seems to me that Dr. Bridle's voiced concerns regarding the COVID-19 genetic vaccines are being acknowledged by increasing more biomedical researchers and the general public.

Section F. Harms for Alleging Dr. Bridle is "An Immunologist Spreading Misinformation"

66. In reading through Dr. Fisman's affidavit, I noticed that he claimed in paragraph 21 that "*I am not the author or creator of the website byrambridle.com, nor do I play any role in its maintenance*." He further stated "*I directed users to the website as it contains data-based information on COVID-19 vaccine safety concerns*." While Dr. Fisman seems to be ambiguous on whether he actually provided any content or assisted in the creation of content for this website, in any event, he promoted and supported the fraudulent, derogatory, and highly defamatory website by directing traffic to it. As more data continues to emerge about issues with the production, efficacy and safety of the COVID-19 genetic vaccines, Dr. Fisman's own credibility is at jeopardy through his repeated actions that strike me as disingenuous. It is evident from Dr. Fisman's statements in his affidavit that he was well aware that Dr. Bridle was eager to engage him in discussions about the COVID-19 vaccines even privately, and clearly this would have been an excellent opportunity to steer Dr. Bridle straight if he was in error. He was not.

67. It is also clear to me that Dr. Fisman and others have harmed the research and reputation of a highly qualified and otherwise successful expert scientist through their labelling of Dr. Bridle

[104] (2023) Respiratory viruses. Vaccination trends-Adults. Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/respiratory-viruses/data-research/dashboard/vaccination-trends-adults.html

as a "spreader of misinformation." Dr. Bridle has not been able to set foot in his own laboratory at the University of Guelph for over two years, and there is no doubt in my mind that his ability to secure research grant funding and attract graduate student and post-doctoral fellow trainees has been compromised. The Canadian biomedical research community is very small and it is easy to tarnish someone's reputation, especially if that person is placed in a position where they are unable to defend their opinions against prevailing dogma.

SWORN BEFORE ME by Steven Pelech in the City of Richmond, in the Province of British Columbia, on this 1st day of December, 2023, in accordance with O. Reg. 431/20 Administering Oath or Declaration Remotely

A Commissioner for Taking Oaths
Rocco Galati B.A., LL.B., LL.M.

Dr. Steven Pelech

This is Exhibit "A" to the Affidavit of Steven Pelech, sworn before me on this 1st day of December 2023

A Commissioner for Taking Affidavits

Rocco Galati, , B.A., LL.B., LL.M.

University of British Columbia

Curriculum Vitae for Faculty Members

Date: **May 12, 2023**

Initial: _____

1. SURNAME: Pelech

FIRST NAME: Steven

MIDDLE NAME(S):

2. DEPARTMENT/SCHOOL: Medicine, Div. Neurology

3. FACULTY: Medicine

JOINT APPOINTMENTS:

4. PRESENT RANK: Professor **SINCE:** Jul 1, 1998

5. POST-SECONDARY EDUCATION

(a)

University or Institution	Degree	Subject Area	Dates
University of British Columbia	B.Sc.	Biochemistry	1975-1979
University of British Columbia	Ph.D.	Biochemistry	1979-1982

(b) Title of Dissertation and Name of Supervisor

Regulation of Phosphatidylcholine Biosynthesis - with Dr. Dennis E. Vance

(c) Continuing Education or Training

(d) Continuing Medical Education

(e) Professional Qualifications

1 Biomedical Research Scientist

6. EMPLOYMENT RECORD

Prior

University, Company or Organization	Rank or title	Dates
University of British Columbia	Assistant Professor	July 1, 1988 - June 30, 1993
University of British Columbia	Associate Professor	July 1, 1993 - June 30, 1997
University of British Columbia	Postdoctoral Fellow (with Dr. Dennis Vance)	1983-1983
University of Dundee, Scotland	Postdoctoral Fellow (with Dr. Philip Cohen, knighted as Sir Philip Cohen)	1983-1984
University of Washington, Seattle	Postdoctoral Fellow (with Dr. Edwin Krebs, Nobel Prize recipient)	1984-1987
Biomedical Research Centre, Vancouver (Immunology Institute)	Senior Scientist	1987-1998
Kinetek Pharmaceuticals, Inc.	Founder, President & Chief Executive Officer	1992-1997

Present

University, Company or Organization	Rank or title	Dates
University of British Columbia	Professor	July 1, 1997 - present
Kinexus Bioinformatics Corporation	Founder, President & Chief Scientific Officer, Director	1999-present

c) Date of granting tenure at UBC:

July 1, 1993

7. LEAVES OF ABSENCE

University, Company Or Organization at which Leave was taken	Type of Leave	Dates

None taken since starting as a UBC faculty member. However, from November 3, 2004 through to April 15, 2005, I was summoned for 24 full days to appear in a B.C. Human Rights Hearing Case. I also had to appear in the BC Supreme Court for a judicial review of this case over a week's period in April 2009.

8. TEACHING

(a) Areas of special interest and accomplishments

1 Percentage of Overall Time Devoted to:

Non-clinical instruction:	20%
Clinical instruction:	0%
Research/publication:	55% (includes R&D at private biotechnology company)
Administration (UBC):	20%
Administration (Kinexus):	5%
Clinical practice:	0%

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2 For over 30 years, I was very active in the establishment of the Experimental Medicine Graduate Program and have worked closely with its six directors (i.e. Drs. Rabkin, Quamme, Wong, Duronio, Sly and Tang). My goal was to develop courses that would provide practical, useful skills to graduate students. In particular, the students should acquire a solid knowledge base, be able to read the scientific literature and on-line websites critically, adapt to new lab environments and assimilate new techniques, deliver clear oral presentations, and write competitive grants for funding.

3 To improve the knowledge-base of Experimental Medicine students, I became the course coordinator for MEDI 501, a lecture course that is required of all students in the program and focuses on the molecular basis of disease. I originally presented the opening four lectures for this course, which is taught by several faculty members. I am convinced that future improvements in the treatment of diseases will depend upon a firm understanding of the molecular mechanisms underlying the diseases. Imparting this knowledge to graduate students will better prepare them for disease-related research. In 2022, I taught one 90 minutes lecture each term. I also provide an examination question for the mid-term exam and graded 19 answers.

4 To improve the laboratory skills of Experimental Medicine students, I became the course coordinator for MEDI 502, which is the second course that is required of all students in the program. Previously, the students went on mass together to a different lab each week to see a technique taught by a faculty member. I altered the course so that each student could select two host labs out of two dozen possible labs in which they would spend half a day per week for two months in each lab learning about the research area and various techniques in use in that lab. This improved research interactions among various members of the Department of Medicine. Half way through this course, the student has to give to the other students in the course a 20 minutes

oral presentation that outines the nature of the research in the first host lab and a technique that is being used to approach a biological problem in that lab. At the conclusion of the rotation in the second host lab, the student has to write an MRC grant application that combines aspects of his experience in the host laboratories. The oral presentation and the grant application account for the majority of the final grade for this course. This is the only course of this kind that is offered through the U.B.C. Currently, I take on one to two students per term in my laboratory for this course.

5 I have also provided the opportunity for many undergraduate students to obtain research experience in my laboratory through the BIOL 448A and MEDI 548 Directed Studies courses and the cooperative education programs at the Department of Microbiology and Immunology at U.B.C. and the Simon Fraser University Science Coop. From these coop programs, over 200 undergraduate students have work full-time in my laboratory under my supervision for 4 to 12 month terms.

6 My area of research expertise is signal transduction, and there is growing appreciation that defective cell signalling is at the root of cancer, Alzheimer's, diabetes, immune disfunction and many other chronic diseases of aging. As there was no advanced, graduate level course in signal transduction that was offered each year at U.B.C., I decided to create one. The majority of my teaching is in the MEDI 590 Cell Regulation course, which I coordinate and deliver all of the lectures. The course is very advanced and covers a lot of ground, but most students perform very well. The final mark for MEDI 590 course is now largely dependent upon an exercise to gather detailed information about various members of a family of cell signalling proteins. This exercise forces the students to read the scientific literature and collect data from relevant websites, and present their results organized in Excel tables. The collected information is made available to the scientific community after it is integrated into a database. In 2022, there were 11 registered graduate students that initially took the course as well as one Ph.D. student that audited the course. All of the 56 hours of PowerPoint lectures and supporting materials are provided to all the students in pdf format in advance of each class. I devoted over 30 hours additional outside of the classroom in 2022 in MEDI 590 course preparation, including the development of new original content and marking midterms and final assignments. I have made much of these educational materials available to wider audiences on the Kinexus Bioinformatics website at www.kinexus.ca. My long term objective is to produce 10 minute teaching videos of portions of the lectures for the MEDI590 course that will be posted on-line with open-access.

7 Another course that I originally coordinated for five years is MEDI 535, which I designed to be a journal club in which the participants critically analyze recent scientific papers based on signal transduction research. In this course, the students received a scientific paper a week before the next class that they are expected to read and critically review. The following week, the student that originally selected the paper provided a brief synopsis of the paper and then led the round table discussion among myself and the other students of the paper's strengths and deficiencies. I believe that this course provides the students with strong analytical skills that are useful when the students prepare their own scientific manuscripts and for when they read the literature. I have not tutored in this course in recent years.

8 I have also provided 2 hours of lecture per year in the Neuroscience 500 course (1999-2001), I participated as a medical student PBL tutor in the Endocrinology Block for Second Year (1999, 2000) and Hyperplasia Block for First Year), gave a 1 hour lecture to First Year Medical Students (2002) and 2 hours of lecture per year in Pathology 500 (2001, 2002) and 2 hours of lecture to Pharmaceutical Sciences graduate students in PHAR 545 (2003).

(b) Recent Courses Taught at UBC:

Year	Session	Course Number	Scheduled Hours	Class Size	Hours Taught			
					Lecture	Tutorials	Labs	Other
2019 + 2020	Fall 2019 + Winter [illegible]	BIOL 448 – Directed Studies	60	1 – Kevin Wong	0	5	>250 h	1
2019 + 2020	Fall 2019 + Winter [illegible]	ISCI 448 – Directed Studies	60	1 – Abiel Kwok	0	5	>250 h	1
2020	Winter 2020	MEDI 502 - Molecular and Cellular Biology	30	1 – Jackie Ho	0	4	10	1
2020	Fall 2020	MEDI 590 - Molecular Regulation of Cell Growth	>100	9	56	0	0	>100 h (see Note 1)
2020	Fall 2020	MEDI 501 - Molecular and Cellular Biology	7	19	1.5	0	0	+5.5 h (see Note 2)
2021	Fall 2021	MEDI 590 - Molecular Regulation of Cell Growth	>100	4	52	0	0	>50 h (see Note 1)
2021	Fall 2021	MEDI 501 - Molecular and Cellular Biology	10	30	1.5	0	0	+5.5 h (see Note 2)
2022	Fall 2022	MEDI 590 - Molecular Regulation of Cell Growth	>100	6-12	52	0	0	>50 h (see Note 1)
2022	Fall 2022	MEDI 501 - Molecular and Cellular Biology	10	24	1.5	0	0	+5.5 h (see Note 2)

Note 1 - +50-150 h course preparation; +2 h for midterm; +2 h midterm marking; + >50 h final assignment marking

Note 2 - +4.5-10 h lecture preparation and mid-term or final exam marking

(c) Graduate Students directly supervised at UBC:

Student Name	Program Type	Year		Principal Supervisor	Co-Supervisors
		Start	Finish		
Palaty, Chrystal	Exp. Med. Ph.D.	1990	1995	Pelech	
Samiei, Mitra	Exp. Med. Ph.D.	1990	1994	Pelech	Devine
Mordred, Guy	Biochemistry Ph.D.	1991	1993	Paucellier	Pelech
Charest, David	Exp. Med. Ph.D.	1991	1998	Pelech	
Charlton, Lorin	Exp. Med. Ph.D.	1991	1998	Pelech	
Morrison, Donna	Exp. Med. Ph.D.	1992	1998	Pelech	
Kim, Sung	Pharm. Sci. Ph.D.	1992	1998	Katz	Pelech
Tudan, Christopher	Exp. Med. Ph.D.	1993	1999	Pelech	
Tao, Jingsong	Microbiol. Ph.D.	1995	1998	Levy	Pelech
Marotta, Anthony	Exp. Med. Ph.D.	1996	1999	Sahl	Pelech
Wagey, Ravenska	Exp. Med. Ph.D.	1996	2000	Krieger	Pelech
Sayed, Mohamed	Exp. Med. Ph.D.	1998	2002	Pelech	Sahl
Vilimek, Dino	Exp. Med. M.Sc.	1999	1999	Duronio	Pelech
Je-Hong Hu	Simon Fraser	2000	2004	Krieger	Pelech
Gobind Sun	Exp. Med. Ph.D.	2006	2008	Pelech	
Amy Lai	Exp. Med. Ph.D.	2007	2008	Pelech	
Shenshen Lai	Exp. Med. Ph.D.	2009	2015	Pelech	
Javad Safaei	Math. & Comp. Sci. Ph.D	2009	2015	Gupta	Pelech
Dominik Sommerfeld	Exp. Med. Ph.D.	2010	2012	Pelech	
S.M. Shabab Hossain	Comp. Sci. M.Sc.	2011	2011	Gupta	Pelech
Lambert Yue	Exp. Med. Ph.D.	2016	2020	Pelech	
Hamidreza Galavi	Exp. Med. Ph.D.	2020	2023	Pelech	
Andréa Bleret	M.Sc. Université catholique de Louvain	2022 Feb.	2022 May	Bernard Hallet	Pelech

Ghada Maged Ali	M.Sc.(Neuro-science) Alexandria Univ., Egypt	2022 Feb.	present	Ahmad Raafat Bassiouny	Pelech

(d) MEDI 502 Graduate Student Rotation Supervision

1	Julian Vasilescu	UBC , MEDI 502	January 27-31, 2003
2	Lisa Bradley	UBC , MEDI 502	January 13-17, 2003
3	Loutfig Demirjian	UBC , MEDI 502	March 23 – April 23, 2004
4	Edgar Lam	UBC , MEDI 502	February 28 – March 4, 2005
5	Philip Ly	UBC , MEDI 502	January 10, 2006 – February 28, 2006
6	Michael Butt	UBC , MEDI 502	April 12, 2007 – April 30, 2007
7	Alastair Davies	UBC , MEDI 502	January 15 – February 15, 2008
8	Chengcheng Zhang	UBC , MEDI 502	February 15, 2009 – March 15, 2009
9	Anthony Tam	UBC , MEDI 502	January 15 – February 15, 2010
10	Helen Chen	UBC , MEDI 502	February 15 – February 28, 2011
11	Jack Lui	UBC , MEDI 502	March 1 – March 16, 2011
12	Saeideh Davoodi	UBC , MEDI 502	January 10 – January 30, 2012
13	Soojin Kim	UBC , MEDI 502	January 11 – February 1, 2013
14	Sehyun Cho	UBC , MEDI 502	February 1 – February 28, 2013
15	Paul Toren	UBC , MEDI 502	January 11 – February 1, 2014
16	Franco Cavaleri	UBC , MEDI 502	February 1 – February 28, 2015
17	Ryan Yue	UBC, MEDI 502	January 14 – February 28, 2016
18	Alexandre Kadhim	UBC, MEDI 502	January 14 – February 28, 2016
19	Jian Gao	UBC, MEDI 502	January 14 – February 28, 2017
20	Muyan Cao	UBC, MEDI 502	January 29 – February 28, 2018
21	Jackie Ho	UBC, MEDI 502	January 29 – February 28, 2020

In 2012, I also marked mock grant reviews prepared by Mary Rose Pambid and Saeideh Davoodi as part of the MEDI-502 course.

(e) MBA Student Supervision (at my industrial lab at Kinexus)

1	Deborah Bender	SFU, MBA Student	May 1 - July 31, 2001
2	Darius Panaligan	SFU, MBA Student	June 5 - August 31, 2001

(f) Undergraduate Coop Student Research Supervision (at my industrial lab at Kinexus)

I have taken on over 175 undergraduate students from the Simon Fraser University, University of Victoria and University of B.C. Coop programs through my companies Kinetek Pharmaceuticals Inc. (1992-1998) and Kinexus Bioinformatics Corp. (1999-present). Most of these students worked on average for 8 months full work-terms. I have only listed my trainees at Kinexus below.

No.	Name of Student	Months	Start Date	End Date
1	Korine Ung	4	1-Sep-1999	30-Dec-1999
2	David Brewster	4	1-Jan-2000	30-Apr-2000
3	Michael Hsing	8	1-Jan-2000	31-Aug-2000
4	Pinky Chua	4	1-May-2000	31-Aug-2000
5	Bonnie Jones	8	1-May-2000	31-Dec-2000
6	Claire Hou	4	1-Sep-2000	31-Dec-2000
7	Tiffany Chen	8	2-Jan-2001	31-Aug-2001
8	Christopher Huang	8	2-Jan-2001	31-Aug-2001
9	Kevin Ma	8	1-May-2001	31-Dec-2001
10	Jason Sterne	8	7-May-2001	31-Dec-2001
11	Kristy Lynn Williams	8	27-Aug-2001	31-Dec-2001
12	Jeff Druce	8	27-Aug-2001	31-Dec-2001
13	Mark White	4	27-Aug-2001	31-Dec-2001
14	Jack Min	4	4-Sep-2001	31-Dec-2001
15	Jill Youds	8	1-Jan-2002	31-Aug-2002
16	Jackie To	8	1-Jan-2002	31-Aug-2002
17	Marina Kanjer	4	1-Jan-2002	30-Apr-2002
18	Andrea Ramalho	8	1-Jan-2002	30-Aug-2002
19	Leon Poznanski	8	1-May-2002	31-Dec-2002
20	Devon Yeoman	8	1-May-2002	31-Dec-2002
21	Kyla Hingwing	8	1-Sep-2002	30-Apr-2003
22	Gavin Lee	4	10-Sep-2002	31-Dec-2002
23	Richard Li	8	1-Jan-2003	30-Aug-2003
24	Anna Moorhouse	8	1-Jan-2003	30-Aug-2003
25	Beth Clendening	8	22-Apr-2003	31-Dec-2003
26	Shauna Murray	12	25-Aug-2003	31-Aug-2004
27	Heidi Cheung	8	1-Sep-2003	30-Apr-2004
28	Sharan Swarup	16	1-Sep-2004	31-Dec-2004
29	Nadia Brinkman	8	1-Jan-2004	31-Aug-2004
30	Elbert Chang	4	1-Jan-2004	30-Apr-2004
31	Wilson Luk	8	3-May-2004	31-Dec-2004
32	Tina Chen	8	26-Aug-2004	30-Apr-2005
33	Anar Dhallar	8	26-Aug-2004	30-Apr-2005
34	Sylive Bryant	8	4-Jan-2005	31-Aug-2005
35	Melissa Hogg	4	4-Jan-2005	30-Apr-2005
36	Benjamin Jong	8	4-Jan-2005	31-Aug-2005

37	Amanda Heiler	8	2-May-2005	31-Dec-2005
38	Poonam Jassi	8	2-May-2005	31-Dec-2005
39	Theresa Connor	8	1-Sep-2005	30-Apr-2006
40	Gavin Ha	8	1-Jan-2006	31-Aug-2006
41	Megan Kofoed	16	1-Jan-2006	30-Apr-2007
42	Iris Juan	8	1-May-2006	31-Dec-2006
43	Andrew Park	5	1-May-2006	1-Oct-2006
44	Ryan Whitehead	4	1-May-2006	25-Aug-2006
45	Bryanna Grace	4	1-Sep-2006	31-Dec-2006
46	Michael Peabody	8	1-Sep-2006	30-Apr-2007
47	Joanna Kam	8	19-Dec-2006	31-Aug-2007
48	Nova Do	8	1-Jan-2007	31-Aug-2007
49	Jason Wong	8	1-Jan-2007	31-Aug-2007
50	Charrise Pagarigan	4	1-Jan-2007	30-Apr-2007
51	Sabrina Rayworth	8	1-May-2007	31-Dec-2007
52	Fredrick Bantandos (SFU)	8	1-Sep-2007	30-Apr-2008
53	Pringle Comia (SFU)	8	1-Sep-2007	30-Apr-2008
54	Raymond Leung (SFU)	8	1-Sep-2007	30-Apr-2008
55	Adam Leigh (UBC)	8	1-Jan-2008	31-Aug-2008
56	Ellen Sung (UBC)	4	1-Jan-2008	30-Apr-2008
57	Angie Chu (UBC)	4	1-May-2008	31-Aug-2008
58	Stephanie Lam (SFU)	8	1-May-2008	31-Dec-2008
59	Amy Tam (UBC)	8	1-May-2008	31-Dec-2008
60	Ken Ng (SFU)	8	1-May-2008	31-Dec-2008
61	Ryan Saranchuk (UBC)	4	1-Sep-2008	31-Dec-2008
62	Sarah Zaidi (SFU)	3.5	1-Sep-2008	15-Dec-2008
63	Anna Chau (UBC)	8	1-Jan-2009	31-Aug-2009
64	Kerrie Law (UBC)	8	1-Jan-2009	31-Aug-2009
65	Jose Canas (SFU)	8	1-Jan-2009	31-Aug-2009
66	Steven Pham (UBC)	8	1-Jan-2009	31-Aug-2009
67	Connie Drewbrook (SFU)	4	1-May-2009	31-Aug-2009
68	Justin Yu (UBC)	4	1-May-2009	31-Aug-2009
69	Ryan Foyle (UBC)	8	1-May-2009	31-Dec-2009
70	Tak Poon (UBC)	8	1-May-2009	31-Dec-2009
71	Tammy Wang (UBC)	4	1-Sept-2009	31-Dec-2009
72	Yan Zhou (SFU)	4	1-Sept-2009	31-Dec-2009
73	Tommy Lee (UBC)	4	1-Sept-2009	31-Dec-2009
74	Kerrie Tian (SFU)	8	1-Sept-2009	30-Apr-2010
75	Christine Yu (UBC)	4	1-Jan-2010	30-Apr-2010
76	Vivienne Chan (UBC)	8	1-Jan-2010	31-Aug-2010
77	Katelyn Fines (UBC)	4	1-Jan-2010	30-Apr-2010
78	Katelyn Janzen (UBC)	8	1-Jan-2010	31-Aug-2010
79	Mandy Hu (UBC)	8	1-Jan-2010	31-Aug-2010
80	Mandy Chung (SFU)	4	1-May-2010	31-Aug-2010

81	Abby Yang (UBC)	8	1-May-2010	31-Dec-2010
82	Christopher Bond (SFU)	8	1-Sep-2010	31-Dec-2010
83	Jarrod Mackay (SFU)	4	1-Sep-2010	31-Dec-2010
84	Karyll Magtibay (UBC)	8	1-Sep-2010	30-Apr-2011
85	Kathryn Marshall (SFU)	4	1-Sep-2010	30-Apr-2011
86	Christopher Meschino (SFU)	4	1-Sep-2010	30-Apr-2011
87	Bonnie Cheung (UBC)	8	1-Jan-2011	31-Aug-2011
88	Lisa Luo (UBC)	8	1-Jan-2011	31-Aug-2011
89	Abhinav Sharma (UBC)	8	1-Jan-2011	31-Aug-2011
90	Cherie Tan (UBC)	8	1-Jan-2011	31-Aug-2011
91	Puneet Litt (SFU)	4	1-May-2011	31-Aug-2011
92	Kingsley Shih (UBC)	8	1-May-2011	31-Dec-2011
93	Sophie Tsai (SFU)	8	1-May-2011	31-Dec-2011
94	Sze Wing Wong (UBC)	4	1-May-2011	31-Aug-2011
95	J.C. Cheng (UBC)	4	1-Sep-2011	31-Dec-2011
96	Dennis Chau (SFU)	4	1-Sep-2011	31-Dec-2011
97	Jarrod Mackay (SFU)	8	1-Sep-2011	30-Apr-2012
98	Lisa Ying (UBC)	8	1-Jan-2012	31-Aug-2012
99	Krista Wong (UBC)	8	1-Jan-2012	31-Aug-2012
100	Gurjot Dhaliwal (UBC)	8	1-Jan-2012	31-Aug-2012
101	Michael Ni (UBC)	4	1-May-2012	31-Aug-2012
102	Chelsea Lee (Emily Carr)	3	20-May-2012	31-Aug-2012
103	Inderpal Gill (UBC)	4	1-Sep-2012	31-Dec-2012
104	Ryan Lee (SFU)	4	1-Sep-2012	31-Dec-2012
105	Ashley Steuck (UBC)	4	1-Sep-2012	31-Dec-2012
106	Kaitlin Hong Tai (SFU)	12	1-Sep-2012	31-August-2013
107	Roanette Postma (SFU)	8	1-Jan-2013	31-Aug-2013
108	Christine Chan (UBC)	8	1-Jan-2013	31-Aug-2013
109	James Hopkins (SFU)	8	1-Jan-2013	31-Aug-2013
110	Sally Maguet (SFU)	4	1-Sep-2013	31-Dec-2013
111	Martin Radvenis (UBC)	4	1-Sep-2013	31-Dec-2013
112	Katy Tan (UBC)	4	1-Sep-2013	31-Dec-2013
113	Alisa Too (UBC)	8	1-Jan-2014	31-Aug-2014
114	Lambert Yue (UBC)	8	1-Jan-2014	31-Aug-2014
115	Enoli de Silva (UBC)	8	1-Jan-2014	31-Aug-2014
116	Sonia Hessels (SFU)	8	1-Jan-2014	31-Aug-2014
117	Jeremy Nan (UBC)	8	1-Jan-2014	31-Aug-2014
118	Alexander Mann (UBC)	8	1-May-2014	31-Dec-2014
119	Alexa Creenan (UBC)	4	1-Sep-2014	31-Dec-2014
120	Maggie Fu (UBC)	4	1-Sep-2014	31-Dec-2014
121	Lisa Lee (UBC)	4	1-Sep-2014	31-Dec-2014
122	Colm Quirke (UBC)	8	1-Sep-2014	30-April-2015
123	Kristy Dever (UBC)	8	1-Sep-2014	30-April-2015
124	Jordan Chiu (UBC)	8	1-Jan-2015	31-August-2015

125	Tam Dang (UBC)	8	1-Jan-2015	31-August-2015
126	Minnie Huang (UBC)	8	1-Jan-2015	31-August-2015
127	Marti Hua (UBC)	8	1-Jan-2015	31-August-2015
128	Nimisha Arora (India)	6	1-Jan-2015	30-June-2015
129	Jeffrey White (UBC)	8	1- May-2015	31-December-2015
130	Alex Sweeten (SFU)	4	1- May-2015	30-August-2015
131	Lambert Yue (UBC)	8	1- May-2015	31-December-2015
	Lambert Yue (UBC)	8	1-May-2016	31-December-2016
132	Ryan Hounjet (UBC)	4	1-Sept-2015	31-December-2015
133	Andy Lam (UBC)	4	1-Sept-2015	31-December-2015
134	Tianna Sun (UBC)	4	1-Sept-2015	31-December-2015
135	Johnathan Wong (SFU)	4	1-Jan-2016	30-April-2016
136	Paula Tao (UBC)	8	1-Jan-2016	31-August-2016
137	Tony Han (UBC)	8	1-Jan-2016	31-August-2016
138	Desiree Pagulayan (UBC)	4	1-Jan-2016	30-April-2016
139	Jason Liu (UBC)	8	1-Jan-2016	31-August-2016
140	Jenny Chan (UBC)	8	1-Jan-2016	31-August-2016
141	Claire Doyon (UBC)	12	1-May-2016	30-April-2017
142	Christine Sam (UBC)	4	1-Sept-2016	31-December-2016
143	Yezen Dean (SFU)	8	1-Sept-2016	30-April-2017
144	Kevin Gonzalez (UBC)	12	1-Sept-2016	31-August-2017
145	Karin Parkeh (UBC)	4	1-Sept-2016	31-December-2016
146	Ayasha Brown (UBC)	8	1-Jan-2017	31-August-2017
147	Sarina Chen (UBC)	4	1-May-2017	31-August-2017
148	Jenna Grose (SFU)	8	1-May-2017	31-December-2017
149	Dhiraj Mannar (UBC)	8	1-May-2017	31-December-2017
150	Aster Fan (SFU)	8	1-Sept-2017	30-April-2018
151	Leo Escano (SFU)	4	1-Sept-2017	31-December-2017
152	Ashley Perron (UBC)	8	1-Jan-2018	31-August-2018
153	Eva Momchilova (SFU)	8	1-Jan-2018	31-August-2018
154	Iqbal Sarai (SFU)	8	1-May-2018	31-December-2018
156	Angela Wu (UBC)	8	1-May-2018	31-December-2018
157	Joanne Chan (UBC)	4	1-Sept-2018	31-December-2018
158	Abiel Kwok (UBC)	12	1-Sept-2018	31-August-2019
159	Jazica Chan (SFU)	12	1-Sept-2018	31-August-2019
160	Zhong Yuan Zhang (UBC)	4	1-Jan-2019	30-April-2019
161	Guravneet Gill (UBC)	4	1-May-2019	31-August-2019
162	Naiomi Khan (UBC)	4	1-May-2019	31-August-2019
163	Mona Golmohammadzadeh (UBC)	8	1-Sept-2019	30-April-2020
164	Avery Mak (SFU)	8	1-Sept-2019	30-April-2020
165	Mataya Lukas (SFU)	8	1-Jan-2020	31-August-2020
166	Sarah Agnew (UBC/BCIT)	8	1-May-2020	31-December-2020
167	Gage Fairlie (UBC)	8	1-May-2020	31-December-2020

168	Akshra Atrey (UBC)	12	1-Sept-2020	15-August-2021
169	Hallie Emory (UBC)	8	1-Sept-2020	30-April-2021
170	Tammy Yu (SFU)	8	1-Jan-2021	31-August-2021
171	Britney Yuen (UBC)	8	1-May-2021	31-December-2021
172	Jason Zhao (UBC)	10	1 July-2021	30-April-2022
172	Melody Lam (UBC)	8	1-Sept-2021	30-April-2022
173	Ekaterina Galysheva (UBC)	8	1-Jan-2022	31-August-2022
174	Trang Ngyen (UBC)	4	1-May-2022	31-August-2022
175	Trinity Truong (UBC)	8	1-May-2022	31-December-2022
176	Sierra Neff (UBC)	3.5	1-May-2022	15-August-2022

(g) Undergraduate BC Institute of Technology Student Supervision (at my industrial lab at Kinexus)

I directly worked with each of these students in the development of the open-access, on-line databases and knowledgebases hosted Kinexus Bioinformatics Corporation. These usually involved bi-weekly interactions for 1 to 2 hours over a 5 to 6 week period.

1	Anchal Jain	BCIT Computer Sci. Prgm.	21-June-2005 to 10 –Sep-2005
2	Eric Chua	BCIT Computer Sci. Prgm.	21-June-2005 to 10 –Sep-2005
3	Ho Sand (Alex) Lee	BCIT Computer Sci. Prgm.	21-June-2005 to 10 –Sep-2005
4	Jimmy Chan	BCIT Computer Sci. Prgm.	12-Oct-2005 to 25 –Nov-2005
5	Kevin Rabang	BCIT Computer Sci. Prgm.	12-Oct-2005 to 25 –Nov-2005
6	Kannon Woo	BCIT Computer Sci. Prgm.	12-Oct-2005 to 25 –Nov-2005
7	Norma Wong	BCIT Computer Sci. Prgm.	12-Oct-2005 to 25 –Nov-2005
8	Kevin Odger	BCIT Computer Sci. Prgm.	1-Nov-2006 to 30-Jan-2007
9	Travis Nicholson	BCIT Computer Sci. Prgm.	21-Apr-2008 to 21-May-2008
10	Jonathan Jose	BCIT Computer Sci. Prgm.	21-Apr-2008 to 21-May-2008
11	Ryan Pattinson	BCIT Computer Sci. Prgm.	21-Apr-2008 to 21-May-2008
12	Hannah Rosellon	BCIT Computer Sci. Prgm.	21-Apr-2008 to 21-May-2008
13	John Liau	BCIT Computer Sci. Prgm.	1-Oct-2008 to 28-Feb-2009
14	Joe Hu	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
15	Ysabel Lago	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
16	David Liau	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
17	Christine Livingstone	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
18	Melissa Manalac	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
19	Nevin Petersen	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
20	Janice Sargent	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
21	Brandon Wang	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
22	Alvin Yip	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
23	Nicholas Tagle	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
24	Igor Kozlov	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
25	Fausto Faioli	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
26	Justin Ma	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
27	Simon Ho	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
28	Isan Chen	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
29	Keegan Kelly	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011

30	Aly Jamani	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
31	Colin Nguyen	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
32	David Gannon	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
33	Lili Hao	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
34	Mila Khadarina	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
35	Andrii Skrynnyk	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
36	Kyle Li	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
37	Theo Mutia	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
38	Travis Ryder	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
39	Clarence Sng	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
40	James Chen	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
41	Andy Chow	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
42	Sunju Christine Jeong	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
43	Dan Stephenson	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
44	Nadezhda Dobrianskaia	BCIT Computer Sci. Prgm.	20-Apr-2015 to 18-May-2015
45	Guanyi Fang	BCIT Computer Sci. Prgm.	20-Apr-2015 to 18-May-2015
46	Calvin Truong	BCIT Computer Sci. Prgm.	20-Apr-2015 to 18-May-2015
47	Kevin Thet	BCIT Computer Sci. Prgm.	20-Apr-2015 to 18-May-2015
48	Haruna Kakinoki	BCIT Computer Sci. Prgm.	20-Apr-2018 to 18-May-2018
49	Matthew Lau	BCIT Computer Sci. Prgm.	20-Apr-2018 to 18-May-2018
50	Noah McMurchy	BCIT Computer Sci. Prgm.	20-Apr-2018 to 18-May-2018
51	Roberg Koeing	BCIT Computer Sci. Prgm.	20-Apr-2018 to 18-May-2018
52	Ryan Liang	BCIT Computer Sci. Prgm.	10-Sept-2018 to 30-Nov-2018
53	Garth Nelson	BCIT Computer Sci. Prgm.	10-Sept-2019 to 30-Nov-2018
54	Andy Tang	BCIT Computer Sci. Prgm.	10-Sept-2018 to 30-Nov-2018
55	Thomas Bui	BCIT Computer Sci. Prgm.	10-Sept-2019 to 25-May-2020
56	Saeed Naguib	BCIT Computer Sci. Prgm.	10-Sept-2019 to 25-May-2020
57	Daria Dimchuk	BCIT Computer Sci. Prgm.	10-Sept-2019 to 25-May-2020
58	Dawson Verboven	BCIT Computer Sci. Prgm.	10-Sept-2019 to 25-May-2020

I have also provided co-supervision for UBC Computer Science Ph.D. candidate Mr. Alireza Davoodi with Dr. Jan Manuch in a MITAC Project from April 1, 2013 for the KinATLAS website.

(h) Continuing Education Activities

1 February 9, 2005 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

2 November 9, 2005 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

3 November 30, 2005 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

4 February 15, 2006 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

5 March 15, 2006 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and

Tenure

6 November 8, 2006 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

7 April 11, 2007 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

8 November 14, 2007 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

9 November 21, 2007 - UBC TAG Workshop for Dept. of Urology – Preparation of Teaching Dossier for Promotion and Tenure

10 March 5, 2008 - UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

11 January 26, 2022 - UBC Ethics in the Arts Workshop

12 July 20, August 31, October 26 - UBC Racism Workshop - Decolonial and Anti-Racist Approaches to Wellbeing with Future Ancestors' Larissa Crawford

(i) Visiting Lecturer (indicate university/organization and dates)

This is included with my invited presentation list in Section 9(d).

(j) Mentor for Sabbatical

1	Dr. Byung Soon Moon – Professor and Head of Surgery, WONKWANG University Iksan Oriental Medical Center, Korea, February 1, 2007 - January 31, 2008

(k) Other

1 MRC Representative for Scholarships Day at U.B.C. - October 25, 1991; Sept. 24, 1992

2 Volunteer for Careers Presentation - Science World, Vancouver - March 9, 1993

3 Scientists & Innovators in the Schools, Kitsilano Secondary School, Vancouver -Feb. 14, 1993

4 Volunteer for Careers Presentation - Science World, Vancouver - March 1, 1996

5 Scientists & Innovators in the Schools, Gladstone Secondary School, Vancouver -January 24, 1997

6 Volunteer for B.C. Regional Science Fair, University of B.C. - April 5, 2001

High School Student Mentorship (1 day to 2 weeks) at my industrial lab at Kinexus

1 Davita Fuchs - Windermere Secondary School, Vancouver, 24-29-Jul-2001

2 Ariella Zbar – Eric Hamber High School, Vancouver, 26-30-Aug-2002

3 Tom Chan - Windermere Secondary School, Vancouver, 27-31-Jan-2003

4 Nga Wailau - Windermere Secondary School, Vancouver, 23-27-Jun-2003

5 Maggie Lau - Windermere Secondary School, Vancouver, 21-25-Jul-2003

6 Winnie Chen – Prince of Wales Secondary School, Vancouver, 18-22-Aug-2003

7 Peter Quon - Windermere Secondary School, Vancouver, 26-30-Jan-2004

8 Reginald Naidu - Windermere Secondary School, Vancouver, 17-30-Jun-2004
9 Anthony Leung - Windermere Secondary School, Vancouver, 24-28-Jan-2005
10 Ricky Quan - Windermere Secondary School, Vancouver, 20-25-Jun-2005
11 Dorothy Yeung - Windermere Secondary School, Vancouver, 23-27-Jan-2006
12 Sophia Guerrero - Windermere Secondary School, Vancouver, 19 – 30-Jun-2006
13 Alex Sutter- McMath Secondary School, Richmond, 26-30-Jun-2006
14 Yin Woo - Windermere Secondary School, Vancouver, 14-31-Dec-2007
15 Gail Ng - Windermere Secondary School, Vancouver, 26-30-Jan-2009
16 Fiona Leung - Windermere Secondary School, Vancouver, 25-29-Jan-2010
17 Leanne Huang - Windermere Secondary School, Vancouver, 21-Jun - 2-Jul-2010
18 Wilkin Chou - Windermere Secondary School, Vancouver, 21-Jun - 2-Jul-2010
19 Rebecca Hu – Templeton Secondary School, Vancouver, 24-25-Jun-2010
20 Angela Pinto – Windermere Secondary School, Vancouver, 22-Jun - 30-Jun-2011
21 Katie Piper – Windermere Secondary School, Vancouver, 22-Jun - 30-Jun-2011
22 Hailey Xi - Secondary School, Vancouver, 16-Dec-2022

(l) Post-doctoral Fellows

1 Dr. Hong Zhang – 2000-2002
2 Dr. Y. J. Xu – 1998-1999
3 Dr. D. F. Liao – 1998 (3 months)
4 Dr. Ian Melhado – 1998 (6 months)
5 Dr. Sanjay Bhanot – 1995-1997
6 Dr. Baljinder Sahl – 1994-1998
7 Dr. Diana Lefebvre – 1994-1996
8 Dr. Brook Koide – 1993-1995
9 Dr. Yaw Loon Siow – 1992-1997
10 Dr. Jasbinder Sanghera – 1989-1995
11 Dr. Maleki Daya-Makin – 1989-1991

9. SCHOLARLY AND PROFESSIONAL ACTIVITIES

(a) Areas of special interest and accomplishments

Role of protein phosphorylation in cellular signal transduction.

1 My research focuses on the characterization of protein-serine kinases involved in mitogen- and stress-signalling and cell cycle control. Protein kinases are major intracellular transducers of information from extracellular stimuli. Their defective signalling, as a consequence of mutations in the genes that encode these enzymes, underlies many degenerative diseases of aging such as cancer, diabetes, immune cell disfunction, heart disease and neurological disorders.

2 The main model systems that are under investigation in my laboratory are oocytes from sea stars and frogs, human solid tumours, insulin-target tissues such as skeletal muscle and heart from normal and diabetic rats, and human brain and spinal cord tissues from patients with neurological disorders. Many of the same protein kinases that are abnormally activated in cancer cells are stimulated in a controlled fashion during the meiotic maturation of oocytes or during activation of terminally differentiated immune cells of the blood, heart and brain.

3 As a postdoctoral fellow in the laboratory of Dr. Edwin Krebs, I was one of the co-discoverers of MAP kinase. Over the last 29 years, my research team and I have shown that MAP kinases such as Erk1 and Erk2 operate in the following mitogen-activated protein kinase cascade: Raf1-Mek-Erk1/2-Rsk1/2. My laboratory examined the role of this protein kinase cascade in platelets, T cells, B cells, macrophages, neutrophils, keratinocytes, cardiomyocytes, oligodendrocytes and neurons. These studies have been expanded for analysis of the related MAP kinase-dependent pathways that involve JNK and p38 MAP kinases.

4 Other protein kinases under scrutiny in my lab include cyclin-dependent kinases, p70 S6 kinase, protein kinase C, oncogene-encoded kinases (e.g. Pim1, Cot and PKB), and a novel protein-histidine kinase. Some of these kinases are activated by second messengers such as calcium, whereas others are regulated by small GTP-binding proteins such as Ras and Rac or via direct phosphorylation by upstream kinases. Anti-peptide antibodies developed in my laboratory have been produced for the specific detection of all of these kinases. Recombinant forms of mammalian versions of kinases are expressed in E. coli, COS cells and baculovirus-infected Sf9 cells. Site-directed mutagenesis is used to identify important regulatory phosphorylation sites in Erk1, Mek1, Mekk and Pim1. Synthetic peptide substrates are used to identify the critical amino acid residues that are required for kinase recognition. Specific roles for these kinases are being defined by identification of their target substrates and by establishing how the kinases are integrated into signaling networks.

5 Other technologies that are applied in my research program include antibody microarrays, multi-immunoblotting, protein sequencing, cDNA cloning, sequencing and site-directed mutagenesis, cell culture and microinjection, and immunocytochemical localization. We can now track over 600 protein kinases, phosphatases, stress, cell cycle and apoptosis proteins in addition to over 900 phosphorylation sites in many of these phosphoproteins. This technology has led to the spin-out of Kinexus Bioinformatics Corporation from my UBC lab.

6 Over the last 20 and a half years, in collaboration with my company Kinexus, I have built a strong bioinformatics program to create databases and knowledgebases that are available online with free

access for the scientific community. KiNET (http://www.kinet.ca) has the results from the analysis of over 10,000 multi-immunoblots performed in-house at Kinexus using the Kinetworks methodology that was development in my UBC lab. It is the largest repository of quantitative proteomics data on cell signalling proteins available. In 2010, we launched the PhosphoNET knowledgebase (www.phosphoNET.ca). It presently has detailed information on over 180,000 experimentally confirmed and 780,000 predicted human phosphorylation sites. PhosphoNET also provides evolutionary analysis and kinase prediction for all 967,000 phosphosites. In 2011, we launched the TranscriptoNET knowledgebase (www.transcriptonet.ca) with detailed mRNA expression data information on 21,000 genes in over 600 different human tissues, tumour types and cancer cell lines. We also released the KiNET-AM database (www.kinet-am.ca) which contains antibody microarray data on 650-800 proteins and phosphosites levels tracked in over 2000 cell and tissues lysates from diverse experimental model systems. In 2013, we launched the DrugKiNET knowledgebase (www.drugkinet.ca) with information on the sensitivities of over 400 protein kinases to more than 850 drugs and other kinase inhibitory compounds. In 2015, we produced beta-versions of the OncoNET knowledgebase (www.onconet.ca) with detailed information on over 3000 proteins related to cancer, and the KinaseNET knowledgebase (www.kinasenet.ca) with detailed information on 536 human protein kinases. Most of these knowledgebases were further updated in 2017 and 2018. In 2018, we also developed a website for drug-protein interactions with identification of the most critical amino acid residues in proteins for the binding of over 2000 approved and experimental drugs (www.drugpronet.ca). I am also working on online knowledgebases for protein phosphatases, adaptor proteins, stress protein and transcription factors. My ultimate goal is to create an atlas of cell signalling maps and the ability to track key proteins and phosphosites within these networks with protein microarrays. Towards this end, I have also been working on producing signalling maps online with Kinections Maps that detail experimentally verified interactions with protein kinases and KinATLAS (www.kinatlas.ca), which features customizable maps of kinase-drug, protein-protein interactions, and kinase-substrate interactions with KiNector (www.kinector.ca).

7 Ultimately, the research undertaken in my laboratory should help identify rational targets for the development of pharmacological agents for the treatment of cancer, neurological diseases, diabetes, autoimmune diseases, and other disorders that involve protein kinases. In addition, it is helping to identify biomarkers that may be useful for diagnosing diseases and defining the most appropriate therapeutic strategies to treat these diseases.

(b)+(c) Research or equivalent grants/contracts (indicate under COMP whether grants were obtained competitively (C) or non-competitively (NC))

Grants

Granting Agency	Subject	COMP	$ Per Year	Year	Principal Investigator	Co-Investigator(s)
Med. Res. Council of Canada	Role of Protein phosphorylation in viral action	C	54,000 -2 yr	1987-1989	Pelech	

B.C. Health Care Res. Foundation	Phosphatidylcholine turnover and protein phosphorylation in lymphokine action	C	12,000 -2 yr	1988-1990	Pelech	
B.C. Health Care Res. Foundation	TL-100 ultracentrifuge - Role of protein phosphorylation in cell cycle progression	C	17,000	1989	Pelech	
Med. Res. Council of Canada	Purification and characterization of cell cycle-regulated protein kinases	C	57,640 -2 yr	1989-1991	Pelech	
B.C. Health Care Res. Foundation	Role of protein phosphorylation in signal transduction by platelet agonists	C	22,000 -1 yr	1990		
B.C. Health Care Res. Foundation	Oocyte microinjection system & microscope	C	19,600	1990	Pelech	
B.C. Health Care Res. Foundation	Role of protein kinase C in signal transduction by platelet agonists	C	23,320 -1 yr	1991	Pelech	
Medical Research Council of Canada	Sorvall RC28S supraspeed centrifuge & F28/36 rotor	C	32,736	1991	Pelech	
B.C. Heart & Stroke Foundation	Protein kinase cascades in signal transduction by platelet agonists	C	60,000 -2 yr	1991-1993	Pelech	
Nat'l Cancer Inst. of Canada	Tyrosine-phosphorylated MBP/MAP-2 kinases in haemopoietic signal transduction	C	59,438 -3 yr	1991-1994	Pelech	
Nat'l Cancer Inst. of Canada	Characterization of oncogene-encoded protein-serine kinases	C	64,050 -3 yr	1991-1994	Pelech	
Med. Res. Council of Canada	Protein kinase cascades in cell cycle control	C	81,488 -3 yr	1991-1994	Pelech	
B.C. Health Care Res. Foundation	Elutriator Centrifuge	C	48,000	1992	Pelech	Berger, Weeks, Sadowski, Astell
B.C. Health Care Res. Foundation	HPLC system	C	29,000	1993	Pelech	

National Cancer Institute of Canada	HPLC system	C	29,000 (declined)	1993	Pelech	
B.C. Heart & Stroke Foundation	Role of protein kinase cascades in platelets	C	84,500 -2 yr	1993-1995	Pelech	
NRC of Canada IRAP	Protein kinase assay kit development	C	50,000	1994-1995	Pelech(Kinetek)	
Med. Res. Council of Canada	Protein kinase cascades in cell cycle control	C	84,748 -3 yr	1994-1997	Pelech	
Nat'l Cancer Inst. of Canada	MAP kinase pathways in haemopoietic signal transduction	C	77,825 -4 yr	1994-1998	Pelech	
Nat'l Cancer Inst. of Canada	Characterization of oncogene-encoded protein-serine kinases	C	99,063 -4 yr	1994-1998	Pelech	
B.C. Heart & Stroke Foundation	Role of protein kinase cascades in platelets	C	10,000 -1 yr	1995-1996	Pelech	
B.C. Science Council	Assay for activated Ras-related G proteins	C	50,000	1995-1996	Pelech (Kinetek)	Kalmar (Simon Fraser Univ.)
B.C. Heart & Stroke Foundation	Activation of protein kinases in heart	C	82,000 -3 yr	1996-1999	Katz	Pelech
Kinetek Pharmaceuticals, Inc.	Histidine kinase and tumour-activated protein kinases	NC	65,000 - 3 yr	1996 - 1999	Pelech	
Med. Res. Council of Canada	Characterization of insulin-inhibited serine kinases	C	82,000 -1 yr	1997-1998	Pelech	McNeill
Nat'l Cancer Inst. of Canada	MAP kinase pathways in seastar oocyte cell cycle control	C	10,000	1998-1999	Pelech	
Nat'l Cancer Inst. of Canada	Structure-function analysis of protein-serine kinase complexes	C	37,500	1998-1999	Pelech	

BC Heart & Stroke Foundation	Regulation of cardiomyocyte differentiation by protein kinases	C	58,450 - 2 yr	1999 - 2001	Pelech	
JDF/MRC NCE	Cell signalling in NOD mice	C	5,000 - 3 yr	1999 - 2001	Delovich Ochi et al.	Pelech
Nat'l Cancer Inst. of Canada	Identification of putative breast cancer-linked protein kinases	C	49,000 - 1 yr	1999 - 2001	Pelech	
BC Heart & Stroke Foundation	MAP kinase pathways in normal and disease heart	C	92,970 - 3 yr	1999 - 2002	Pelech	Katz
Can. Inst. Health Res.	MAP kinase pathways in seastar oocycte cell cycle control	C	82,000 - 3 year	2000-2003	Pelech	
National Research Council of Canada IRAP	Development of Relational Functional Proteomics Databases	C	48,000 - 9 months	2004-2005	Pelech	Kinexus Bioinformatics Corporation
National Research Council of Canada IRAP	Development of Protein Kinase-Based Arrays for Diagnostics and Drug Discovery	C	80,000 - 2 year	2004-2006	Pelech	Kinexus Bioinformatics Corporation
Can. Inst. Health Res.	Protein kinase pathways in seastar oocyte cell cycle control	C	107,000 - 5 year	2005-2007	Pelech	
Can. Foundation for Innovation	Brain Research Centre: A Platform for Basic and Translational Neuroscience.	C	$6.8 million	2007	Cynader	Pelech + 10 other co-investigators. I wrote approximately 30% of this successful
National Research Council of Canada IRAP	Building the On-line SigNET KnowledgeBank	C	50,000 – 1 year	2009-2010	Pelech	Kinexus Bioinformatics Corporation
Nati. Sci. & Eng. Res. Council of Canada	Mapping the human kineome and phosphoproteome	C	80,000 – 2 years	2009-2011	Stacho + Pelech	Simon Fraser Univ. + Kinexus Bioinformatics Corporation. I wrote 95% of this successful grant

National Research Council of Canada IRAP	Production of Epitope-mapped Phosphosite Antibodies	C	38,000 – 1 year	2011-2011	Pelech	Kinexus Bioinformatics Corporation
National Research Council of Canada IRAP	Development of Protein Kinase/Phosphatase Substrate Microarrays	C	178,000 – 2 years	2012-2014	Pelech	Kinexus Bioinformatics Corporation
National Research Council of Canada IRAP	Development of Protein Kinase/Phosphatase Assays (Salary support for Iqbal Sarai)	C	20,000 – 9 months	2020	Pelech	Kinexus Bioinformatics Corporation
Neurodegenerative Disease Research (NDR), Inc.	Development of Phosphosite Antibodies for ALS Target Proteins	C	US$140,000	2021	Pelech	Kinexus Bioinformatics Corporation
COVID-19 Immunity Task Force	Immmunogenicity of current SARS-CoV-2 vaccine schedules in BC and Ontario	C	$729,149	2021	Pascal Lavoie	Pelech
Neurodegenerative Disease Research (NDR), Inc.	Development of Phosphosite Antibodies for ALS Target Proteins (Salary support for Ghada Maged)	C	US$15,000	2022	Pelech	Kinexus Bioinformatics Corporation

(d) Invited Presentations

83 Local in B.C.; 35 in Canada outside B.C.; 64 in U.S.A.; 36 Internationally, outside of Canada and USA

1 July 1987 - Biochemistry Department, Univ. of B.C.

2 December 1988 - Biochemistry & Molecular Biology, Univ. of Manitoba, Winnipeg, Manitoba.

3 14 December 1989 - Dept. of Obstetrics & Gynaecology, Univ. of B.C., Grace Hospital Site. Regulation of meiotic maturation and egg mitosis by protein phosphorylation.

4 6 February 1989 - Vancouver Council of Woman, Unitarian Church, Vancouver. Present and future of human embryo and fetal research.

5 12 March 1990 - Dept. of Paediatrics, Univ. of B.C., Shaughnessy Hospital Site.

Protein phosphorylation in cell cycle control.

6 21 March 1990 - Pharmacology Department, Univ. of B.C. Cell cycle-regulated protein kinase cascades.

7 July 1990 - Ludwig Cancer Institute, London, U.K.

8 July 1990 - Imperial Cancer Research Fund, London, U.K. Regulation of protein kinase C in haemopoietic cells.

9 July 1990 - Wellcome Biotech., Beckenham, U.K.

10 February 1991 - Biotechnology Building, Cornell University, Itheca, NY, USA. p44mpk - a paradigm for a family of mitogen-regulated, tyrosine-phosphorylated protein-serine kinases implicated in cell cycle control.

11 4 October 1991 - Inst. Molecular Biol. & Biochem., Simon Fraser Univ., Burnaby. MAP kinases, a family of tyrosyl-phosphorylated and activated protein-seryl kinases.

12 8 October 1991 - Dept. of Ophthalmology, Univ. of B.C., Eye Care Centre, V.G.H. MAP kinases, a family of tyrosine-phosphorylated & activated protein-serine kinases.

13 7 November 1991 - Manitoba Inst. of Cell Biology, Univ. of Manitoba, Winnipeg, Manitoba.

14 6 December 1991 - Dept. of Biochemistry, Queens University, Kingston, Ontario. MAP kinases, a family of tyrosyl-phosphorylated and activated protein-seryl kinases.

15 15 January 1992 - Department of Physiology, Univ. of B.C. MAP kinases, God's gift to the Pelech lab.

16 28 February 1992 - Dept. of Microbiology, University of Virginia, Charlottesville, VA, USA. Charting regulatory pathways with MAP kinase.

17 11 March 1992 - Department of Microbiology, Univ. of B.C.

18 9 April 1992 - Department of Anatomy & Cell Biology, University of Kansas, Kansas, USA.

19 8 May 1992 - Department of Biochemistry, University of Calgary, Calgary, AB. Charting regulatory pathways with MAP kinase.

20 17 September 1992 - Div. Endocrinology, Dept. Medicine, Univ. of B.C. Charting regulatory pathways with MAP kinase.

21 11 July 1992 - D. Vance Honourary Symposium, Univ. of B.C.

22 25 October 1992 – Keystone A.S.B.M.B. Symposium, Keystone, CO, USA Chairperson

23 14 November 1992 - Frontiers in Science, Shrum Science Centre, Simon Fraser Univ., Burnaby. The power and promise of biomedical research.

24 3 March 1993 - Dept. of Biochemistry, University of Alberta, Edmonton, AB

25 26 October 1993 - Department of Medicine, Univ. of B.C. Abnormal insulin regulation of protein kinases during diabetes.

26 28 October 1993 - Pharmaceutical Sciences, Univ. of B.C. Insulin-activated protein kinase cascades - A paradigm for mitogenic signalling.

27 4 November 1993 - Department of Obstetrics & Gynaecology, Univ. of B.C. Networking with MAP kinases.

28 8 December 1993 - Department of Biochemistry, McGill Univ., Montreal, QC. Charting regulatory pathways with MAP kinases.

29 18 June 1993 - C.F.B.S. Meeting, Windsor, ON. Merck Frosst Canada Prize Award Lecture for C.S.B.M.B.

30 21 June 1993 - Hotel Dieu Hospital, Montreal, QC. Regulation of insulin-activated protein kinases in diabetic rats.

31 22 June 1993 - N.R.C. Biotechnology Research Institute, Montreal, QC. Networking with protein

kinases.

32 22 September 1993 - European Cell Cycle Conference, La Rochelle, France.

33 1 October 1993 - Biological Regulatory Mechanisms, Rossiter Conference, Barrie, ON. Cell cycle-regulation of serine/threonine kinases

34 18 April 1994 - Dept. Anatomy & Cell Biology, University of Toronto, Toronto, ON. At the cross-roads of diverse signal transduction pathways.

35 April 1994 - Department of Biochemistry, University of Minnosota, St. Paul, MN, USA. Networking with protein kinases.

36 November 1994 - N.R.C. Workshop-Biotechnology Research Institute, Montreal, QC. Signal transduction: Advances and applications.

37 21 May 1994 - Schmitt Symposium: The Cytoskeleton in Alzheimer's Disease, Univ. of Rochester, Rochester, NY. Phosphorylation cascades.

38 14 June 1994 - Dupont Symposium on Biological Signals, C.F.B.S. Meeting, Montreal, QC. Mitogen-activated protein kinases: at the cross-roads of diverse signal transduction pathways.

39 21 June 1994 - XIIth Annual Workshop on Membrane Transport, University of Montreal, Montreal, QC. Protein kinase and phosphatase networks in cell signaling.

40 21 July 1994 - XVI Annual Meeting Internatl. Society Heart Research Symposium, London, ON. Regulation of protein kinase circuitry by growth factors.

41 November 1994 - Onyx Pharmaceuticals, Richmond, CA. U.S.A. MEK'ing connections in MAP kinase-dependent signalling pathways.

42 28 March 1995 - Dept. of Pathology, Univ. of B.C., St. Paul's Hospital. MAP kinase networks in cell proliferation and stress.

43 16 May 1995 - Dept. of Pharmacology, Vanderbilt University, Nashville, TN, USA. Mitogenic and stress-activated protein kinase modules in cellular signalling.

44 29 June 1995 - Internatl. Soc. Neurochemistry Workshop, Nagoya Japan.

45 18 July 1995 - Cornell University, Ithaca, NY, USA.

46 28 August 1995 - Virological and Immunological Mechanisms, Functional Outcomes and Possibilities for Therapy in Enteroviral Heart Disease: An International Workshop, St. Paul's Hospital, Vancouver, Moderator, Ventricular function, myocyte biology, therapeutics.

47 26 January 1995 - Pacific NorthWest Biotechnology Exposition, Westin Hotel, Vancouver.

48 27 January 1995 - Aquatech'95 Conference, Westin Hotel, Vancouver.

49 9 May 1995- John P. Robarts Research Institute, London, ON. MAP kinase pathways in hemopoietic cell activation.

50 15 February 1995 - Merck Frosst - Growth Factor Meeting, Hyatt Regency, Vancouver.

51 11 May 1995 - Weis Centre for Research, Geisinger Clinic, Dansville, PE, USA. Regulation of mitogenic and stress-activated protein kinases.

52 19 May 1995 - ICOS Inc., Bothell, WA, USA.

53 20 July 1995 - W. Alton Jones Science Centre, Lake Placid, NY, USA. Protein kinase circuitry in mitogenic and stress signalling.

54 6 December 1995 - Upstate Biotechnology Inc., Lake Placid, NY, USA.

55 3 May 1996 - Dept. of Surgery, Univ. of B.C., Jack Bell Research Centre. Malfunctions in cell

signaling systems - the molecular basis of chronic diseases.

56 9 May 1996 - Dept. of Pathology, Univ. of B.C., Eye Care Centre. Protein kinases and disease.

57 22 January 1996 - Pierce Chemicals, Rockford, IL, USA.

58 21 February 1996 - Hospital for Sick Children, Toronto, ON.

59 4 March 1996 - Biochemistry, Pharmacology & Physiol. Club of Univ. of B.C.- Keynote Speaker. Your future in the basic medical sciences-bridging academia, government & industry.

60 23 March 1996 - Fisher Winternational Conference, Banff, AB.

61 26 March 1996 - Vancouver Enterprise Forum, Science World, Vancouver. Coaching the captain: the mentoring process.

62 October 1996 - Signal Transduction Conference, Lake Tahoe, Nevada, USA. Insulin signaling through protein kinase cascades.

63 October 1996 - Insulin Signaling & Diabetes, Washington, D.C. , USA Vanadium compounds for treatment of diabetes in rats.

64 November 1996 - Biochem. Pharma, Laval, QC. Insulin signal transduction through protein kinases.

65 November 1996 - Life Sciences Venture Forum, Toronto, ON. Kinetek Pharmaceuticals Inc.

66 20 December 1996 - Biochemistry, Pharmacology & Physiol. Club of U.B.C.- Vancouver Keynote Speaker - Careers in Biotechnology.

67 7 November 1997 - Dept. of Medicine, Univ. of B.C., St. Paul’s Diabetes Centre. Insulin signalling and organovanandium compounds.

68 23 July 1997 -1997 International Society for Heart Research International Conference, Vancouver. Protein kinase workshop.

69 22 September 1997 - IBC Signal Transduction Therapy, San Diego, CA, USA. Insulin signalling and vanadium compounds for treatment of diabetes in rats.

70 23 June 1997 - University of Calgary, Dept. of Pharmacology, Calgary, AB. Insulin signalling through kinase cascades.

71 18 December 1997 - Dept. of Medicine, University of B.C., St. Paul's Diabetes Centre. Insulin signalling and organovandandium compounds.

72 29 November 1997 - Brain and Spinal Cord Research Centre Symposium. UBC, Vancouver. Signal transduction research.

73 6 June 1998 - Bridging the Straight of Georgia Cancer Conference, Cowichan Bay, BC. Protein kinases for cancer diagnosis and therapeutic targets for chemotherapy.

74 11 June 1998 - Dept. of Pharmacology, University of Virginia, Charlottesville, Virginia, USA. MAP kinases in sea star oocyte cell cycle control.

75 5 March 1998 - Biochemistry, Pharmacology & Physiol. Club of University of BC, Vancouver. Keynote speaker - Career opportunities in the biotechnology industry.

76 7 May 1998 - Association of University Anaethesists Annual General Meeting, San Francisco, CA, USA. Pursuit of scientific excellence in industry.

77 11 March 1999 - Dept. of Physiology, Univ. of B.C. Introduction to protein kinases.

78 8 April 1999 - Dept. of Pharmacology, Univ. of B.C. Introduction to protein kinases.

79 25 June 1999 - American Society for Microbiology Conference, Vancouver. Analysis of protein

kinase networks.

80 24 August 1999 - Pacific Institute for the Mathematical Sciences Symposium, Univ. of B.C. Mathematical analysis of prtoein kinase networks.

81 14 October 1999 - Simon Fraser University - Harbour Centre, Vancouver. Canadian Brain drain to United States.

82 3 February 2000 - Dept. of Pharmacology, University of South Alabama, Mobile, Alabama, USA. MAP kinases in cardiovascular disease.

83 21 February 2000 - UBC Signal Transduction Network, Univ. of B.C. Mapping kineomes - protein kinase network analysis.

84 28 April 2000 - Dept. of Biochemistry, University of Alberta, Edmonton, AB. p38 MAP kinase pathways.

85 6 October 2000 - Montreal Heart Institute, Montreal, QC. Analysis of protein kinase networks in muscle models.

86 14 March 2000 - BC Biotechnology Alliance, Hyatt Regency, Vancouver. Genomics, proteomics and bioinformatics.

87 8 June 2000 - Canadian Society Pharmaceutical Sciences, Crowne Plaza Hotel, Vancouver. Spinning out companies from university research.

88 21 August 2000 - Univ. of B.C. Dept. of Medicine Jubilee CME, Galaxy Cruise, Alaska. What you need to know about molecular biology.

89 30 September 2000 - Foresight Capital Corporation, Delta Resort, Whistler, BC. Human genome project benefits for disease diagnosis and treatment.

90 13 November 2000 - Pacific Rim biotechnology Conference, Hotel Vancouver, Vancouver. The Midas Touch.

91 30 November 2000 - Eldercollege/Capilano College, North Vancouver. How to invest in biotechnology with dollars and sense.

92 30 November 2000 - Biofuture Fund conference, Vancouver. Human genome and personalized medicine.

93 25 January 2001 - PENCE Group, University of Toronto, Toronto, ON. Proteomic analysis of signal transduction pathways.

94 24 April 2001 - Vancouver Enterprise Forum - Proteomics, bioinformatics and personalized medicine.

95 26 April 2001 - Aventis Biotechnology Fair - BCIT, Burnaby - Genomics, proteomics and bioinformatics.

96 27 April 2001 - UBC Department of Pharmacology and Therapeutics - Proteomics analyses of protein kinase networks.

97 28 May 2001 - UBC Department of Biochemistry and Molecular Biology. MAP kinase networks in cell signaling.

98 11 June 2001 - University of Calgary, Calgary, AB. Kinetworks mapping of cell signaling pathways.

99 28 June 2001 - BC Canacer Agency - Advanced Therapeutics Group. Analysis of protein kinase networks.

100 4 October 2001 - UBC Faulty of Medicine Distinguished Lecture. MAP kinase signalling pathways in human cancer.

101 3 July 2001 Institute of Molecular and Cell Biology, National University of Singapore - Proteomic analyses of cell signalling networks: Mapping protein kinase networks.

102 27 February 2002 - Children's Hospital Eastern Ontario, Univ. of Ottawa, Ottawa, ON. Kinetworks proteomics analyses: Mapping protein kinase networks in neural disorders.

103 5 March 2002 - Scripps Institute, San Diego, CA, USA. Kineome analysis: Mapping cell signalling networks.

104 6 March 2002 - International Business Communications - Protein Kinase Drug Discovery Conference, San Diego, CA, USA. Kineome analysis: Mapping protein kinase networks.

105 21 March 2002 - Cambridge Health Institute- Protein to Profits Conference, Munich, Germany. Kinetworks analysis: Mapping cell signalling networks.

106 4 April 2002 - First Forward Network/BC Biotech, Vancouver Terminal City Club. Bioinformatics for Biotech Executives - Keynote talk - A history of Bioinformatics: The past and beyond.

107 12 April 2002 - The Prostate Centre at Vancouver General Hospital Seminar. Mapping cell signalling systems by Kinetworks analysis.

108 26 April 2002 -BC Institute of Technology, Aventis Student Biotech Challenge Talk. Biotechnology in your future.

109 3 June 2002 - 85th Meeting of the Canadian Chemical Society, Vancouver. Drug profiling by Kinetworks analysis.

110 9 September 2002 - IBC 2nd Annual Protein Kinase Conference, Boston, MA, USA Mapping protein kinase pathways by Kinetworks.

111 19 September 2002 - The First Pacific North-West Cell Signalling Conference, Vancouver. Charting protein kinase pathways involved in mitotic checkpoint control.

112 20 September 2002 - The 4th Annual Pacific Northwest Venture Forum- Monte Jade, Vancouver. Kinexus Bioinformatics.

113 9 October 2002 - Laval University, Quebec City, QC. Mapping protein kinase networks.

114 21 November 2002 - BioFuture 2002 Conference and Exhibition, Vancouver. Stress Molecules - Listening to cells to silence disease.

115 29 November 2002 - University of Calgary, Calgary, AB. Promise of proteomics in the post-genomic era.

116 29 November 2002 - University of Calgary, Calgary, AB. Challenge to the entrepreneur scientist in the pursuit of academic excellence and success in the biotechnology industry.

117 3 March 2003 - Strategic Health Institute's Protein Kinase Meeting, San Diego, CA, USA. Kinetworks analysis: Elucidating the cell specific architecture of protein kinase networks.

118 6 March 2003 - Bioinformatics Training Initiative - BC Institute of Technology. Drug discovery in the post-genomics era: The Bioinformatics challenge and opportunity.

119 10 March 2003 - Invest NorthWest Conference, Seattle, WA, USA. Drug target discovery by Kinetworks analysis.

120 19 March 2003 - Cambridge Health Institutes, Molecular Market Place Meeting, Santa Clara, CA, USA. Tracking protein kinase pathways for identification and validation of drug targets.

121 21 March 2003 - Cambridge Health Institute's TriGenome Conference - Santa Clara, CA, USA. Kinetworks analysis: Elucidating the cell-specific architecture of protein kinase networks.

122 29 March 2003 - BC Pharmacy Assoc. Continuing Education Association - Richmond, BC. The

promise of proteomics in the post-genomics era of personalized medicine.

123 4 April 2003 - Eric Hamber Secondary School, Vancouver, BC. Careers in biotechnology.

124 25 April 2003 - British Columbia Institute of Technology - Burnaby, BC. Genomics and proteomics and the future of medicine.

125 29 April 2003 - Pt. Grey Secondary School, Vancouver BC. Careers in biotechnology.

126 29 May 2003 - International Council of Electrophoresis Society on Proteomics: Present perspectives and future challenges. Glasgow, Scotland. Mapping protein kinase pathways in mitotic checkpoint control by Kinetworks.

127 16 June 2003 - University of California San Francisco Cancer Centre, San Francisco, CA, USA. Proteomics analysis of cancer.

128 15 September 2003 - Parkinson's Disease Conference. Painter's Lodge, BC. Proteomics analysis of neurodegenerstive diseases.

129 8 October 2003 - Human Proteome Organization Meeting. Montreal, QC. Tracking protein kinase signalling on macroarrays with antibodies and pepetide antibody mimetics (PAM's).

130 20 October 2003 - Strategic Health Institute - Protein Kinase Meeting – Philadelphia, PA, USA. Mapping protein kinase signalling oathways by Kinetworks analysis.

131 23 October 2003 - IIR Life Science Conference - 2nd Annual Protein Kinase Meeting - Amsterdam, Holland. Monitoring protein kinase networks with arrays of antibodies and peptide antibody mimetics (PAM's).

132 10-17 Jan 2004 - Cambridge Health Institute - PEPTalk Meetin, San Diego, CA, USA. Tracking protein kinases and protein phosphorylation on macroarrays with antibodies and paptide antibody mimetics (PAM's).

133 2+3 March 2004 - GenomeCanada presentation in Toronto, ON.

134 8 March 2004 - Univ. of British Columbia, Robson Square, Public Address for Research Awareness Week. Dr. Professor/Mr. President - The curse of the entrepreneur scientist.

135 9 June 2004 - Cmabridge Health Institute - Protein Kinase targets - Strategies for Drug Development. Boston, MA, USA. Tracking the kinome by multiblotting with antibodies and peptide antibody mimetics (PAM's).

136 19-23 September 2004 - International Business Communications - CHIPS to Hits, Boston MA, USA. Kineome analysis: Mapping protein kinase networks.

137 22-23 Jan. 2005 - Ramandhai Foundation 2nd International Symposium “Current Trends in Pharmaceutical Sciences: Role of Genomics and Proteomics. Ahmedabad, India. (Had to cancel 2 days before departure due to illness)

138 28 Feb. 2005 - Strategic Research Institute – 3rd Annual Protein Phosphorylation Drug Discovery World Summit, San Diego, CA, USA. Tracking the kineome and phosphoproteome in arrays with antibodies and peptide antibody mimetics (PAM’s).

139 14 May 2005 - B.C. Pharmacy Association Annual Meeting, Vancouver. The promise of pharmacoproteomics for disease diagnosis and drug discovery.

140 20 March 2005 - World Congress on Microarray Technology, Vancouver. Tracking the kineome and phosphoproteome in arrays with antibodies and peptide antibody mimetics (PAM’s).

141 13 September 2005 - International Consortium on Anti-Virals Symposium and Workshop, Trent University, Peterborough, ON. Mapping cell signaling pathways.

142 28 September 2005 - National Research Council of Canada Genomics and Health Initiative Annual General Meeting. Ottawa, ON. Commercialization of technology.

143 9 January 2006 - Cambridge Healthtech Institute PepTalk Conference. Coronado, CA. Mapping the phosphoproteome by Kinex™ antibody arrays.

144 24 March 2006 - World Congress on Microarray Technology, Vancouver. Tracking cell signalling protein expression and phosphorylation by antibody microarrays.

145 8 May 2006 - GTCbio Protein Kinases in Drug Discovery Conference. Boston, MA, USA. Tracking the regulation of protein kinases and phosphorylation by quantitative antibody microarrays and multi-immunoblotting.

146 3 July 2006 - IIR's 5th Annual Protein Kinases Congress. Zurich, Switzerland. Kinase pathway analysis for target identification. Chair.

147 26 September 2006 - NRC-Biotechnology Research Institute, Montreal, QC. Meta-analyses of the human kineome and phosphoproteome.

148 2 December 2006 - GTCBio Drug Discovery Meeting. Philadelphia, PA. Antibody multi-immunoblotting and microarray analysis for CNS biomarker discovery in Alzheimer, Parkinson and ALS disease.

149 22 February 2007 - UBC Department of Medicine, Division of Neurology Grand Rounds. Vancouver. Phosphoproteomics and neurodegenerative diseases of the CNS.

150 8 March 2007 - SSP,.PSC.CSCO.WPS Joint meeting. Banff, AB. Mapping cell signalling networks with multi-immunoblotting and antibody microarrays.

151 22+24 May 2007 - Workshop Course - Informa 6th Annual Protein Kinases Congress – Biomarker profiling for kinase target evaluation– Principal Instructor and Coordinator. Lisbon, Portugal

152 18 June 2007 – Frontiers in Bioinformatics Workshop – University of British Columbia, Vancouver. Mapping the human phosphoproteome.

153 30 June 2007 - Workshop Course - World Congress on Microarray Technology, Vancouver. Tracking cell signalling protein expression and phosphorylation by antibody microarrays.

154 29 August 2007 – Seminar Presentation - University of Bath, Bath, UK. Tracking the human phosphoproteome.

155 30 August 2007 – Seminar Presentation - University of Liverpoole, Liverpoole, UK. Tracking the human phosphoproteome.

156 3 September 2007 - Workshop Course - Discovery – Select European Biomarkers Summit and Proteomics Europe Conference. Principal Instructor and Coordinator. Amsterdam, Holland. Mining the kineome and phosphoproteome with protein microarrays for biomarker and drug target.

157 28 October 2007 - Seminar Presentation - Joint meeting of 3rd Czech Proteomic conference and 1st Central and Eastern European Proteomic Conference. Olomouc, Czech Republic. Protein microarrays and phosphoproteomics.

158 6 December 2007 – Seminar Presentation – Lousiana State University Health Sciences Center – Shreveport, LO, USA – Proteomics methodologies.

159 6 December 2007 – Seminar Presentation – Lousiana State University Health Sciences Center – Shreveport, LO, USA – The human kineome and phosphoproteome.

160 9 February 2008 – Visiongain Protein Kinase Conference – London, UK (This meeting was cancelled 4 weeks before, but I was invited as a speaker and chairperson)

161 March 11, 2008 – Max Planck Institute– Berlin, Germany. The human kineome and

phosphoproteome.

162 March 12, 2008 - Informa 7th Protein Kinase Congress – Berlin, Germany. Antibody-based phosphoproteomics for biomarker and drug target identification. (Speaker and panelist)

163 March 27, 2008 - Canadian-Dutch Dementia Colloquium, University of British Columbia, Vancouver. Proteomic approaches for the diagnosis of Alzheimer's disease: What is the rationale and what are the prospects?

164 April 17, 2008 – Department of Biochemistry, Vanderbilt University, Nashville, TN, USA. The human kineome and phosphoproteome.

165 July 4-17, 2008 – In collaboration with the Japanese company Cosmo-Bio, I gave 90 to 120 minute scientific presentations to the following 13 companies. The number of scientists at these presentations ranged from about 6 to 40. The talk was entitled: Tracking the human kineome and phosphoproteome.

Daiichi-Sankyo Pharma (Tokyo)

Ono Pharma (Tsukuba)

Ono Pharma (Osaka)

Astella Pharma (Tsukuba)

Banyu Pharma (Merck) (Tsukuba)

Takeda Pharma (Tsukuba)

Takeda Pharma (Osaka)

Tanabe-Mitsubishi (Saitama)

Japan Tobacco (Osaka)

Dainippon-Sumitomo Pharma (Osaka)

Santen Pharma (Nara)

Shionogi Pharma (Osaka)

Nippon Shinyaku (Kyoto)

167 September 8-10 - Informa Drug Discovery Summer School in Cambridge, UK with Dr. Pelech as an invited speaker and chairperson. (This workshop was cancelled 6 weeks before it was to have transpired).

168 September 24, 2008 - IBC ACT 2008: Protein Kinase Target Conference, San Diego, CA. Mapping the human phosphoproteome. (Speaker, panelist and chair)

169 October 23, 2008 – Omeros Pharmaceuticals, Inc., Seattle, WA, USA. Kinase Inhibitors in the Clinic. Tracking the human kinome and phosphoproteome.

170 February 3, 2009 – University of Washington, Seattle, WA, USA. Breakfast Club Seminar. Tracking the kineome and phosphoproteome.

171 March 3, 2009 – Informa 8th Annual Protein Kinase Congress. Barcelona, Spain. Validation of protein kinase drug targets and drug leads with microarray approaches. (Speaker, panelist and chair)

172 May 8, 2009 – Prostate Centre Grand Round at VGH. Vancouver, BC. Mapping the human kineome and phosphoproteome by protein microarray and bioinformatics analyses.

173 August 6, 2009 – Select Biosciences Microarray World Congress. South San Francisco, CA, USA. Antibody microarrays for biomarker discovery and kinase microarrays for drug screening.

174 December 10, 2009 – Bristol Meyer Squibb. Princeton, NJ, USA. Kinase Inhibitors in the Clinic. Phosphoprotein biomarker and kinase drug target discovery with protein microarrays.

175 February 1, 2010 – University of British Columbia, Coop Program Networking Workshop. Vancouver, B.C.

176 June 21-23, 2010 - Cambridge Healthtech "Next–gen kinase inhibitors: Oncology and Beyond" Meeting. Cambridge, MA, USA. Mapping protein kinase networks and drug interactions with protein microarrays and predictive bioinformatics. (Speaker, panelist and chair)

177 March 24, 2010 – University of British Columbia, Department of Biochemistry Career Workshop. Vancouver, B.C.

178 September 10, 2010 – Global Biomarker Conference & Workshop. Vancouver, B.C. Mapping the human kineome and phosphoproteome with predictive bioinformatics and protein microarrays.

179 September 26 to 30, 2010 - International Society of Hypertension 23rd Scientific Meeting (ISH 2010). Vancouver, B.C. Mapping protein kinase networks for diagnostics and therapeutics development.

180 October 29, 2010 – Select Biosciences – Microarray World Congress, La Jolla, CA, USA. Protein and peptide microarrays for tracking human protein kineome regulation.

181 February 27, 2011 – Student Biotechnology Network. University of Victoria, Victoria, BC. Mapping and tracking the human kineome and proteome.

182 June 9, 2011 – Experimental Medicine Research Day Keynote Talk. University of British Columbia. Vancouver, BC. Confronting the uncertain future of biomedical research and the biotechnology industry in this decade.

183 September 30, 2011 – Select Biosciences – Microarray World Congress. South San Francisco, CA, USA. Protein kinase and phosphosite biomarker discovery and validation with protein microarrays with antibodies, lysates, protein kinases and substrate peptides.

184 February 10, 2012 – Bristol-Meyer-Squibb, Wallingford, CT, USA. Signalling network analyses and biomarker discovery and validation with protein and peptide microarrays.

185 March 7, 2012 – Department of Biochemistry Career Workshop. University of British Columbia. Vancouver, B.C.

186 July 10, 2012 - Merck Molecular Biomarkers: Translational Research Deep Dive Conference. Long Branch, NJ, USA. Tracking the human Kineome, Phosphatome and Phosphoproteome for biomarkers with antibody-based array technologies.

187 July 11, 2012 – Johnson & Johnson Pharmaceuticals. Springfield, PA, USA. Tracking the human Kineome, Phosphatome and Phosphoproteome for biomarkers with antibody-based array technologies.

188 July 12, 2012 - Bristol Myer-Squibb. Princeton, NJ, USA. Tracking the human Kineome, Phosphatome and Phosphoproteome for biomarkers with antibody-based array technologies.

189 July 13, 2012 – Novartis Institute for Biomedical Research Inc., Cambridge, MA, USA. Tracking the human Kineome, Phosphatome and Phosphoproteome for biomarkers with antibody-based array technologies.

190 October 2, 2012 – Purdue University, Department of Biochemistry. West Lafayette, IN, USA. Mapping the human Kineome, Phosphatome and Proteome with cell lysate, antibody and peptide microarrays.

191 March 8, 2013 – University of Missouri, Biochemistry Department. Columbia, MO, USA. Hierarchical molecular, cellular and social intelligence systems in the evolution of life.

192 July 17, 2013 – OMICS Group 3rd International Conference on Proteomics and Bioinformatics. Philadelphia, PA, USA. SigNET KnowledgeBank Workshop.

193 May 29, 2014 – BioConference Live Clinical Diagnostics & Research. On-line, CA, USA. Navigating the complexities of the human oncoproteome with the SigNET KnowledgeBank.

194 August 5, 2014 – OMICS Group 4th International Conference on Proteomics and Bioinformatics. Northbrook (Chicago), IL, USA. Phosphoproteomics and the origin and operations of the kineome. (also session chair)

195 August 6, 2014 – OMICS Group 4th International Conference on Proteomics and Bioinformatics. Northbrook (Chicago), IL, USA. Oncoproteomics for uncovering cancer biomarkers and therapeutics targets. (1 hour workshop)

196 September 10, 2014 – Biochemistry, Biology and Pathology of MAP Kinase II Conference. Vilnius, Lithuania. Navigating human phosphorylation networks with SigNET suite of on-line knowledge bases.

197 September 11, 2014 – Biochemistry, Biology and Pathology of MAP Kinase II Conference. Vilnius, Lithuania. Regulatory roles of conserved phosphorylation sites in the activation T-loop of the MAP kinase ERK1.

198 May 6, 2015 – Division of Neurology, University of British Columbia. Vancouver, BC. The protein kineome: Tracking and manipulating the predominant molecular intelligence system of cells with proteomics and bioinformatics.

199 September 29, 2015 – Human Proteome Organization (HUPO) Conference. Vancouver, BC. Profiling protein expression, modifications and interactions with antibody microarrays.

200 March 14, 2016 – Cure Huntington's Disease Initiative (CHDI) Foundation. Los Angeles, CA, USA. Overview of the Kinexus integrated proteomics and bioinformatics services platform.

201 March 29, 2016 – OMICS Group World Proteomics 6th Meeting. Atlanta, GE, USA. Two oral presentations: The SigNET KnowledgeBank - A series of on-line, open-access proteomics websites for biomarker identification and drug development; Tracking protein expression, modifications and interactions with antibody microarrays. (I also chaired two oral sessions)

202 July 18, 2016 – International Union of Molecular Biology and Biochemistry Meeting. Vancouver, BC. Positive and negative control of protein-serine/threonine kinases by phosphorylation in the catalytic domain T-loop. (I also chaired two oral sessions)

203 February 6, 2017 – Samsung Medical Center. Seoul, Korea. Tracking protein biomarkers in human lung tumour biopsies.

204 February 9, 2017 – 13th Korea Genome Organization (KOGO) Winter Symposium. Vivaldi Park, Korea. Tracking protein expression, modifications and interactions with antibody microarrays.

205 July 24th, 2017 – COSMO Bio. Toyko, Japan. Tracking protein expression, post-translational modifications and interactions with antibody microarrays.

206 July 26th, 2017 – Ono Pharmaceutical. Kyoto, Japan. Tracking protein expression, post-translationa modifications and interactions with antibody microarrays.

207 July 27th and 28th, 2017 – JPrOS 15th JHUPO Conference. Osaka, Japan. Two oral presentations: Tracking protein expression, post-translational modifications and interactions with antibody microarrays; Structure-function analyses of the catalytic domains of eukaryotic protein kinases.

208 August 30, 2017 – Bridging Discovery Research with Therapeutics Conference. Banff, Alberta. Investigations of the multi-site phosphorylation of CTP:phosphocholine cytidylyltransferase in huma

cancer cell lines.

May 1, 2018 – Vancouver, BC. Tracking cell signalling protein expression, post-translation modifications, interactions and activation with antibody microarrays.

July, 2018 – EuroScicon Proteomics Meeting. London, England. Monitoring protein expression, phosphorylation and interactions with high content antibody microarrays. Structure-function studies of the catalytic domains of eukaryotic protein kinases. Meta-analyses of small molecule inhibitors of protein kinases. (Invited chair) (Meeting was cancelled by conference organizers 6 weeks in advance of the meeting)

November 19th and 20th, 2018 – 2nd Global Summit & Expo on Proteomics – 2018. Dallas, Texas. Structure-function studies of the catalytic domains of eukaryotic protein kinases. Monitoring protein expression, post-translational modifications and interactions with high content antibody microarrays Workshop – The open-access suite of bioinformatics websites in the SigNET KnowledgeBank. (Invited chair).

February 12, 2019 - 15th Korea Genome Organization (KOGO) Winter Symposium. Vivaldi Park, Korea. Tracking protein expression, post-translational modifications and interactions with high content antibody microarrays.

February 13, 2019 - Daegu Gyeongbuk Institute of Science and Technology. Daegu, Korea. Trackir protein expression, post-translational modifications and interactions with high content antibody microarrays.

January 15, 2021 – Overview of Kinexus Bioinformatics Corporation and the NDR ALS Biomarker Project. Neurodegenerative Disease Research (NDR), Inc. Group via ZOOM in USA

October 28, 2021 - Dr Steven Pelech - Science or fear vaccine mandates UBC. UBC Students for Freedom of Expression. Vancouver, B.C.

February 2, 2022 – Pandemic of the unvaccinated. Canadian Covid Care Alliance. Live Zoom presentation.

April 9, 2022 – Third Annual Med Ed Conference. Lions Gate Hospital Foundation Youth Advisory Committee. My past and your future in medical research and practice. Vancouver, B.C.

May 7, 2022 – Unity Conference. COVID-19, natural immunity and vaccines. Kelowna, B.C.

May 28 and 29, 2022 - Restore Canada Conference. We Unify Canada. Victoria, B.C.

June 23, 2022 – COVID-19 and natural immunity: Do I need to get vaccinated. Langley, B.C.

June 30, 2022 – Progress report for the Kinexus Bioinformatics Corporation and the NDR ALS Biomarker Project. Neurodegenerative Disease Research (NDR), Inc. Group via ZOOM in USA

September 10, 2022 – Natural versus COVID-19 vaccine-induced immunity. Victory Canada Candlelight Vigil. Vancouver Art Gallery Plaza. Vancouver, B.C.

September 26, 2022 – Conference on Idaho Victims of Pandemic Policy and Law. Prevalence of natural and COVID-19 vaccine induced immunity: What does SARS-CoV-2 antibody testing show Via Zoom in USA.

224 October 1, 2022 – White Rock SDA Church. Natural immunity … Science or science fiction? Part 1 and Part 2. White Rock, B.C.

225 December 10, 2022 – Vancouver Art Gallery Plaza. Natural Immunity versus COVID-19 vaccine-induced immunity. Vancouver, B.C.

226 January 18, 2023 – David Eby Constituent Office. Why Bill 36 is dangerous to our healthcare system. Vancouver, B.C.

227 January 21, 2023 – UBC Cancer Association. The discovery of the molecular basis of cancer. UBC SUB Nest, Vancouver, B.C.

228 January 23, 2023 – Fraserview Community Hall. Natural versus COVID-19 vaccine-induced immunity … The Dwindling case for vaccination. Maple Ridge, B.C.

229 January 29, 2023 – Heritage Hall. Natural versus COVID-19 vaccine-induced immunity … The Dwindling case for vaccination. Canadian Film Workers for Human Rights & Ethics Association Town Hall. Vancouver, B.C.

230 February 4, 2023 - White Rock SDA Church. The crumbling case for COVID-19 vaccination. White Rock, B.C.

231 February 18, 2023 - World Wide Rally for Freedom at 999 Robson Street. Vancouver, B.C.

232 May 3, 2023 – The COVID-19 Pandemic…What Really Happened. Testimony at the National Citizen's Inquiry in Canada's COVID-19 Response. Langley, B.C.

(e) Other Presentations

(f) Other - Poster (only Poster Presentations from 2016 are listed)

1 April 16, 2016 – American Association for Cancer Research Annual Meeting. New Orleans, LA, USA. Steven Pelech, Lambert Yue, Jeff White, Ryan Hounjet, and Dirk Winkler. Profiling signalling protein expression,
modifications and interactions with multi-dimensional antibody microarrays.

2 April, 2016 – Federation of American Societies for Experimental Biology Annual Meeting. San Diego, CA, USA. Two posters: Steven Pelech, Lambert Yue, Jeff White, and Dirk Winkler. Modifications and interactions with multi-dimensional antibody microarrays; Steven Pelech, Lambert Yue, Shenshen Lai, Dirk Winkler, Jane Shi and Hong Zhang. Production and Characterization of polyclonal generic phosphotyrosine-specific antibodies.

3 July 18, 2016 – International Union of Molecular Biology and Biochemistry Meeting. Vancouver, BC. Two posters: Lambert Yue and Steven Pelech - Multi-dimensional analyses of protein expression, modifications and interactions with high content antibody microarrays (PP01.108); Steven Pelech, Shenshen Lai, Javad Safaei and Lambert Yue - Positive and negative regulation of protein-

serine/threonine kinases by their phosphorylation upstream of subdomain VIII in the T-loop (CS02.04).

4

April 2017 – American Association for Cancer Research Annual Meeting. Washington, DC. Poster: Lambert Yue and Steven Pelech - Tracking expression, post-translational modifications and interactions of EGF signalling proteins in A431 cells with antibody microarrays.

5

April 2018 – Canadian National Proteomics Network Annual Meeting. Vancouver, BC. Two posters: Kevin Gonzales, Lambert Yue and Steven Pelech - Phosphorylation of CTP:phosphocholine cytidylyltransferase (PCYT1A); Dirk Winkler, Lambert Yue, Javad Safaei, Zhoung Hua and Steven Pelech - Identification of optimal substrate peptides for protein kinases.

6

October 2019 - Canadian Association of Neuropathologists. Kingston, ON. Poster: Koeppen, A., Travis, A.M., Sutter, C., Pelech, S., and Mazurkiewicz, J.E. - Friedreich cardiomyopathy is a secondary desminopathy.

7

November 13-16, 2019 - International Ataxia Research Conference. Washington, DC. Poster: Koeppen, A.H., Travis, A.M., Qian, J., Mazurkiewicz, J.E., Gelman, B.B., Pelech, S., Sutter, C. The tissue proteome of dorsal root ganglia in Friedreich ataxia.

8.

December 11-14, 2021 - American Society for Hematology. Atlanta, GA. Oral presentation: Yen, R, Yue, L. Pelech, S., Jiang, X. Identification of a highly deregulated eIF4F translation initiation complex in drug-resistant BCR-ABL^{+} cells by a phospho-proteomic antibody microarray.

(g) Conference Participation (Organizer, Keynote Speaker, etc.)

1 1991 - Vancouver organizing committee for 1991 Society for the Study of Reproduction International Conference

2 25 October 1992 - Keystone, Colorado A.S.B.M.B. Symposium, Chairperson

3 1996 - 1997 Vancouver organizing committee for 1997 International Society for Heart Research International Conference

10.1 SERVICE TO THE UNIVERSITY

(a) Memberships on committees, including offices held and dates

Departmental

1 1988 - 2023 - Univ. of B.C. Dept. Medicine - Experimental Medicine Graduate Program Committee

In 2022, I attended two formal meetings of the Committee, reviewed over 80 scholarship applications, as well as faculty and student admissions to the graduate program

2 1993 - 1997 - Univ. of B.C. Department of Medicine Grant Review Committee - Active Member

3 1998 - 2002 - Univ. of B.C. Dept. Medicine - Academic Appointments, Reappointments, Promotions and Tenure Committee, Co-chair

4 July 24, 2000 - VHHSC Grant Panel

5 Brain Research Centre – Space Planning Committee – Meetings: April 8, 2009; May 1, 2009;

Divisional

6 1998 - 2004 - Brain Research Centre - Space Planning Committee - Active Member

7 1987 - 1996 - Univ. of B.C. Biomedical Research Centre - Safety Committee - Active Member

Faculty

8 1998 - 2001 - Faculty of Medicine MD/PhD Graduate Program Committee

9 2000 - 2003 - Faculty of Medicine Research Advisory Committee - Member

10 2003 - 2007 - Faculty of Medicine Senior Academic Appointments, Reappointments, Promotions and Tenure Committee - Member

11 2006-2008 – Faculty of Medicine Internal Reviewer (HeRRO) of grants prior to submission to C.I.H.R. (1 grant per year). In 2008, I reviewed a grant application prepared by Dr. Brian Kwon. He was successful in funding.

12 2004-2008 – TAG Workshop Instructor for Preparation of Teaching Dossiers (2-3 workshops per year). In 2008, one was given on March 5 at VGH and another was given on September 22 at Richmond General Hospital.

13 November, 2014 – Reviewer for VCHRI Top Graduate Doctoral Student Award – Preparation of reports for 7 applicants.

14 April 18, 2017 and May 10, 2017 – Facilitator for UBC Responsible Conduct Course

15 January 23, 2018 and February 6, 2018 – Facilitator for UBC Responsible Conduct Course

University

16 1998 - 2007 - Brain Research Centre - Space Planning Committee - Active Member

17 March 14, 1992 Judge - Second Annual Research Workshop, Reproductive & Developmental Sciences Program, Dept. Obstetrics & Gynaecology, U.B.C.

18 June 22, 2000 - Chairman of the Degree Validation Panel convened to review the Proposal for a joint British Columbia Institute of Technology/University of British Columbia Program for a Bachelor of Science degree in Biotechnology

19 2001 - 2004 - Faculty of Medicine Research Planning Committee - Member

20 2001 - 2003 - University of British Columbia Research Awareness Committee Member

21 May 2, 2001 - Canada Research Chairs Selection Committee Member

22 March 12, 2002 - Vancouver Hospital Health Sciences Centre Salary Awards Panel

23 January 24, 2008 – Judge – UBC Faculty of Dentistry Graduate Research Poster Competition

24 February 27, 2008 – Panelist - UBC Department of Biochemistry and Molecular Biology Careers
25 Evening

March 13, 2014 – Panel member for 2014 Science Career Information Fair (SCIFair) at the Life Sciences Centre, UBC.
26

March 19, 2014 – Panel member for 2014 Biochemistry Careers Night for the Department of Biochemistry and Molecular Biology at the Abdul Ladha Science Student Centre, UBC.

27 January 11, 2017 – Poster judge for the Faculty of Dentistry Graduate Student Program

28 November 7, 2018 – Poster judge for the UBC Faculty of Medicine and VGH Research Expo

29 January 17, 2019 – Panelist – UBC Computer Science/Life Sciences Panel – Careers Evening

30 March 9, 2019 – Panelist and speaker at 2 workshops - Operation Med School Vancouver (OMS) – Career event for high school students at the Robert H. Lee Alumni Centre

31 October 1, 2020 – present – UBC Senate. Faculty of Graduate and Postdoctoral Studies Representation. Also serve on the Senate Admissions Committee, and the Senate Admissions Appeals Committee

(b) Other service, including dates

1 October 25, 1991 Medical Research Council representative for Scholarships Day at UBC

2 September 24, 1992 Medical Research Council Representative for Scholarships Day at UBC

3 October 29, 2008 - Representative for Brain Research Centre for strategic discussion meeting in Waterfront Hotel in downtown Vancouver with Deputy Minister David Molony from Industry Canada to review government support for translational research

4 December 11, 2008 – Representative for UBC for strategic discussion meeting with N.S.E.R.C. at Pinnacle Marriott Hotel in downtown Vancouver to review government support for translational research

5 September 29, 2014 – Panel member for biotechnology curriculum development at the Langara College – Teaching and Curriculum Development Centre

6 October 15, 2020 to December 31, 2022– Panel member for Langara College B.Sc. in Bioinformatics Advisory Committee

Dissertation Committee and Examinations

Ph.D. & M.Sc. Supervisory Committee Membership

1 Dr. Paul Sunga - Dept. of Medicine (1989-1992 until Ph.D.)

2 Dr. Yong Hei - Pharmaceutical Sciences (1990-1993 until Ph.D.)

3 Ms. Elham Ettehadieh - Dept. of Biochemistry (1990-1993)

4 Mr. Brett Gabelman - Dept. of Anatomy (1990-1992 until M.Sc.)

5 Mr. Liren Tang - Dept. of Zoology (1991-1995 until Ph.D. & Ph.D. Examiner)

6 Ms. Rachel Zhande - Dept. of Biochemistry (1991-1998 until Ph.D.)

7 Mr. Aswin Patel - Pharmaceutical Sciences (1992-1996 until Ph.D.)

8 Ms. Patricia Herrera-Velt - Dept. of Microbio. Immunol. (1992-1997 until Ph.D.)

9 Mr. Sep Farahbakhian - Pharmaceutical Sciences (1992-1994 until M.Sc.)

10 Ms. Marie-Terese Little - Dept. Obsteterics & Geynecology (until 1993)

11 Mr. Patrick Tang - Dept. Microbio. Immunol. (1993-1997 until Ph.D.)

12 Mr. Mohammed Hasham - Dept. of Medicine (1994-1995 until M.S.)

13 Ms. Krista McCutcheon - Dept. of Anatomy (1994-1996 until M.Sc.)

14 Mr. Allen Young - Dept. of Oral Biology (1995-1997)

15 Mr. Brent Hehn - Dept. of Oral Biology (1995-1997 until Ph.D.)

Mr. Steven Drew - Dept. of Medicine (1995-1998 until M.Sc.)
Mr. Alaa El-Husseini - Dept. of Psychiatry (1995-1997 until Ph.D.)
Ms. Julia Mills - Dept. of Psychiatry (1995-1998 until Ph.D.)
Ms. Claire Sutherland - Dept. Microbiology Immunology (1995-1999 until Ph.D.)
Ms. Rochelle Starhe - Dept. of Medicine (1996-2001 until Ph.D.)
Mr. Mark Ware - Dept. of Medicine (1996-2000)
Mr. Vijay Viswanathan - Dept. Psychiatry (1998-2004 until Ph.D.)
Mr. Olaf Heisel - Dept. of Medicine (1999-2001 until Ph.D.)
Mr. Godfrey Miles - Dept. of Plant Sciences (1999-present)
Mr. Jan Ehses - Dept. of Physiology (1999-2003 Ph.D.)
Ms. Shu Hong Li - Pharmaceutical Sciences (2000 until 2001 Ph.D.)
Ms. Doris Chiu - Dept. of Medicine (2000-until 2001 M.Sc.)
Ms. Lucy Marzban - Pharmaceutical Sciences (2000 until 2001 Ph.D.)
Ms. Somrudee Sritubtim - Dept. Plant Sciences (2000 until 2005 Ph.D.)
Mr. Steven Drews - Dept. of Medicine (2000-2003 until Ph.D.)
Mr. Farrell MacKenzie - Dept. of Pathology (2001-2003 until M.Sc)
Ms. Jiehong Ju - Dept. of Kinesiology, Simon Fraser University (2001-2004 until Ph.D.)
Ms. Mannie Fan - Neuroscience Program (2002-2008 until Ph.D.)
Ms. Gina Rossi - Dept of Medicine (2002-2010)
Ms. Michelle Woo - Dept. Medicine (2003-2007 until Ph.D.)
Ms. Catherine Tucker - Dept. Medicine (2004-2007 until Ph.D.)
Mr. Tyson Brust – Neuroscience Program (2005-2008 until Ph.D.)
Mr. Philip Ly – Dept. Medicine (2005-2007 until M.Sc.)
Mr. Ebrima Gibbs – Dept. Medicine (2005-2008 until Ph.D.)
Ms. Shirley Chen – Dept. Medicine (2005-2009)
Mr. Scott Widenmaier – Dept. Cellular Physiological Sciences (2006-2010 until PhD)
Mr. Gobind Sun – Dept. Medicine (2006-2007 until transfer to new supervisor)
Ms. Amy Lai - Dept. Medicine (2007-2008 until transfer to new supervisor)
Ms. Arezoo Ostenehe – Dept. Medicine (2009-2013)
Ms. Shenshen Lai - Dept. Medicine (2009-2015 until Ph.D.)
Mr. Dominik Sommerfeld - Dept. Medicine (2010-2012 until transfer to new supervisor)
Mr. Javad Safaei – Dept. Mathematics & Computer Science (2008-2015 until Ph.D.)
Ms. Trisha Kostesky – Dept. Medicine (2010-2011 until M.Sc.)
Mr. Mazyar Ghaffari – Dept. Medicine (2011-2015)
Ms. Valerie Poirier - Dept. Medicine (2011-2015 until Ph.D.)
Mr. Dennis Wong - Dept. Medicine (2011-2013)
Ms. Melissa Richard-Greenblat - Dept. Medicine (2012-2016 until Ph.D.)

53 Ms. Anna Cecilia Sjoestroem – Dept. Medicine (2013-2014 until M.Sc.)
54 Mr. Franco Cavaleri - Dept. Medicine (2014-2017)
55 Mr. Bisher Hassan Abuyassin – Dept. Pharmacology (2015-2018)
56 Mr. Lambert Yue - Dept. Medicine (2016-2020)
57 Mr. Ryan Yen – Dept. Medicine (2017-2022)
58 Ms. Anam Nan Nan Liu – Dept. Pathology and Laboratory Medicine (2017-2019)

Directed Research Studies Supervision

1 Mr. Gordon Cheung – 4th year Zoology (2003-2004) 8 months
2 Ms. Nastaran Mohammadi – 5th year unclassified (2006) 7 months
3 Ms. Sharon Zhao – Department of Mathematics & Computer Sciences, Simon Fraser University. Ph.D. graduate student. Joint MITACS project supervision. (2005-2006) 8 months
4 Mr. Mazyar Ghaffari – 1st year graduate student (2008) 6 months starting March 1
5 Mr. Javad Safaei – Department of Mathematics & Computer Sciences, Simon Fraser University. Ph.D. graduate student. Joint MITACS project supervision. (2008-2015)
6 Ms. Parisa Shoosht – Department of Mathematics & Computer Sciences, Simon Fraser University. Ph.D. graduate student. Joint MITACS project supervision. (2008)
7 Mr. M. Shabab Hossain – Department of Computer Science, University of B.C., M.Sc. graduate student. Joint MITACS project supervision. (2011)
8 Mr. Alireza Davoodi - Department of Computer Science, University of B.C., M.Sc. graduate student. Joint MITACS project supervision. (2013-2014)
9 Ms. Nishima Arora – Biotech Biotechnology, Vellore Institute of Technology, India., undergraduate student. Six months full-time directed research studies (January 1 – June 30, 2015).
10 Mr. Lambert Yue – Department of Biology, University of B.C. 5th undergraduate student. Four months full-time directed research studies (January 1 – April 30, 2016).
11 Mr. Kevin Gonzales – Department of Biology, University of B.C. 5th year undergraduate. Eight months, part-time directed research studies (September 1, 2017-April 30, 2018).
12 Mr. Abiel Kwok – Integrated Sciences Program, University of B.C. 4th year undergraduate. Eight months, part-time directed research studies (September 1, 2019-April 30, 2020).
13 Mr. Kevin Wong – Department of Biology, University of B.C. 3th year undergraduate. Eight months, part-time directed research studies (September 1, 2019-April 30, 2020).

B.Sc. Honours Thesis Examiner

1 Ms. Maryam Baghannazary - Dept. of Biology (1992)
2 Mr. Danny Leung - Dept. of Biochemistry, Simon Fraser University (1994)
3 Ms. Monika Aluweilla - Dept. of Biochemistry, Simon Fraser University (1995)

M.Sc. Thesis Examiner

1 Mr. Jonathan Kao - Dept. of Medicine (1990)
2 Ms. Rachel Zhande - Dept. of Biochemistry (1991)
3 Mr. Peter Dreyden - Dept. of Medicine (1992)
4 Mr. John Stingl - Dept. of Anatomy (1992)
5 Mr. Brett Gabelman - Dept. of Anatomy (1992)
6 Mr. Sep Farahbakhian - Pharmaceutical Sciences, U.B.C (1994)
7 Mr. Mohammed Hasham - Dept. of Medicine, UBC (1996)
8 Ms. Krista McCutcheon - Dept. of Anatomy, UBC (1996)
9 Mr. Steven Drew - Dept. of Medicine (May 19, 1998)
10 Ms. Shu Hong Li - Pharmaceutical Sciences, UBC (May 23, 2000)
11 Mr. Tom Yokogawa - Dept. of Medicine (October 10, 2000)
12 Ms. Doris Chiu - Dept. of Medicine (October 4, 2001)
13 Mr. Farrell Mackenzie - Dept. Pathology (April 23, 2003)
14 Mr. Geoff Karjala – Dept. of Biochemistry & Molecular Biology (November 30, 2004)
15 Mr. Philip Ly – Dept. of Medicine (October 9, 2007)
16 Ms. Trisha Kostesky – Dept. Medicine (June 21, 2011)
17 Ms. Anna Cecilia Sjoestroem – Dept. of Medicine (October 7, 2013)
18 Ms. Anam Lui - Dept. of Medicine (September 30, 2019)

Ph.D. Oral Comprehensive Examiner
1 Ms. Marie Terese Little - Dept. Obstetrics & Gynaecology (June 10, 1991)
2 Dr. Amanda Jones - Dept. Medicine (December 11, 1991)
3 Ms. Patricia Herrarez - Dept. Microbiol. Immunol. (December 14, 1992)
4 Ms. Julia Mills - Dept. Psychiatry (June 21, 1995)
5 Mr. Alaa El-Husseini - Dept. Psychiatry (January 24, 1996)
6 Ms. Rochelle Starhe - Dept. of Medicine (May 27, 1997)
7 Mr. Olaf Heisel - Dept. of Medicine (2000)
8 Mr. Vijay Viswanathan - Dept. Psychiatry (June 15, 2000)
9 Mr. Godfrey Miles - Dept. Plant Sciences (September 15, 2000)
10 Mr. Jan Ehses - Dept. of Physiology (November 21, 2000)
11 Mr. Mohamed Sayed - Dept. of Medicine (December 19, 2000)
12 Mr. Steven Drews - Dept. of Medicine (February 7, 2001)
13 Mr. Kelvin Chang - Dept. of Obstetrics and Gynaecology (April 17, 2002)
14 Ms. Gina Rossi - Dept. Medicine (Sept 17 and Nov 10, 2004)
15 Mr. Gobind Sun – Dept. Medicine (May 28, 2007)
16 Mr. Scott Weidermaier – Dept. of Physiology (September 30, 2008)
17 Ms. Arezoo Astenehe – Dept. of Medicine (April 17, 2009)

18 Mr. Dennis Wong – Dept. of Medicine (September 30, 2009)
19 Mr. Darryl Bannon - Dept. of Medicine (November 10, 2011)
20 Ms. Valerie Poirer - Dept. of Medicine (November 25, 2011)
21 Ms. Shenshen Lai - Dept. of Medicine (December 14, 2011)
22 Mr. Darryl Bannon - Dept. of Medicine (May 17, 2012)
23 Ms. Joanna Triscott - Dept. of Medicine (June 4, 2012)
24 Ms. Melissa Richard – Dept. of Medicine (February 7, 2013)
25 Mr. Franco Cavaleri – Dept. of Medicine (April 17, 2015)
26 Mr. Bisher Hassan Abuyassin – Dept. of Medicine (December 12, 2016)
27 Mr. Ryan Yen – Dept. of Medicine (January 17, 2019)

Ph.D. Thesis Examiner

1 Mr. Grant Hatch - Dept. of Biochemistry, University of Manitoba (1989)
2 Dr. Poul Sorenson - Dept. of Pathology, UBC (1990)
3 Ms. Alice Mui - Dept. of Pathology, UBC (1992)
4 Mr. Paul Sunga - Dept. of Medicine, UBC (1992)
5 Dr. Jong Hei - Pharmaceutical Sciences, UBC (1993)
6 Mr. Guy Mordret - Dept. of Biochemistry, University of Brest, France (1993)
7 Ms. Corinne Reimer - Dept. of Anatomy, UBC (1994)
8 Mr. John Hill - Dept. of Pathology, UBC (1994)
9 Ms. Ruth Lanius - Dept. of Opthomology, UBC (1994)
10 Mr. Ashwin Patel - Pharmaceutical Sciences, UBC (1996)
11 Mr. Patrick Rebstein - Dept. of Microbiol. Immunol., UBC (1996)
12 Ms. Patricia Herrera-Velt - Dept. Microbio. Immunol, UBC (1997)
13 Mr. Xi-Long Zheng - Dept. of Medical Biochemistry, University of Calgary (June 23, 1997)
14 Mr. Vuk Stambolic - Dept. of Biochemistry, University of Toronto (August 7, 1997)
15 Mr. Alaa El-Husseini - Dept. of Psychiatry, UBC (October 17, 1997)
16 Ms. Rachel Zhande - Dept. of Biochemistry, UBC (December 1, 1997)
17 Mr. David Ng - Dept. of Microbio. Immunol., UBC (April 24, 1998)
18 Mr. Jeffrey Posaconi - Dept. of Chemistry, UBC (June 19, 1998)
19 Ms. Adrienne Boone - Dept. Biochemistry, UBC (April 5, 2000)
20 Ms. Zahara Jaffer - Dept. Microbiol. & Immunology, UBC (August 14, 2000)
21 Mr. Abdulaziz Al-Fahim - Dept. of Medicine, UBC (August 11, 2000)
22 Ms. Ravenska Wagey - Dept. of Medicine (December 14, 2000)
23 Ms. Amy Dambrowitz - Dept. of Biochemistry (June 6, 2001)
24 Ms. Rochelle Heisel - Dept. of Medicine (July 30, 2001)

25 Ms. Lucy Marzban - Faculty of Pharmaceutical Sciences (September 6, 2001)
26 Mr. Mohamed Sayed - Dept. of Medicine (October 26, 2001)
27 Ms. Xiaoli Cheng - Dept. of Biochemistry (December 10, 2002)
28 Mr. Steven Drews - Dept. Medicine (June 24, 2003)
29 Mr. Jan Ehsus - Dept. Physiology (July 18, 2003)
30 Mr. Kelvin Cheng - Dept. Gynaecology and Obstretics (Feb 4, 2004)
31 Ms. Sherri Christian - Dept. Microbiology and Immunology (May 5, 2004)
32 Ms. Elizabeth Slow - Dept. Medicine (November 26, 2004)
33 Ms. Rita Maghsoodi – (January 17, 2005) - Chair
34 Ms. Tanya Griffith – Department of Biochemistry and Molecular Biology (January 27, 2006) - Chair
35 Ms. Zhou Hongyan – University of Hong Kong (November 12, 2006) – External Examiner
36 Ms. Justine Karst – Department of Botany (July 9, 2007) - Chair
37 Mr. Robert Ferdman – Department of Astronomy (December 13, 2007) - Chair
38 Ms. Catherine Tucker – Department of Medicine (December 21, 2007)
39 Ms. Jin Suk Lee – Department of Botany (January 18, 2008) – University Examiner
40 Mr. Ebrima Gibbs – Dept. of Medicine (August 22, 2008)
41 Mr. Mark Romanish – Faculty of Science (July 22, 2009) – Chair
42 Mr. Douglas Sweeney – Faculty of Engineering (Nov. 12, 2009) - Chair
43 Mr. Scott Widenmaier – Dept. Cellular Physiological Sciences (June 30, 2010)
44 Mr. David Morin – Dept. of Medicine (December 22, 2011) - Chair
45 Ms. Grace Lee Kam – Dept. of Medicine (December 23, 2011)
46 Ms. Valerie Poirier – Dept. of Medicine (January 23, 2015)
47 Mr. Too Jin Park – Dept. of Medicine (February 10, 2015)
48 Ms. Shenshen Lai – Dept. of Medicine (March 25, 2015)
49 Mr. Javad Safaei – Dept. of Computer Science and Mathematics (April 9, 2015)
50 Ms. Melissa Richard – Dept. of Medicine (June 28, 2016)
51 Ms. Sylvia Cheung – Dept. of Surgery (September 15, 2016)
52 Mr. Saleem Iqbal – Crystallography and Biophysics, University of Madras, Chennai, India (November 9, 2018) – External Examiner
53 Mr. Bisher Hassan Abuyassin – Dept. of Medicine (December 21, 2018)
54 Mr. Ryan Yen – Dept. of Medicine (August 25, 2022)
55 Mr. Andrew Santos – Dept. Microbiology and Immunology (December 15, 2022)

10.2 SERVICE TO THE HOSPITAL

(a) Memberships on committees, including offices held and dates

(b) Other service, including dates

11. SERVICE TO THE COMMUNITY

(a) Memberships on scholarly societies, including offices held and dates

1 1990-present Canadian Society for Biochemistry and Molecular Biology - Active Member

2 1990-1992 Society for the Study of Reproduction (on local organizing committee for 1991 S.S.R. International Conference)

3 1996-1997 International Society for Heart Research (on local organizing committee for 1997 I.S.H.R. Conference)

4 1996-1999 American Society for Microbiology - Active Member

5 2016-2018 American Society for Biochemistry and Molecular Biology – Active Member

(b) Memberships on other societies, including offices held and dates

1 1980-1987, Canadian for Health Research - Active Member

2 1996-2002, 2008 Vancouver Public Aquarium - Active Member

2021-present, Vice-President, Chair of the Scientific and Medical Advisory Panel, Canadian Covid Care Alliance

(c) Memberships on scholarly committees, including offices held and dates

1 1992-present Lunar Society - Active Member

(d) Memberships on other committees, including offices held and dates

1 1980-1983 - Executive Committee of B.C. Chapter of Canadian for Health Research

2 1991-1993 - M.R.C. of Canada Studentship Committee

3 1991-1994 – Canadian Heart & Stroke Foundation Operating Grant Panel

4 1994-1995 - Committee for West Vancouver High Schools Cooperative Education Program

5 1994- M.R.C. of Canada Program Grant Committee

6 1994- American Heart Association Grant Panel

7 1995-1996 -M.R.C. of Canada Operating Grant Committee - Biochem. Mol. Biol. Panel B

8 May 29-31, 2000 - Invited Member Strategic Planning Committee for the National Research Council of Canada Industrial Research Assistance Program

9 November 6-9, 2000 - Canadian Institute for Health Research - Operating Grant Committee - Cardiovascular Panel

10 July 31, 2001 - Michael Smith Foundation for Medical Research Senior Scholars and Scientist Award Committee

11 2001 - 2006 - Member Advisory Committee for the National Research Council of Canada Industrial Research Assistance Program

12 2001-2006 - Genome Prairie Scientific Advisory Board

13 2002 - 2007 - Simon Fraser University Biotechnology Advisory Council - Member

14 2003-2005 - Canadian Bioinformatics Resource Initiative - Chairman

15 2004-2010 - National Research Council of Canada Genome Health Initiative Expert Panel. In 2009, I attended the Annual Meeting of the GHI in Montreal in June 1st and 2nd, and provided mid-term reviews of 5 GHI projects for the NRC at an Expert Panel Meeting in Ottawa on December 6. In 2010, I judged new GHI projects on September 27 & 28 in Ottawa.

16 2005-2007 - Simon Fraser University Master of Technology Advisory Board

17 2005 - U.S. National Institutes of Health Director's Roadmap Initiatives, Technology Centers for Networks and Pathways (TCNP) Grant Panel (I was invited to join this panel again in 2008, but declined due to a timing conflict.)

18 2006 – Alberta Cancer Board Grant Review Panel for Programs of Distinction

19 2009 – Canadian Institutes for Health Research - Catalyst Grant: Invention and High-Risk, High-Benefit Research Panel. June 3-5 in Ottawa.

20 2010 – Canadian Institutes for Health Research - Catalyst Grant: Invention and High-Risk, High-Benefit Research Panel. June 3-5 in Ottawa.

21 2021 – 2022 Langara University Bioinformatics Advisory Committee

(e) Reviewer (journal, agency, etc. including dates) - Peer-reviewer of grant-in-aid applications

1 Medical Research Foundation of Canada: 1988 - 4; 1989 - 9; 1990 - 4; 1991 - 2; 1993 - 5; 1994 - 20; 1995 - 21; 1996 - 19; 1997 - 11; 1998 -6; 1999 -10; 2000 -5

2 Alberta Heritage Foundation: 1988 - 1; 1990 - 1; 1991 - 3; 1992- 2; 1993 - 4; 1994 -1; 1995 -2; 2000 - 4; 2001-1; 2005-1

3 Canadian Diabetes Association: 1988 - 1; 1990 - 1; 1993 -1; 1994 -2; 1995 - 2; 1996 -1; 2002-2; 2003-3

4 Canadian Arthritis Society: 1988 - 1; 1989 - 1

5 National Cancer Institute of Canada: 1988 - 1; 1995 -1; 2001 -8

6 Heart & Stroke Foundation of Canada: 1988 - 1; 1990 - 1; 1991 - 16; 1992 - 16; 1993 - 16, 1994 - 12; 1998 -1; 1999 -3; 2000-4; 2002-1

7 Kidney Foundation of Canada: 1989 - 1; 1990 - 1

8 Natural Sciences & Research Council of Canada: 1990 - 1; 1995 -1; 1996 -1; 2002-1; 2004-2; 2006-1; 2015-1; 2016-1

9 Manitoba Health Research Council: 1992 - 1; 1993 -1; 1994 -1; 1997-2

10 National Science Foundation (USA): 1992 - 1; 1993 - 4; 1994 -2; 1996 -1; 1997 -2; 1998 -2; 2004-1

11 American Diabetes Association: 1994-1

12 Israel Science Foundation: 1994-1; 1996 - 4

13 American Heart Association (USA): 1994 - 5

14 Alberta Cancer Board: 1996 - 2; 2000 –1; 2007-2

15 U.S.-Israel Binational Science Foundation: 1996 -1
16 British Columbia Health Research Foundation: 1999 -7
17 Canadian Institute for Health Research: 2000 -11; 2001-5; 2002-2; 2003-2; 2004-1; 2005-1; 2009-12; 2010-13
18 Hong Kong Research Granting Council: 2000 -1; 2003-2
19 Vancouver Hospital Health Sciences Centre: 2000 -2; 2002-5; 2005-1; 2006-1
20 Michael Smith Foundation Health Research: 2001-4; 2003-1
21 GenomePrairie: 2001-21; 2003-3; 2004-5; 2006-2
22 B.C. Lung Assoc.: 2002-1
23 Canadian Blood Services: 2002-1
24 Carcinogenesis: 2002-2
25 Biotechniques: 2002-1
26 Scottish Rite Charitable Foundation: 2003-1
27 International Cancer Research Agency: 2004-1
28 Biotechnology and Biological Sciences Research Council (United Kingdom): 2004-1
29 National Research Council of Canada: 2004-5; 2006-5; 2007-16; 2009-5; 2010-3
30 U.S. National Institutes of Health: 2005-13
31 Singapore Biomedical Research Council: 2010-1
32 Genome Alberta: 2012-4
33 Cancer Research UK: 2012-1

(f) Reviewer (journal, agency, etc. including dates) - Peer-reviewer of scientific manuscripts

1 Analytical Chemistry: 2005 - 2
2 Biochem. Cell Biology: 1989 - 1; 1990 - 1; 1992 - 1; 1993 -2
3 Biochim. Biophys. Acta: 1989 - 9; 1990 - 5; 1991 - 4; 1992 - 3; 1993 -1; 1994 - 3; 1995 - 3; 1998 -1; 2000 –1; 2005 - 2
4 Brain Research: 2005 - 1
5 Molecular Cellular Biology: 1989 - 2; 1992 - 1; 1993 - 5; 1994 - 3; 1995 -2; 1996-1; 2003-1
6 Science: 1989 - 1; 1991 - 1, 1992 - 1; 1993 -1; 1994 - 2
7 Digestive Diseases & Sciences: 1990 -1; 1991 -1
8 Endocrinology: 1990 -1
9 Experimental Eye Research: 1990 - 1
10 FEBS Reviews: 2005 - 1
11 Journal Biol. Chem.: 1989 - 1, 1997 -1
12 Journal of Interferon Research: 1990 - 1
13 Journal Clinical Invest.: 1992 - 1

14 Journal of Immunology: 1992 - 2, 1995 -1
15 Nature: 1992 - 2, 1993 - 4
16 Proc. Natl. Acad. Sci. USA: 1992 -1, 1994 - 3; 1995 -1
17 American Journal of Physiology: 1993 - 1
18 Developmental Biology: 1993 -2
19 Diabetes: 1993 -1
20 European J. Biochemistry: 1994-2, 1995-1
21 Blood: 1993 -1; 1995 -1; 1998 -1;1999 -1
22 Analytical Biochemistry: 1996 - 2
23 Trends in Cardiovascular Medicine: 1996 -1
24 Cancer Res.: 1997 -1
25 Journal of Neurochemistry: 1997- 2; 2001-1
26 Neurobiology of Aging: 1998 -1
27 Biochemistry: 2000 -1
28 Journal of Endotoxin Research: 2000 -2
29 Life Sciences: 2000 -1
30 Carcinogenesis: 2007-1
31 Public Library of Science (PloS): 2008-1
32 Journal of Neurological Sciences: 2010-1
33 Science – Cell Signaling: 2010-1
34 Systems Biology of Free Radicals and Anti-oxidants – 2012-1
35 Proteomics – 2016-1
36 Molecular and Cellular Proteomics – 2016-1
37 Journal of Proteome Research – 2017 -1
38 Cell Signalling – 2019-1
39 J. Alzheimer's Disease – 2021 - 1
40 Vaccines – 2022 – 2; 2023 -1
41 Journal of Radiology and Oncology – 2023 -1

(g) External examiner (indicate universities and dates)

1 1989 Ph.D. Defence of Grant Hatch - Dept. of Biochemistry, Univ. of Manitoba
2 1993 Ph.D. Defence of Guy Mordret - Dept. of Biochemistry, Univ. of Brest, France
3 1997 Ph.D. Defence of Xi-Long Zheng - Dept. of Medical Biochemistry, Univ. of Calgary
4 1997 Ph.D. Defence of Vuk Stambolic - Dept. of Biochemistry, Univ. of Toronto
5 2006 Ph.D. Defence of Zhou Hongyan - Department of Biochemistry, Univ. of Hong Kong
6 2018 Ph.D. Defence of Saleem Iqbal – Crystallography and Biophysics, Univ. of Madras, Chennai, India

(h) Consultant (indicate organization and dates)

1 1991-1999 Upstate Biotechnology Inc., Lake Placid, N.Y.

2 1995-present Kinections Consulting Ltd, Richmond, B.C.

3 1995-1999 Biozyme, Vancouver, B.C. (member of scientific advisory board)

4 1996-2000 Viratest, Burnaby, B.C. (member of scientific advisory board)

5 1997-2000 StressGen, Victoria, B.C.

6 1999 - present Kinexus Bioinformatics Corporation, Vancouver, B.C. (member Board of Directors)

7 2001 - 2006 GenomePraire Scientific Advisory Board

8 2001 - ARC Pharmaceuticals, Vancouver BC (member of Scientific Advisory Board)

9 2018 - present – GLG, Austin, Texas and London, UK (member of advisory council for industry)

10 2020 – present – Neurodegenerative Disease Research, Inc. (member of research consortium)

(i) Other service to the community

1 1990-present - Cooperative Education Program - Simon Fraser University

2 1991-2007 - Scientist in The School Program - coordinated by Science World

3 1992 – 2010 - Cooperative Education Program - University of Victoria

4 March 9, 1993 - Volunteer for Careers Presentation - Science World, Vancouver.

5 February 14, 1993 - Scientists and Innovators in the Schools, Kitsilano Secondary School, Vancouver

6 1994-present - Cooperative Education Program - West Vancouver Secondary Schools

7 1994-present - Mentor for B.C. Institute of Technology Biotechnology Program

8 1996-present Cooperative Education Program - University of B.C.

9 March 1, 1996 - Volunteer for Careers Presentation - Science World, Vancouver.

10 January 24, 1997 - Scientists & Innovators in the Schools, Gladstone Secondary School, Vancouver.

11 April 2, 1998 - Judge for 1998 Greater Vancouver Regional Science Fair at the University of BC

12 February 4, 1999 - Judge for 1999 BC Biotechnology Alliance Awards

13 April 8, 1999 - Judge for 1999 Greater Vancouver Regional Science Fair at the University of BC

14 April 19, 1999 - Judge for 1999 Caunaught Biotechnology Science Fair, Vancouver

15 February 8, 2000 - Judge for 2000 BC Biotechnology Alliance Awards

16 April 6, 2000 - Judge for 2000 Greater Vancouver Regional Science Fair at the University of BC

17 2001 - Judge for 2001 Aventis Biotechnology Science Fair

18 February 1, 2001 - Judge for 2001 BC Biotechnology Alliance Awards

19 April 26, 2001 - Judge for 2001 Aventis Biotechnology Science Fair

20 March 2002 - Scientists & Innovators in the Schools, University Hill Secondary School, Vancouver.

21 2002 - Judge for 2002 Aventis Biotechnology Science Fair

22 January 17, 2019 - Invited Panelist – UBC Computer Science/Life Sciences Panel –
23 Careers Evening

March 9, 2019 - Invited Speaker at Operation Med School Vancouver (OMS) Workshop for
24 high school students. Career mentoring workshop (2 x 30 minute sessions) held at the Robert H. Lee Alumni Centre at UBC

September 1, 2020 – present – Langara College Bioinformatics Advisory Board member

12. AWARDS AND DISTINCTIONS

(a) Awards for Teaching (indicate name of award, awarding organizations, date)

1 2001 Faculty of Medicine Distinguished lecturer - Basic Sciences

(b) Awards for Scholarship (indicate name of award, awarding organizations, date)

2 1975 Killarney Secondary School Scholarship, Killarney Sec. School, Vancouver

3 1975 B.C. Government Scholarship, Killarney Sec. School, Vancouver

4 1977 Canadian Found. for Diseases of the Liver Summer Studentship, Univ. of B.C.

5 1978 Natural Sciences and Engineering Research Council of Canada Postgraduate Scholarship, Univ. of B.C.

6 1979-1982 Medical Research Council of Canada Studentship, Univ. of B.C.

7 1982 Univ. of B.C. Graduate Student Speaker Competition (1st Place)

8 1982 Izaak Walton Killam Postdoctoral Fellowship

9 1982-1984 M.R.C. of Canada Postdoctoral Fellowship

10 1985 M.R.C. of Canada 1967 Centennial Fellowship

11 1988-1993 M.R.C. of Canada Scholarship Award

12 1993-1996 M.R.C. of Canada Scientist Award

13 1996-1998 M.R.C. of Canada Industrial Scientist Award

(d) Other Awards

14 1993 Canadian Soc. for Biochem. & Molec. Biol. Merck-Frosst Award - for outstanding research in the area of biochemistry and molecular biology in Canada

15 1993 Martin M. Hoffman Award - Univ. of B.C. Hospital Site for Research in Dept. of Medicine

16 1996 Business in Vancouver Top Forty Under Forty Award for Business Achievement

17 1998 International Who's Who

18 2001 Faculty of Medicine 2001 Distinguished Lecturer, University of BC

Fellowship Awards (won by Post-Doctoral Fellows under supervision)

19 Lefebrve, D. - MRC Fellowship 1995-1996

20 Sahl, B. -MRC Fellowship 1995-1997

21 Bhanot, S. - BC Heart & Stroke Fellowship 1995-1997

22 Bhanot, S. - MRC Fellowship (declined) 1995-1997

23 Koide, B. - MRC Fellowship 1995

24 Xu, Yan-Jun - MRC Fellowship 1998-1999

25 Zhang, Hong - NSERC Industrial Fellowship 2003-2004

Studentship Awards (won by Graduate Students under supervision)

26 Palaty, C. - NSERC Studentship 1991-1994

27 Samiei, M. - MRC Studentship 1992-1994

28 Charest, D. L. - Walter Babicki Studentship 1992

29 Charlton, L. - NSERC Studentship 1992-1995

30 Charest, D. L. - MRC Studentship 1993-1997

31 Morrison, D. L. - MRC Studentship 1993-1997

32 Tudan, C. - MRC Studentship 1993-1996

33 Kim, S. - MRC Studentship 1993-1997

34 Palaty, C. - Walter Babicki Studentship 1995

35 Charlton, L. - Killam Studentship 1996-1997

36 Wagey, V. - University Graduate Fellowship 1997-1998

37 Marotta, A. - Evelyn Martin Fellowship 1998-1999

38 Sayed, M. - MRC Studentship 2000-2002

39 Shenshen Lai – University of B.C. Graduate Fellowship 2010-2014

40 Lambert Yue – UBC Experimental Medicine Graduate Program Entrance Award (2016); NSERC Graduate Fellowship 2017-2018; UBC 4YF Scholarship 2018-2020

41 Hamidreza Galavi - UBC Experimental Medicine Graduate Program Entrance Award (2020); UBC 4YF Scholarship 2020-2023; Vanier Award 2022-2024

13. OTHER RELEVANT INFORMATION (Maximum One Page)

1992-1998 - President, CEO and major stock owner of Kinetek Pharmaceuticals, Inc.

Kinetek was a private, early stage biotechnology company that employed 15 Ph.D./M.D. level scientists and 25 other technical and other supporting personnel at the time that I left the company. It was engaged in the discovery and development of drugs for the treatment of cancer, diabetes and other chronic diseases of aging. The Kinetek activities occupied over 18,000 square feet at two locations in south Vancouver. It was acquired by QLT, Inc. in 2004.

1995 - present - President and major stock owner of Kinections Consulting Ltd.

Kinections is a private company that provides consulting advise related to cellular signal transduction and the biotechnology industry. Its services also include the preparation of scientific reports and illustrations.

1999 - present - Founder, President, Chief Scientific Officer and major stock owner of Kinexus Bioinformatics Corporation

Kinexus Bioinformatics is a private company that provides analytical services related to the tracking of protein kinases and bioinformatics related to protein kinases. It has provided proteomics services to over 2000 laboratories in 40 countries. Over 200 of the company's clients are in companies. Twenty-nine of the top 30 pharmaceutical companies in the world are clients of Kinexus.

2021 – present – Founder, Vice-President, Co-Chair of the Scientific and Medical Advisory Committee (SMAC) of the Canadian Covid Care Alliance (CCCA). The CCCA was founded to provide balanced, evidence-based and scientifically sound analyses of recommendations related to COVID-19 with respect to it diagnosis, prevention and treatment. It has over 1600 members across Canada, which includes over 600 research scientists, professors, medical doctors and other health practitioners, and lawyers amongst other professionals. I participate in weekly meetings throughout the year, Tuesdays 4:00 pm - 5:00 pm – SMAC meetings, Tuesdays 5:00 pm - 8:00 pm – Steering Committee meetings, Wednesdays 5:00 pm - 8:00 pm – General Membership meetings.

14. SCIENTIFIC PUBLICATIONS

Total Peer Reviewed in Published in Journals: 196
Total Reviews, Book Chapters, Pre-prints Published: 61
Patents Applied and Issued: 2
Websites: 9

i. REFEREED PUBLICATIONS IN PEER-REVIEWED JOURNALS

1. PELECH, S.L., Pritchard, P.H., and Vance, D.E. cAMP analogues inhibit phosphatidylcholine biosynthesis in cultured rat hepatocytes. J. Biol. Chem. 256: 8283-8286 (1981).

2. Pritchard, P.H., PELECH, S.L., and Vance, D.E. Analogues of cAMP inhibit phosphatidylethanolamine N-methylation by cultured rat hepatocytes. Biochim. Biophys. Acta 666: 301-306 (1981).

3. PELECH, S.L. and Vance, D.E. Regulation of rat liver cytosolic CTP:phosphocholine cytidylyltransferase by phosphorylation and dephosphorylation. J. Biol. Chem. 257: 14198-14202 (1982).

4. PELECH, S.L., Pritchard, P.H., and Vance, D.E. Prolonged effects of cyclic AMP analogues on phosphatidylcholine biosynthesis in cultured rat hepatocytes. Biochim. Biophys. Acta 713:260-269 (1982).

5. PELECH, S.L., Pritchard, P.H., Brindley, D.N. & Vance, D.E. Fatty acids promote translocation of CTP:phosphocholine cytidylyltransferase to the endoplasmic reticulum and stimulate rat hepatic phosphatidylcholine synthesis. J. Biol. Chem. 258: 6782-6788 (1983).

6. PELECH, S.L., Jetha, F. & Vance, D.E. Trifluoperazine and other anaesthetics inhibit rat liver CTP: phosphocholine cytidylyltransferase. FEBS Lett. 158: 89-92 (1983).

7. PELECH, S.L., Pritchard, P.H., Brindley, D.N. & Vance, D.E. Fatty acids reverse the cyclic AMP inhibition of triacylglycerol and phosphatidylcholine synthesis in rat hepatocytes. Biochem. J. 216: 129-136 (1983).

8. PELECH, S.L., Power, E. and Vance, D.E. Activities of the phosphatidylcholine biosynthetic enzymes in rat liver during development. Can. J. Biochem. Cell Biol. 61: 1147-1152 (1983).

9. Audubert, F., PELECH, S.L. & Vance, D.E. Fatty acids inhibit N-methylation of phosphatidylethanolamine in rat hepatocytes and liver microsomes. Biochim. Biophys. Acta 792: 348-357 (1984).

10. PELECH, S.L., Pritchard, P.H., Sommerman, E.F., Percival-Smith, A. & Vance, D.E. Glucagon inhibits phosphatidylcholine biosynthesis via the CDP-choline and transmethylation pathways in cultured rat hepatocytes. Can. J. Biochem. Cell Biol. 62: 196-202 (1984).

11. PELECH, S.L., Cook, H.W., Paddon, H.B. & Vance, D.E. Membrane-bound CTP: phosphocholine cytidylyltransferase regulates the rate of phosphatidylcholine synthesis in HeLa cells treated with unsaturated fatty acids. Biochim. Biophys. Acta 795: 433-440 (1984).

12. PELECH, S.L. & Vance, D.E. Trifluoperazine and chlorpromazine inhibit phosphatidylcholine biosynthesis and CTP:phosphocholine cytidylyltransferase in HeLa cells. Biochim. Biophys. Acta 795: 441-446 (1984).

13. PELECH, S.L., Paddon, H.B. & Vance, D.E. Phorbol esters stimulate phosphatidylcholine biosynthesis by translocation of CTP: phosphocholine cytidylyltransferase from cytosol to microsomes. Biochim. Biophys. Acta 795: 447-451 (1984).

14. PELECH, S.L., Cohen, P., Fisher, M.J., Pogson, C.I., El-Maghrabi, M.R. & Pilkis, S.J. The protein phosphates involved in cellular regulation: Glycolysis, gluconeogenesis and aromatic amino acid breakdown in rat liver. Eur. J. Biochem. 145: 39-49 (1984).

15. PELECH, S.L. & Cohen, P. The protein phosphatase involved in cellular regulation: Modulation of protein phosphatases-1 and 2A by histone H1, protamine, polylysine and heparin. Eur. J. Biochem. 148: 245-251 (1985).

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ii. MANUSCRIPTS IN PREPARATION

Lai, S., Sommerfeld, D., Safaei, J., Winkler, D., Shi, J., Zhang, H., Sanghera, J., Yan, J., and PELECH, S. Determination of the specificities of 200 protein kinases with peptide microarrays.

PELECH, S. and Safaei, J. Quantification of amino acid interactions in protein complexes.

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Safaei, J., Manuch, J., Gupta, A., Stacho, L. and PELECH, S. Prediction of the phosphotyrosine binding specificities of 200 human SH2 and PTB domains.

Shi, J., Zhang, H., Sun, G., Paddon, H.B., Cheung, G., Mirzaei, S., and PELECH, S.L. Meta-analysis of the kineome, phosphatome and phosphoproteome during seastar oocyte maturation.

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Shi, J., Zhang, H., Paddon, H.B., and PELECH, S.L. Growth factor induced tyrosine phosphorylation of glycogen synthase kinase 3 (GSK3) via the Mek1/2 MAP kinase kinases.

Lai, S., Zhang, H., Shi, J., Winkler, D., Lambert Yue and PELECH, S. Production method and evaluation of a new generic polyclonal phosphotyrosine antibody.

iii. REVIEWS, BOOK CHAPTERS AND OTHER

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v. PATENTS

1. PELECH, S.L. Algorithm for elucidation of structure of protein kinase networks. U.S. Issued 2005. (also issued in United Kingdom 2007). This patent describes an algorithm to map out cell signalling pathways using the data collected from the quantifying protein levels in diverse cell/tissue extracts using the Kinetworks™ methodology that was developed in my UBC lab and licensed to Kinexus.

2. PELECH, S. L., Feldman, H., and Zhang, H. Biomarkers of Alzheimer's Disease. US Provisional Application – Jan. 30, 2008.

3. Shapira, T., Rens, C., Puchler, V., Rees, W., Steiner, T., Jean, F., Winkler, D., Sarai, I., PELECH, S., Av-Gay, Y. Inhibition of glycogen synthase kinase-3-beta (GSK3) blocks nucleocapsid phosphorylation and SARS-CoV-2 replication. Provisional Application to UBC UILO in November 2021.

vi. WEBSITES

In the last few years, I have begun to develop on-line, open-access databases and knowledgebases with comprehensive information on proteins, their mRNA and protein expression as well as their phosphorylation. While many people have been involved in the coding of the interfaces for these websites, I have personally devoted much of my time into their conception, design, data annotation, data inspection and coordinating their production. The following is a listing of these websites.

1. KiNET-IB – Kinetworks™ Immunoblotting DataBase (www.kinet.ca)
   First in 2006, KiNET-IB features over 200,000 measurements of the expression and phosphorylation states of hundreds of signal transduction proteins from over 6000 Kinetworks™ multi-immunoblots performed with control and treated tissue/cell samples. Immunoblotting remains the gold standard for protein quantification and the Kinetworks™ methodology was originally developed in my UBC lab. KiNET-IB is a useful tool for evaluating proteins that may participate in the control of diverse cellular processes and their connection with other proteins in signaling pathways. Over 95% of this data has been previously unpublished.

2. KiNET-AM – Kinex™ Antibody Microarray DataBase (www.kinet-am.ca)
   First launched in 2011, KiNET-AM features the quantitative results from nearly 2000 Kinex™ Antibody Microarray analyses with over 1.5 million measurements of 650 to 800 hundred different signalling proteins and phosphosites tracked per microarray. The data can be queried based on biological samples, treatments, specific proteins and phosphosites. Over 98% of this data has not been previously unpublished and was produced from analyses performed at Kinexus.

3. PhosphoNET – Human Phosphorylation Site KnowledgeBase (www.phosphonet.ca)
   First launched in 2010, PhosphoNET is the world's largest repository of known and predicted information on human phosphorylation sites, their evolutionary conservation and the identities of protein kinases that may target these sites. PhosphoNET presently holds data on over 970,000 known and putative phosphorylation sites (P-sites) in over 20,000 human proteins that have been collected from the scientific literature and other reputable websites. Over 177,000 of these phosphosites have been experimentally validated. The rest have been predicted with a novel Phosphosite Predictor algorithm developed at Kinexus. With the PhosphoNET Evolution module, this website also provides information about cognate proteins in over 20 other species that may share these human phospho-sites. This helps to define the most functionally important phosphosites as these are expected to be highly conserved in nature. With the Kinase Predictor module, listings are provided for the top 50 human protein kinases that are likely to phosphorylate each of these phospho-sites using another proprietary kinase substrate prediction algorithm that I helped to develop at Kinexus. With the Phosphosite Match module added in 2017, it is possible to identify phosphosites that are highly related in amino acid sequence. This helps to identity phosphosites that may be detected in cross-reactive off target proteins with phosphosite-specific antibodies. Over 8 million kinase-substrate phospho-site pairs are quantified in PhosphoNET, and over 200 signalling pathway maps are available.

4. TranscriptoNET – Human mRNA Expression KnowledgeBase (http://207.150.202.175)

First launched in 2011, TranscriptoNET features comprehensive information on the mRNA expression levels of about 21,000 genes in about 600 types of human organs, tissues and cells as measured with gene microarrays. The original data used in TranscriptoNET was retrieved from the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO), which serves as a repository of experimental gene microarray results submitted by diverse academic and industrial laboratories around the world. We normalized the data from over 900 different studies with over 6000 biological specimens to permit investigations of gene expression and potential interactions that can only be undertaken with such a large dataset of over 125 million gene expression measurements. This normalization process was based on the identification of 60 genes that were commonly and highly expressed in all of the biological samples. This site was first posted in 2013.

5. DrugKiNET – Human Kinase Drug Interaction KnowledgeBase (www.drugkinet.ca)
First launched in 2013, DrugKiNET is an open-access, online resource to foster the identification and characterization of inhibitors of protein kinases for academic and industrial research. It features comprehensive information on over 850 compounds that have been experimentally determined to inhibit human protein kinases. This includes the retrieval of the lowest reported compound IC50, Ki and Kd values from several sources, including the National Center for Biotechnology Information (NCBI) PubChem Compound database, the Kinase SARfari database from the European Molecular Biology Laboratory (EMBL) European Bioinformatics Institute, The International Centre for Kinase Profiling at the University of Dundee, Ambit Biosciences and hundreds of original research publications. In some cases, estimates for IC50 values were derived from limited measurements of kinase inhibition at only one to three different concentrations of the compounds. Using over 105,000 experimentally tested, non-redundant kinase-compound pairs for training, we have developed two kinase inhibitor prediction algorithms to further predict another 200,000 kinase-compound interactions. In 2017, we added a new module to DrugKiNET that provides information on the bond distances between the atoms of over 1500 drugs and the atoms in protein kinases as determined from their x-ray crystallographic structures.

6. OncoNET – Human Cancer Protein KnowledgeBase (www.onconet.ca)
This website features comprehensive information on the mutations and mRNA expression levels for about 3,000 genes in diverse types of human cancers. The mRNA expression data used in OncoNET was originally retrieved from the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO), which serves as a repository of experimental gene microarray results submitted by diverse academic and industrial laboratories around the world. We normalized the data from hundreds of different gene microarray studies using a normalization protocol based on the identification of 60 genes that were commonly and highly expressed in all of the biological samples. To explore the mutation of human cancer-related genes, we relied primarily on the collection of data from the Wellcome Trust Sanger Institute's Catalogue of Somatic Mutations in Cancer (COSMIC) database. Further information on these genes and their encoded proteins was annotated from several other sources, including UniProt and the Atlas of Genetics and Cytogenetics in Oncology and Haematology websites. I have used this database to identify new potential oncogenes, tumour suppressor genes and tumour requiring protein genes. This site was first posted in 2013.

7. KinaseNET – Human Protein Kinase KnowledgeBase (www.kinasenet.ca)
KinaseNET features comprehensive information on 536 human protein kinases, including their primary and tertiary structure, regulation, distribution, evolutionary conservation, protein substrate targets, pathway maps, sensitivities to compounds and linkages to human diseases. Each protein

kinase is represented with a separate webpage. KinaseNET also serves as a portal to many other useful websites with additional data about protein kinases. This site was first posted in 2015 and updated in 2017.

8. Kinetica Online – E-journal for Intelligence Systems Research (www.kinexus.ca/kinetica)
This website has not yet been officially launched, but a beta-version is available for viewing since 2013. This unique resource features commentaries, original research publications, databases and knowledgebases, and it also serve as portal to hundreds of other websites that should be useful to researchers engaged in the investigation of cell signalling. All of the articles in Kinetica Online have been published elsewhere.

9. KinATLAS – Human Protein Interaction Altas
(http://kinatlas.ca:8080/KinAtlas/KinaseDrugQuery.html)
This website is in development and a beta version with the first (Kinase-drug interactions) and second modules (Protein-protein interactions) are available for viewing since 2016. The underlying database is complete, and the web interface is still in the process of being coded for the third module (Kinase-substrate interactions). It will show tissue/cell-specific maps of protein-protein and kinase-drug interactions. The kinase-substrate interactions are prioritized using our updated kinase prediction algorithms, and the viewer will contain filters to permit generation of more customized maps.

10. DrugProNET – Human Protein – Drug Interaction KnowledgeBase (www.drugpronet.ca)
This website provides for the identification of the most critical atomic interactions between drugs and their protein targets based on 3D x-ray crystallographic analyses. Defining the key amino acid residues for drug binding in proteins permits the prediction of specific mutations in human genomes that will affect the sensitivities of individuals to these compounds. The bond distances in Angstroms between the closest protein and drug atoms in each crystal complex are provided in downloadable tables, along with definition of the closest amino acid residue side-chains. The single nucleotide variants (SNV's) that would affect these critical amino acid residues involved in drug interactions are also identified in DrugProNET. This website features comprehensive information on over 2000 compounds that have been co-crystallized with over 480 different human proteins in over 4400 protein-compound structures retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Databank (PDB).

11. KiNector – Human Protein Kinase-Protein Substrate+Phosphosite Interaction KnowledgeBase (www.kinector.ca)
Over 21,450 human kinase-substrate relationships (KSRs) were retrieved from several sources, including the PhosphoNET, PhosphoSitePlus and PhosphoNetworks websites and the scientific literature. The data are presented in a graphic format as maps, and full functional information was provided for at least 6000 of these KSRs. KiNector shows both direct and indirect linkages between a starting protein kinase and a phosphoprotein target that acts downstream in signalling pathways. KiNector also serves as a portal to other reputable websites that contain detailed information on these kinases and substrates, and provides direct links to the Kinexus Products website, which features over 3500 images of full Western blots performed with lysates from diverse rodent tissue panels and human cancer cell lines.

vii. ARTISTIC WORKS

1. Smith, J., Xu, Y., and PELECH, S.L. Human protein kineome. (2006) [This is a large wall chart that contains the identification of all of the known domains and phosphorylation sites in 515 human protein kinases. It was printed and distributed by Kinexus Bioinformatics Corporation.]

2. PELECH, S.L. and Bowyer, C. The human operating system. (2008) [This is a large wall chart that features over 180 cell signalling pathways. It was printed and distributed by Kinexus Bioinformatics Corporation.]

4. PELECH, S.L, Smith, J., and Xu, Y. Human protein kineome. (2010) [This is an updated, large wall chart that contains the identification of all of the known domains sites in 515 human protein kinases, along with Uniprot, size and substrate specificity information. It was printed and distributed by Kinexus Bioinformatics Corporation.]

5. PELECH, S. L. Human Cancer Protein Interaction Network. (2017). This is a wall chart that shows how over 100 of the most frequently mutated oncoproteins and tumour suppressor proteins interact with each other. It was presented and distributed at the 2017 American Association for Cancer Research Meeting and is downloadable from the Kinexus website (http://www.kinexus.ca/pdf/OncoNET_Poster.pdf).

viii. BLOG COMMENTARIES

Over the last decade, I have written commentaries on over 300 blogs as part of an outreach effort to inform the broader scientific community on a wide range of issues ranging from career development to genomics to biotechnology. I have only listed those commentaries that appeared primarily at the GenomeWeb website. Unfortunately, these, like all previous commentaries, are no longer accessible at the GenomeWeb site, but mine can be viewed at www.kineticaonline.ca in the Blog Comments section.

1. Lazy Snobs and Conflict of Interest (1/29/2010). http://www.genomeweb.com/blog/lazy-snobs-and-conflict-interest
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7. Creatures of the Deep Provide Insight into Diabetes (3/23/2010). http://www.genomeweb.com/blog/creatures-deep-provide-insight-diabetes
8. Arguing Over the Epigenome (3/31/2010). http://www.genomeweb.com/blog/arguing-over-epigenome
9. Rocket Scientists, Brain Surgeons, and All That (4/15/2010). http://cdnwww.genomeweb.com/blog/rocket-scientists-brain-surgeons-and-all
10. Paul Nurse on Funding (4/26/2010). http://www.genomeweb.com/blog/paul-nurse-funding
11. Free Personal Genome, with a Catch (4/27/2010). http://www.genomeweb.com/blog/free-personal-genome-catch

12. Study: Discoveries in Non-Human Species Could Directly Benefit Man (4/28/2010). http://www.genomeweb.com/blog/study-discoveries-non-human-species-could-directly-benefit-man
13. Oh, the Vanity (5/3/2010). http://www.genomeweb.com/blog/oh-vanity
14. Because That Would Make Too Much Sense (5/5/2010). http://www.genomeweb.com/blog/because-would-make-too-much-sense
15. Letting Go of the Details (5/10/2010). http://www.genomeweb.com/blog/letting-go-details
16. HIV Makes Music (5/13/2010). http://www.genomeweb.com/blog/hiv-makes-music
17. The Changing Roles of 'The Sequencers' (5/17/2010). http://cdnwww.genomeweb.com/blog/changing-roles-sequencers
18. 'Overstepping Your Authority' With Online Comments? (5/21/2010). http://www.genomeweb.com/blog/careers-overstepping-your-authority-online-comments
19. Why Craig Venter Isn't Actually God (5/28/2010). http://www.genomeweb.com/blog/why-craig-venter-isnt-actually-god
20. Quality vs. Quantity (6/3/2010). http://www.genomeweb.com/blog/quality-vs-quantity
21. GSA: 'Cardinal' Organisms to Human Biology (6/14/2010). http://www.genomeweb.com/blog/gsa-cardinal-organisms-human-biology
22. Small Prize, Big Question (6/18/2010). http://cdnwww.genomeweb.com/blog/small-prize-big-question
23. The Genome and the Economy (6/18/2010). http://www.genomeweb.com/blog/genome-and-economy
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27. What About Hedgehog, Buttonhead, and Bride of Sevenless? (7/8/2010). http://www.genomeweb.com/blog/what-about-hedgehog-buttonhead-and-bride-sevenless
28. The Sound of Genetics (7/12/2010). http://www.genomeweb.com/blog/sound-genetics
29. What to Do About Review (7/12/2010). http://www.genomeweb.com/blog/what-do-about-review
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38. Planning, Precision, and Profit Margins (8/11/2010). http://www.genomeweb.com/blog/planning-precision-and-profit-margins
39. Francis Collins' Funding Problem (8/13/2010). http://www.genomeweb.com/blog/francis-collins-funding-problem
40. Make Way (8/16/2010). http://www.genomeweb.com/blog/make-way
41. A Good Biomarker Is Hard to Find (8/17/2010). http://www.genomeweb.com/blog/good-biomarker-hard-find
42. Dissecting DIY Letters of Rec (8/17/2010). http://www.genomeweb.com/blog/dissecting-diy-letters-rec
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45. The Genome of Sitting Bull (8/23/2010). http://www.genomeweb.com/blog/genome-sitting-bull

46. Six Degrees of Scientific Misconduct (8/30/2010). http://www.genomeweb.com/blog/six-degrees-scientific-misconduct
47. The 'Arbimagical' Goal of the $1,000 Genome (8/30/2010). http://www.genomeweb.com/blog/arbimagical-goal-1000-genome
48. A Dispassionate Look at Gene Patenting (8/31/2010). http://www.genomeweb.com/blog/dispassionate-look-gene-patenting
49. Do We Really Need Posters? (8/31/2010). http://www.genomeweb.com/blog/do-we-really-need-posters
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51. 'How Not to Get a Postdoc' (9/2/2010). http://www.genomeweb.com/blog/careers-how-not-get-postdoc
52. Craig Venter, "Hopeless Businessman" (9/6/2010). http://www.genomeweb.com/blog/craig-venter-hopeless-businessman
53. It Was the Best of Times, It Was the Worst of Times... (9/8/2010). http://www.genomeweb.com/blog/it-was-best-times-it-was-worst-times
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55. Suggestions for Drug Approvals (9/14/2010). http://cdnwww.genomeweb.com/blog/suggestions-drug-approvals
56. George Williams Dies (9/16/2010). http://www.genomeweb.com/blog/george-williams-dies
57. The Money of Sequencing (9/16/2010). http://www.genomeweb.com/blog/money-sequencing
58. Systems Biology Meets 'Real' Biology (9/17/2010). http://www.genomeweb.com/blog/systems-biology-meets-real-biology
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61. Early-Warning DNA Sequencing System (9/21/2010). http://www.genomeweb.com/blog/early-warning-dna-sequencing-system
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ix. MEDIA INTERVIEWS

1. Can We Map the Brain? (21/2/2013). To the Point with Warren Olney. On National Public Radio KCRW. Topic - President Obama wants to do for the human brain what the Human Genome Project did for Genetics. But even scientists backing the idea concede that "mapping the brain" is orders of magnitude more complex. How should it be funded? Is it possible? Would it give scientists powers

nobody wants them to have? Guests: John Markoff: New York Times, @markoff; Terrence Sejnowski: Salk Institute, @sejnowski; Steven Pelech: Kinexus Bioinformatics Corporation; Simon Tripp: Battelle Technology Partnership Practice, @battelle.
http://www.kcrw.com/news/programs/tp/tp130221can_we_map_the_brain

2. The Evolution of Life and Kinases. (7/3/2016). Interview on Round House Radio in Vancouver with Kirk LaPointe. bit.ly/1LM0HYR
3. Overview of Kinexus Bioinformatics Corporation and the NDR ALS Biomarker Project for Neurodegenerative Disease Research (NDR), Inc. Posted on You-tube on January 15, 2021.https://youtu.be/zGyReyoWJmk
4. COVID-19 and vaccinations (6/2021). Doctor Talks with host Wayne Peters and "What's Up Canada." https://www.facebook.com/WhatsUpCanadians/videos/1392691891123832/
5. Canadian doctors who speak out are being attacked but will still speak & stand up for our children (16/7/2021). Take Action Canada. Panel discussion with host Didi Vergados and Drs. Steven Pelech, Charles Hoffe, Francis Christian, Mark Trozzi, Paul Alexander and Stephen Malthouse. https://www.bitchute.com/video/f0do2DOXG4x9/
6. Dr. Steven Pelech – ProVax Scientist and UBC Professor Speaks Out (27/7/21). Children's Health Defense Canada. Interview with Sherry Strong, Alberta Provincial Director of Children's Health Defense Canada. https://rumble.com/vkepmv-dr.-steven-pellech-provax-scientist-and-ubc-professor-speaks-out.html
7. Medical and Scientific Expert Panel (29/7/2021) Canadian Peoples Union. NFP. Interviews with host Nicole Lebrasseur and Drs. Steven Pelech, Ira Bernstein, Harvey Risch, Howard Tenenbaum, Bonnie Mallard and Paul Alexander.
https://www.facebook.com/CPUFREEDOM2017/videos/1475008056199105
8. Doctors Talking Variants (9/8/2021) Doctor Talks with host Wayne Peters and "What's Up Canada." Panel discussions with Drs. Steven Pelech, Paul Alexander and Harvey Risch.
https://www.facebook.com/642959389451042/videos/199723008704299
9. Professor Steven Pelech (30/8/2021) Shawn Newman Podcast Ep. 197 (Lloydminister Alberta/Saskatchewan) https://anchor.fm/shaun-newman/episodes/Ep--197---Professor-Steven-Pelech-e16kiua/a-a6edme0
10. 75th Anniversary of the Nuremberg Trials. Vancouver Art Gallery Plaza (1/8/2021). Organized by Common Ground.
11. Universities in the Time of Covid and Vaccine Mandates (13/10/2021). Civitas Canada with True North podcast with host Lindsay Shepard and Drs. Steven Pelech, Julie Ponesse, Allison Pejovic and Benjamin Gabbay. https://www.facebook.com/watch/?v=222043673325034
12. Dr. Steven Pelech Science or Fear Vaccine Mandates UBC (28/10/2021). UBC Students for Freedom of Expression. https://peoplesworldwar.com/dr-steven-pelech-science-or-fear-vaccine-mandates-ubc/

13. Natural Immunity Part 1. The Hill with MP Dean Alliston (21/10/2021). Embed.vhx.tv show with host MP Dean Alliston and Dr. Steven Pelech and Niel Karrow. https://embed.vhx.tv/videos/1827963?autoplay=1&api=1&authorization=VRxgQxQ3wjPpzGtx2531WkyZ3dgtQwR9&color=9E8959&title=0&sharing=1#

14. Natural Immunity Part 2. The Hill with MP Dean Alliston (21/10/2021). Embed.vhx.tv show with host MP Dean Alliston and Dr. Steven Pelech and Niel Karrow. https://embed.vhx.tv/videos/1838887?autoplay=1&api=1&authorization=VRxgQxQ3wjPpzGtx2531WkyZ3dgtQwR9&color=9E8959&title=0&sharing=1#

15. A Deep Dive into the Real Facts about Natural Immunity: Immunologist Dr. Steven Pelech (4/11/2021). Strong and Free Canada podcast with host Will Dove. https://strongandfreecanada.org/vlog/7646/

16. Dr. Steven Pelech, Ph.D. – The Missing Science that You Need to Know About Antibody Immunity, with Dr. Michael Thiessen Liberty Coalition (25/11/2021) Canada Podcast. https://tv.gab.com/channel/libertycoalitioncanada/view/dr-steven-pelech-phd-the-missing-61de3eb7bedad6c2ac1bb847

17. The Griffin Talks with Dr. Steven Pelech (23/12/2021). With Dr. Bruce Girdler of Novometrix Podcast. https://www.youtube.com/watch?v=QPCKE5JeKMA

18. The Pfizer Inoculation for COVID-19 – More Harm than Good – Co-created with Deanna McLeod, Amy McConnell, Steven Pelech and Byram Bridle (14/12/2021) Canadian Covid Care Alliance. https://www.canadiancovidcarealliance.org/media-resources/the-pfizer-inoculations-for-covid-19-more-harm-than-good-2/ This video had over 1.3 million views on Rumble.

19. Dr. Steven Pelech – UBC professor on COVID shots. Students Against Mandates interview in December 2021 (12/2021) https://rumble.com/vwsinp-dr.-steven-pelech-full-interview-dec-2021.html?mref=7ju1&mrefc=5

20. Dr. Steven Pelech explains why thousands want Canada to stop COVID-19 shots for pregnant women and children. Interview with Drea Humphrey of Rebel News (5/1/2022). https://www.rebelnews.com/dr_steven_pelech_petition_canada_stop_covid-19_shots_for_pregnant_women_and_children

21. Should you vaccinate your children? An interview with BC radio personality Kid Carson with Dr. Steven Pelech (5/3/2022). https://podcasts.apple.com/si/podcast/16-should-you-vaccinate-your-children/id1506974121?i=1000552984530

22. Masking: Following the Science. Episode 2. Interview with Teen Talks Freedom with Dr. Sarah Musavi (11/5/2022). https://www.youtube.com/watch?v=OBhrL9EK8Os

23. Citizens' Hearing June 2022. Examining Canada's COVID-19 response – Natural immunity. An independent inquiry into Canada's response to COVID-19 held in Toronto, June 22-24, 2022. (22/6/2022) Day 1. 2 hours 7 minutes to 2 hours 31 minutes in second video for Pelech testimony. https://vantagevenues.zoom.us/rec/play/YqWrScCmTrGnGHvqjHaqIlhH1a_IpjNVDdWQ_dyBktDaCusRVbUeyd9DVOxpOknv9FoZO_A0r4dJ2g8p.6tpCs8bth4qEi2Ct?_x_zm_rhtaid=999&_x_zm_rtaid=stLONZc-

RP68tjckDufsnA.1655939403378.4a1d6ad726688f0f363c07c24a2f1eae&autoplay=true&continueMode=true&startTime=1655919870000

24. Vaccine Mandates: Science or Fear? Dr. Steven Pelech. Walnut Grove Freedom Rising - Quo Vadis TV – Langley, B.C. Lecture (23/6/2022) https://rumble.com/v1i9bpv-vaccine-mandates-science-or-fear-.html
https://www.canadiancovidcarealliance.org/media-resources/dr-pelech-vaccine-mandates-science-or-fear/

25. Comparing Natural Immunity to Vaccine-Induced Immunity. Interview with Dr. Julie Ponesse (27/6/2022) (https://rumble.com/v1a5oej-comparing-natural-immunity-to-vaccine-induced-immunity-dr.-steven-pelech-an.html)

26. Insights on the COVID-19 pandemic and vaccine with Dr. Steven Pelech of UBC. A Biblical Frame: Current Events in Perspective. Panel discussion with Dr. Ed Gerber, Dr. Jens Zimmermann, Dr. Douglas Farrow, and Ivan DeSilva (7/11/2022). https://abiblicalframe.substack.com/

27. It's time to stop the shots. Co-created with Deanna McLeod, Amy McConnell, Steven Pelech and Byram Bridle (14/7/2022) Canadian Covid Care Alliance https://rumble.com/v1cc9ud-stop-the-shots.html?mref=7ju1&mrefc=3 This video had over 40,000 views on Rumble.

28. UBC prof of Medicine Stephen Pelech speaks out on COVID immunity in vaccinated vs unvaccinated. Interview with Maryann Pousette Gebauer as part of the MaryAnn and the Professor series (7/22/2022). https://www.bitchute.com/video/4UNQCMFOHA12/ and
https://www.bitchute.com/video/C9Kuk1CWCGQk/

29. Interview with Dr. Steven Pelech on natural immunity, COVID-19 vaccines, masking and other public health measures. Interview with CANSEL and Rachel Becher (7/26/2022).
https://cansef.ca/interviews/interview-with-dr-steven-pelech/

30. Immunity to SARS-CoV-2 – Round Table w/ Drs. Steven Pelech and James Lyons-Weiler. Interview with Liam Sturgess, Mathew Crawford and Jame Lyons-Weiler as part of the Rounding the Earth series (8/1/2022). https://rumble.com/v1efue7-immunity-to-sars-cov-2-round-table-w-drs.-steven-pelech-and-james-lyons-wei.html

31. Dr. Steven Pelech – What you should know about the vaccine. An interview with BC radio personality Kid Carson (2/9/2022). https://www.kidcarson.com/71-dr-steven-pelech-what-you-should-know-about-the-vaccine/

32. What's better, natural or COVID-19 vaccine induced immunity? What does SARS-CoV-2 antibody testing show? Youth and Families with Dr. Sara Masavi (19/9/2022) (https://www.youtube.com/watch?v=QF68pO9vfpE).

33. Prevalence of natural and COVID-19 vaccine induced immunity: What does SARS-CoV-2 antibody testing show? Conference on Idaho Victims of Pandemic Policy and Law. (26/9/2022). This was covered Epoch times, Stew Peters, gateway pundit, Dr. Paul Alexander substack.
https://www.theepochtimes.com/victims-of-pandemic-policy-law_4753445.html
https://rumble.com/v1llpah-live-hearing-vaccine-injured-speak-out-stew-peters-and-vaxx-injured-testify.html

34. Natural immunity … Science or science fiction? Part 1 and Part 2. White Rock, B.C. White Rock SDA Church (1/10/2022). https://livestream.com/whiterocksdachurch/events/9259494/videos/233136255

35. Jessica Rose, Ph.D. and Steven Pelech, Ph.D. – Antibody deception. Jessica's Universe - CHD-TV (28/10/2022). www.rumble.com/v1qbrwd-good-morning-chd-episode-165-antibody-deception-with-steven-pelech-ph.d.html?mref=6zof&mrefc=2

36. Jessica Rose, Steven Pelech and Bernadette Pajer – It's all about the spike - CHD-TV (1/11/2022). https://live.childrenshealthdefense.org/chd-tv/shows/an-informed-life-radio-with-bernadette-pajer/its-all-about-that-spike-with-jessica-rose-phd--steven-pelech-phd/

37. Steven Pelech and Nathan Barrett – Accountability…Class action certification hearings. (28/11/22). https://www.instagram.com/reel/ClnZRN9LZn2/?igshid=OTRmMjhlYjM%3D

38. Live with Steven Pelech and Laura-Lynn Tyler-Thompson (13/1/23). https://www.lauralynn.tv/2023/01/live-with-dr-steven-pelech.html

39. The crumbling case for COVID-19 vaccination. White Rock, B.C. White Rock SDA Church (4/2/2023). https://livestream.com/whiterocksdachurch/events/9259494/videos/234894719

40. Dr. Steven Pelech and Controversial Topics. Interview with Maryann Pousette Gebauer as part of the MaryAnn and the Professor series (4/8/2023). https://www.bitchute.com/video/qlPJGDIn1Pfe/.

41. The COVID-19 Pandemic…What Really Happened. Testimony at the National Citizen's Inquiry in Canada's COVID-19 Response (5/3/2023). https://rumble.com/v2m3z3s-ubc-professor-dr-steven-pelech-gives-presentation-on-the-virus-and-vaccine-.html

42. Live interview with Drs. Chris Shaw, Charles Hoffe and Steven Malthouse (5/12/2023. https://live.childrenshealthdefense.org/chd-tv/shows/good-morning-chd/canadian-doctors-testify/

x. TRAINING VIDEOS

1. Kinex KAM-850 Antibody Microarray Kit Components – Directed, scripted and designed by Steven Pelech. Starring Catherine Sutter. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=JtMn-Gk0q_4&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k&index=1
2. Stage 1: Preparation of Lysates from Cultured Cells for Proteomics Analyses – Directed, scripted and designed by Steven Pelech. Starring Dominik Sommerfeld. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=0_YdxuOdGhU&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k&index=2

3. Stage 2: Measurement of Protein Concentrations with the Bradford Protein Assay. Directed, scripted and designed by Steven Pelech. Starring Shenshen Lai. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=TAMrj0Z9FOk&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k&index=3
4. Stage 3: Dye Labelling Cell and Tissue Lysates for the Kinex™ KAM Antibody Microarray. Directed, scripted and designed by Steven Pelech. Starring Jane Shi. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=3sMaRnAC7-4&index=4&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k
5. Stage 4: Incubation of the Kinex™ KAM Antibody Microarray with Dye-Labelled Lysate Protein. Directed and designed by Steven Pelech, and scripted and designed by Hong Zhang and Steven Pelech. Starring Jane Shi. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=LcuQ-1CYJrw&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k&index=5
6. Stage 5: Kinex™ KAM Antibody Microarray Scanning and Quantitation. Directed, scripted and designed by Steven Pelech. Starring Jane Shi and Winnie So. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=wBf0t4xhV5g

xi. EXPERT REPORTS FOR COURT CASES

Over the last year, I have been asked to prepare, expert reports with respect to natural immunity and COVID-19 vaccines for several court and arbitration cases in Canada, South Africa and Ireland. These are usually sworn and notarized documents, and in several cases I have undergone cross-examination in Canadian courts. This is a listing of many of the court cases that I have served in.

1.	COURT FILE NUMBER	210600780
	COURT	COURT OF QUEEN'S BENCH OF ALBERTA
	JUDICIAL CENTRE	LETHBRIDGE
	APPLICANT	HAYLEY NASSICHUK-DEAN
	RESPONDENT	UNIVERSITY OF LETHBRIDGE
2.	COURT FILE NUMBER	T-1694-21
	COURT	FEDERAL COURT OF CANADA (Trial Division)
	APPLICANT	DAVID LAVERGNE-POITRAS
	RESPONDENTS	ATTORNEY GENERAL OF CANADA (Minister of Public Services and Procurement) – and – PMG TECHNOLOGIES INC.

3.	COURT FILE NUMBER	2101-13202
	COURT	COURT OF QUEEN'S BENCH OF ALBERTA
	JUDICIAL CENTRE	CALGARY
	APPLICANTS	DR. ERIC T. PAYNE, DR. JOANNE J. MOSER, DR. DAVID W. L. LOEWEN and DR. GREGORY CHAN
	RESPONDENTS	ALBERTA HEALTH SERVICES, DR. VERNA YIU IN HER CAPACITY AS CHIEF EXECUTIVE OFFICER OF ALBERTA HEALTH SERVICES, DR. JOHN T. CHMELICEK IN HIS CAPACITY AS POST GRADUATE PROGRAM DIRECTOR, DEPARTMENT OF FAMILY MEDICINE, UNIVERSITY OF ALBERTA -and- THE UNIVERSITY OF ALBERTA
4.	COURT FILE NUMBER	CV-21-00670360-0000
	COURT	SUPERIOR COURT OF JUSTICE ONTARIO
	APPLICANTS	SARAH HARJEE, EVAN KRAAYENBRINK, HIBAH AOUN, SARAH LAMB, SAM SABOURIN, JACKIE RAMNAUTH, MARK MCDONOUGH -and- LINDA MCDONOUGH
	RESPONDENT	HER MAJESTY THE QUEEN IN RIGHT OF THE PROVINCE OF ONTARIO
5.	COURT FILE NUMBER	FDF-443-19
	COURT	COURT OF QUEEN'S BENCH OF NEW BRUNSWICK
	JUDICIAL CENTRE	FAMILY DIVISION JUDICIAL DISTRICT OF FREDERICTON
	APPLICANT	VICTORIA LYNN MITHAM
	RESPONDENT	BRADLEY SCOTT FOLLETT
6.	COURT FILE NUMBER	72/2022
	COURT	HIGH COURT OF SOUTH AFRICA
	JUDICIAL CENTRE	FREE STATE DIVISION, HELD AT BLOEMFONTEIN
	APPLICANT	SOLIDARITY obo MEMBERS, SOLIDARITY YOUTH Obo MEMBERS, JOANNA STANDER, SHANIQUE PIENAAR, ALICE FLORENCE MARINA STANDER - and - ANNELI BOTHA
	RESPONDENTS	CHAIRMAN OF THE COUNCIL OF THE UNIVERSITY OF THE FREE STATE– and – THE UNIVERSITY OF THE FREE STATE

7.	COURT FILE NUMBER	C.A.C.V.3903of202 C.A.C.V.3904of2021 C.A.C.V.3908of2021
	COURT	COURT OF APPEAL FOR SASKATCHEWAN ON APPEAL FROM THE QUEEN'S BENCH (FAMILY LAW DIVISION)
	JUDICIAL CENTRE	JUDICIAL CENTRE OF SASKATOON DIV. No. 625 of 2012
	APPLICANT	OLENA MYKOLAYIVNA SCHEMENAUER
	RESPONDENT	EVAN JOSEPH SCHEMENAUER
8.	COURT FILE NUMBER	FD 19-01-22922
	COURT	COURT OF QUEEN'S BENCH (Family Division)
	JUDICIAL CENTRE	WINNIPEG CENTRE
	APPLICANT	JORDAN SARAH CURÉ
	RESPONDENT	KENNETH PETER TYSON CURÉ
9.	COURT FILE NUMBER	E59176
	COURT	SUPREME COURT OF BRITISH COLUMBIA
	JUDICIAL CENTRE	NEW WESTMINISTER
	APPLICANT	VICTORIA LARA DRAPER AKA VICTORIA LARA DRAPER-SMITH
	RESPONDENT	MATTHEW LAWRENCE NEALE SMITH
10.	COURT FILE NUMBER	E17315
	COURT	SUPREME COURT OF BRITISH COLUMBIA
	JUDICIAL CENTRE	CHILLIWACK REGISTRY
	APPLICANT	DALE JAMES HOOGENDOORN
	RESPONDENT	KATIE NADINE HOOGENDOORN
11.	COURT FILE NUMBER	2022/1456 P
	COURT	HIGH COURT OF IRELAND
	APPLICANTS	DAVID EGAN AND SHARON BROWNE AND EMMANUEL LAVERY
	RESPONDENTS	MINISTER FOR HEALTH, AN TAOISEACH, AND HSE
12.	ARBITRATION	
	EMPLOYER	HUMBER RIVER HOSPITAL
	UNION	NATIONAL ORGANIZED WORKERS UNION
		Grievances: NOWU Policy Service #170,2021 (All Bargaining Units) Covid Directive 6, NOWU Policy Service #01,2022 (All Bargaining Units) Covid Policy, 2022-NOWU-Clerical-55-HRH; Grievance of Gail Ackie

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No.: **CV-22-0069-1880-0000**

Dr. BYRAM BRIDLE -and- David Fisman et al

Plaintiffs Defendants

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ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDING COMMENCED AT TORONTO

AFFIDAVIT OF DR. STEVEN PELECH

Name: ROCCO GALATI LAW FIRM
PROFESSIONAL CORPORATION
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Lawyer for the Plaintiff

TAB 9

Court File #: CV-22-0069-1880-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

AFFIDAVIT OF DR. PIERRE MAJOR

I, Dr. Pierre Major, of the City of Hamilton, in the Province of Ontario, MAKE OATH AND SAY:

1. I am a medical oncologist and Chair of the Colorectal Cancer Canada Medical Advisory Board at the Hamilton Regional Cancer Center. I am also an Associate Professor of Oncology at McMaster University and a research partner of the Plaintiff, and as such, have knowledge of the matters contained in this Affidavit.

Professional, Academic and Research background

2. I am a specialist in medicine and medical oncology. My research training is in experimental therapeutics. I have extensive publications in both preclinical laboratory work and clinical studies. I have worked as a translational researcher at Harvard and McGill universities. Translational research seeks to produce more meaningful, applicable results that directly benefit human health. The goal of translational research is to translate (move) basic science discoveries more quickly and efficiently into practice.

3. I have worked in clinical developments at Syntax (now Roche) and Miles (now Bayer). I am very conversant with the regulatory requirements for bringing medicines to the clinic to treat patients. In my current position at McMaster University and the Juravinski Cancer Center I conduct translational research to bring new therapies in the area of prostate cancer. I have used viruses to treat cancer (oncolytic viruses). Attached as **Exhibit A** is a copy of my CV.

Research Collaboration on cancer and COVID-19 vaccines with Dr. Bridle

4. I have had productive scientific collaborations with Dr. Bridle on cancer research and COVID-19 research. This is demonstrated by the following six published peer-reviewed scientific papers that we co-authored, attached as **Exhibit B**.
5. My initial collaboration with Dr Bridle was in the area of oncolytic viruses.
6. Dr. Bridle is an ideal and exceptional candidate for my research collaboration because of his scientific expertise in the fields of virology, immunology and cancer biology; research skills as a top tier reviewer; and his publication record. Of major importance is that he has been granted a U.S. patent for his work with oncolytic viruses, a key element for eventual venture capital funding.
7. He is also an expert in animal models of cancer and in immunology.
8. These factors are optimal for quickly and efficiently bringing new therapies to patients.
9. Patients with advanced cancer are at greater risk of severe morbidity and mortality from COVID-19.
10. Beginning in January 2020 I began collaborating with Dr. Bridle on a viral vectored vaccine for COVID-19. We used the same virus we had used for cancer work. We selected nasal vaccination as the preferred route and simplest method of vaccination.

Testing in hamsters and primates showed the vaccine was effective at reducing morbidity and preventing mortality but not preventing infection. This is the shortcoming of all available COVID 19 vaccines: they do not prevent the infection or the spread of infection. We decided to use a different pharmaceutical formulation to address this major shortcoming.

11. Dr. Bridle and I are co-inventors of a COVID-19 vaccine that showed promise in our pre-clinical research. Over the past three years, Dr. Bridle and I have had multiple opportunities to engage in national and international research collaborations in this area.

12. Dr. Bridle is also an ideal collaborator, especially for complex projects that involve multiple labs and multiple institutions, due to his wide-ranging expertise spanning the fields of immunology, virology, and cancer biology. In particular, the research team managed by Dr. Bridle is known for their technical sophistication and the integrity of their results. Dr. Bridle emphasizes the importance of being able to repeat scientific findings and he insists on only reporting results that he is confident represent the biological reality rather than some kind of technical artifact.

13. Dr. Bridle's U.S. patent on the use of viruses for cancer therapy covers many viruses including NDV. ***It is a very noteworthy accomplishment to have been granted a U.S. patent.*** Non-American applicants have a very low success rate in the U.S. where the patent office gives priority review to U.S. applicants and is known to be much more demanding of foreign applicants. This is a strong indication of his excellence and integrity as a scientist.

14. It has always been an honour to work with Dr. Bridle because of his unwavering integrity and scientific precision. Over the years I have also come to appreciate his gregarious personality and collaborative attitude.

Cancer research dependent on third party funding

15. Cancer research is primarily funded by agencies that raise their funds via donations from the public, such as the Canadian Cancer Society, Terry Fox Research Institute, and Cancer Research Society. Cancer research is also funded by the federal government-run Canadian Institutes of Health Research.

16. Funding applications require a substantial amount of work. For example, it typically takes more than 160 hours to write a competitive grant application for the Canadian Institutes of Health Research.

17. Dr. Bridle, in the past, successfully obtained funds from Canadian Cancer Society, Terry Fox Research Institute, Canadian Breast Cancer Foundation, Pet Trust Fund, the Cancer Research Society, and private donations in the past ***due to his reputation as a scientist with integrity.***

Importance of Dr. Bridle's cancer research

18. Dr. Bridle's cancer research has advanced the fundamental understanding of cancer biology. It has also helped propel oncolytic virotherapies into clinical research, including having one of his treatment strategies tested in four human clinical trials. Dr. Bridle has also made substantial contributions to the field of cancer vaccinology. Moreover, through his use of viruses as vectors for cancer therapies, he has also made contributions to a basic understanding of antiviral immune responses.

19. Dr. Bridle's recognition as a leader in these areas of research has also been demonstrated by him being invited to serve on grant review panels for the Canadian Institutes of Health Research (for which he has received multiple honours as a top-tier reviewer and was admitted to their prestigious college of reviewers), Cancer Research Society, and Prostate Cancer Canada.

Harm to Dr. Bridle's reputation

20. I have read the affidavit of Dr. Fisman filed in this Motion. I also have direct knowledge of how Dr. Bridle's cancer and COVID19 research was destroyed by the online and social media reaction of the defendants to the brief radio interview with journalist Alex Pierson on May 28, 2021 which has ruined Dr. Bridle's reputation as a scientist.
21. Dr. Fisman is a medical doctor, not a vaccinologist. He was also a member of the Ontario Science Table and a prominent media commentator on COVID-19.
22. He refers to Dr. Bridle as conveying "misinformation", "distorting scientific evidence", making claims that are "poppycock"; "biologically implausible"; "not data based" and "not evidence based" on COVID19 vaccines. These allegations are false.
23. Dr. Fisman mocking and vilifying Dr. Bridle on social media, with the above phrases, and as a "quack": by referring to and promoting a website that impersonates him with an image of a duck, has damaged Dr. Bridle's impeccable reputation as scientist.
24. A scientist's reputation is essential in obtaining funding for research. One of the core aspects of the review process for a grant application is evaluation of the quality of the researcher.
25. Grant funding, especially in the field of cancer research, is very competitive, with funding success rates often being lass than ten percent. This means that any negative points raised

during the review process are almost certain to cause an application to not be funded. Grant review panels typically include many experts from across Canada. Two or three primary reviewers are usually held responsible for reading a grant application in detail. Typically, they will establish a mean score for the application. Their discussions are done behind closed doors. Importantly, other reviewers contribute equally to the final score, but they have the option of lowering their score relative to what the primary reviewers agreed upon.

26. So, national-level defamation of a scientist's character would be expected to have a substantially negative impact on the potential for their grant applications being funded.

Harm to research on cancer and viral vectored vaccines

27. The damage to Dr. Bridle's reputation has halted his research collaboration on the oncolytic virus and the COVID-19 vaccines with me.

28. I was forced to seek foreign collaboration outside Canada to continue the research. This a loss to Canadian cancer research.

29. The damage to Dr. Bridle's reputation has also tainted and harmed me. For example, the vector virus was withheld by another co-inventor at the University of Guelph who blocked the ability of Dr. Bridle and I to pursue our collaborative research opportunities. This meant that we could not manufacture research-grade stocks to provide our collaborators. Without the ability to demonstrate the feasibility of the research, our potential collaborations were nullified.

30. Moreover, I have been shunned by previous collaborators at the University of Guelph and am forced to find other collaborators. This has delayed my COVID-19 research project for years and voided the funds I expended through Revenue Canada Scientific Exploitation and Development (SRED) tax credit. This is a substantial financial loss to me as a direct

result of the personal attacks on Dr. Bridle's integrity, and in particular, that he is "spreading misinformation".

Irreparable Harm to future funding for cancer research

31. The personal attacks in social media and, in particular, the allegation of "anti-vaxxer" against Dr. Bridle, who is a vaccinologist, has destroyed his reputation with funders.
32. For this reason alone, any funding application submitted by Dr. Bridle will likely be rejected outright. So, to invest many weeks of work into each application would not be a valuable use of time until Dr. Bridle's reputation is cleared.
33. Because of the tarnishing of his reputation, Dr. Bridle and I have had to abandon our many research projects together.
34. Dr. Bridle's unique combined expertise in virology, immunology (with a focus on vaccinology and antiviral immunity), and cancer biology, makes him the perfect candidate to partner with. This is a rare qualification that is being wasted due to the reputational harm.
35. I would like to continue my productive collaborations with Dr. Bridle in the field of cancer immunotherapy, which is a shared passion of ours. The only reason I cannot work with Dr. Bridle is the damage to his reputation. Otherwise, he is the ideal collaborator. As previously stated, Dr. Bridle has a U.S. patent on the use of viruses for cancer therapy. It covers many viruses. Very few Canadian scientists have U.S. patents. This is extraordinarily valuable and rare asset for a collaborator. It exemplifies Dr. Bridle's excellence in his field of expertise.
36. I am deeply disturbed and disappointed beyond description by the inability to collaborate with Dr. Bridle due to no other reason except those allegations, which in my opinion are false and without justification. Personal attacks of this vile nature have no place in

scientific discourse and discussion. It is not in the public interest to have academics and scientists lacking expertise mock, demean and insult a highly qualified expert in his field.

SWORN BEFORE ME by Pierre Major in the City of Hamilton, in the Province of Ontario, on this 29th day of November, 2023, in accordance with O. Reg. 431/20 Administering Oath or DeclarationRemotely

A Commissioner for Taking Oaths
Rocco Galati B.A.,LL.B.,LL.M.

Dr. Pierre Major

This is Exhibit "A" to the Affidavit of
Dr. Pierre Major, sworn before me on
this 29th day of November 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

Updated 2021 May 7

Pierre Major

NAME Pierre Major

ADDRESS 699 Concession Street
Hamilton
Canada, L8V 5C2

EDUCATIONAL BACKGROUND

Degrees and Diplomas

1974	MD, Medicine, University of Montreal, Montreal, Canada

Qualifications, Licensures and Certifications

1994	Corporation of Physicians of the Province of Quebec(CSPQ) Certification in Medical Oncology
1988	Active Massachusetts License
1979	FRCPC(Internal Medicine), Royal College of Physicians and Surgeons of Canada
1979	Corporation of Physicians of the Province of Quebec(CSPQ) Certification in Internal Medicine
1978	DES(Engineering Science), University of Montreal, Montreal, Canada
1975	License, Medical Council of Canada

Research Training

1982 - 1983	Assistant Professor, Medicine, Harvard Medical School, Boston
1980 - 1982	Experimental Therapeutics, Medicine & Pharmacology, Harvard Medical School, Boston, Supervisor: Instructor
1978 - 1980	Fellow, Medical Oncology and Pharmacology, Dana Farber Cancer Centre, Harvard Medical School, Boston, United States

1978 - 1980	Fellow, Medicine, Peter Bent Brigham Hospital, Boston, Dana-Farber Cancer Institute, Boston
1978 - 1980	Fellow in Medicine, Harvard Medical School, Boston
1977 - 1978	Fellow, Haematology, University of Montreal, Notre-Dame Hospital

Other Specialized Training

2007 - 2008	Senior Adult Oncology, Mofitt Cancer Center, University of South Florida, Tampa, Florida, United States
1976 - 1977	Resident III in Medicine, University of Montreal, Montreal
1975 - 1976	Resident II in Medicine, Univeersity of Montreal, Montreal
1974 - 1975	Intern in Medicine, University of Montreal

CURRENT STATUS AT MCMASTER

2006 - present	Associate Professor, Oncology, CAWAR, Health Sciences, McMaster University

PROFESSIONAL ORGANIZATIONS

American Society of Clinical Oncology, Member

American Association for Cancer Research, Member

American College of Clinical Pharmacology, Member

American Association for the Advancement of Science, Member

American College of Physicians, Member

Fellow of the Royal College of Physicians of Canada, F.R.C.P., Fellow

EMPLOYMENT HISTORY

University Appointments

2006 - present	Associate Professor, Oncology, CAWAR, Faculty of Health Sciences, McMaster University
2000 - 2006	Associate Professor, Medicine, CAWAR, Faculty of Health Sciences, McMaster University
1999 - 2000	Associate Professor, Medicine, Special, Faculty of Health Sciences, McMaster University

1997 - 1999	Associate Professor, Medicine, Contractually Limited, Faculty of Health Sciences, McMaster University

Academic

1987 - 1996	Adjunct Professor, McGill University, Montreal, Department of Medicine
1983 - 1987	Asst. Professor of Medicine, University Full-time, McGill University, Montreal, McGill Cancer Centre
1983 - 1987	Associate Member, Pharmacology and Therapeutics, McGill University, Montreal
1982 - 1983	Asst. Professor of Medicine, Harvard Medical School
1981 - 1982	Junior Associate in Medicine, Brigham and Women's Hospital, Boston
1980 - 1982	Instructor in Medicine, Harvard Medical School

Administrative

2001 - 2002	Co-Chair, Juravinski Cancer Centre, Disease Site Team Council
1997 - 2001	Chairman, Juravinski Cancer Centre, Hamilton, Ontario, Gastrointestinal (GI) Oncology Group
1992 - 1996	Vice-President, Bayer Inc., Medical & Scientific Affairs, Etobicoke, Ontario
1991 - 1992	Vice-President, Scientific Affairs, Syntex Inc. Mississauga, Ontario
1990	Director, Scientific Affairs, Syntex Inc, Mississauga, Ontario
1988 - 1990	Vice-President, Bio-Research Laboratories, Senneville, Quebec, Clinical Research Division
1987 - 1988	Director of Clinical Pharmacology and Medical Director, Bio-Research Laboratories, Senneville, Quebec

Clinical

1996 - present	Medical Oncologist, Juravinski Cancer Centre, Hamilton, Ontario
1983 - 1998	Assistant Physician, Royal Victoria Hospital, Montreal
1987 - 1990	Affiliate Physician, Montreal General Hospital
1983 - 1987	Assistant Physician, Montreal General Hospital
1982 - 1983	Associate Physician, Brigham Women's Hospital, Boston
1980 - 1983	Clinical Associate in Medicine, Dana-Farber Cancer Institute, Boston

Consulting

2004 - present	Oncology Consultant, Guelph General Hospital
1996 - present	Oncology Consultant, Cambridge Memorial Hospital

1998 - 2000	Consultant Physician, Royal Victoria, Hospital, Montreal

Training

1978 - 1980	Fellow in Medical Oncology and Pharmacology, Harvard Medical School, Boston, Dana Farber Cancer Centre
1978 - 1980	Fellow in Medicine, Dana-Farber Cancer Institute, Boston, Peter Bent Brigham Hospital, Boston
1978 - 1980	Fellow in Medicine, Harvard Medical School, Boston
1977 - 1978	Fellow in Haematology, Notre-Dame Hospital, University of Montreal
1976 - 1977	Resident III in Medicine, Hotel-Dieu Hospital, Montreal
1975 - 1976	Resident II in Medicine, Hotel-Dieu Hospital, Montreal
1974 - 1975	Intern in Medicine, University of Montreal

SCHOLARLY AND PROFESSIONAL ACTIVITIES

Editorial Boards

2006 - present	Colorectal Cancer Association Of Canada, Medical Advisory Board
2011	Chair, Medical Advisory Board
2008 - 2011	Cancer Advocacy Coalition of Canada

Grant & Personnel Committees

1996 - 2003	Grant Review Panel B, Cancer Research Society
1992 - 1995	Chairman, Bayer (Miles) CRC R&D Fund
1986 - 1988	Scientific Committee, FRSQ
1985 - 1987	Medical Advisory Board, Cancer Research Society

Executive Positions

2008 - 2010	Vice President, Medical Staff Association
2006 - 2008	Treasurer, Medical Staff Association

Journal Referee

2005 - present	Cancer

1981 - present	Cancer Research

External Grant Reviews

1998	CRS (10)
1997	CRS (15)
1996	CRS (15)
1987	FCAR (1)
1987	MRC (9)
1987	CRS (11)
1987	FRSQ (8)
1986	MRC (4)
1986	CRS(10)
1985	MRC (5)
1985	CRS (8)
1984	MRC (7)
1983	MRC (3)
1983	FCAR (3)
1983	NRC (3)

Chair

2007 - present	International Data Monitoring Committee, Austria Breast Cancer Research Group
2005 - present	Amgen, Data Monitoring Committee

Other Professional Activities

2008	John Collaci Fund Raiser
2008	Colorectal Cancer Association of Canada, Training of cancer coaches for patients with colorectal cancer
2007	Consultant (10% time allocated) to international pharmaceutical companies including: Review of global development plans, FDA Meeting preparation, Protocol reviews
2001	Guest Speaker at the Multiple Myeloma Peer Support Group – Toronto & District, Summer 2001

2001	Guest Speaker at the 2nd Annual Bernie Faloney Invitational Golf Tournament to support the Colorectal Cancer Association of Canada, Spring, 2001
1999	Advisory Board, Colorectal Cancer, Association of Canada

AREAS OF INTEREST

1. MEDICAL ONCOLOGY

Clinical

1. GASTROINTESTINAL ONCOLOGY, Breast Oncology, Geriatric Oncology

Consulting

1. Data Monitoring Committee, Amgen
2. Austrian Breast and Cancer Research Group

Research

1. cancer vaccine, oncolytic viruses

Teaching

1. medical students, residents rotating through clinics

HONOURS AND AWARDS

1991	Syntex, President's Award for Outstanding Achievement
1986	Montreal General Hospital, Stewart Award
1985	Montreal General Hospital, Stewart Award
1984	Montreal General Hospital, Stewart Award
1983	Montreal General Hospital, Stewart Award
1983	Medical Research Council of Canada, Scholar (1983 - 1987)
1980	Medical Research Council of Canada, Fellowship (1980 - 1983)
1978 - 1980	Canadian Cancer Society, McEachern Fellowship
1978	Canadian Cancer Society, McEachern Fellowship (1978 - 6/1980)
1971	Health and Welfare Canada, Research Scholarship

1971	Health & Welfare Canada, Research Scholarship
1971	Health & Welfare Canada, Health & Welfare Canada Research Scholarship
1970	Medical Research Council of Canada, Summer Undergraduate Research Scholarship

COURSES TAUGHT

Undergraduate Teaching

Physician Assistant Education Program

2012 Jul - 2019 Jun Supervisor, Elective, Interviewing, Examination and Reasoning, half-day (12)

Undergraduate Medical

2000 Jul - 2016 Jun Examiner, Observed Structured Clinical Examination, occasion (5)

2010 Jul - 2016 Jun Supervisor, Block Elective (Clinical/Reading/Research), week (22)

2012 Jul - 2014 Jun Supervisor, Elective, Visiting Student, week per student (10)

2006 Jul - 2011 Jun Supervisor, Horizontal Elective, week per student (4)

2007 Jul - 2008 Jun Assessor, Admissions, Multiple Mini Interview, weekend (1)

2007 Jul - 2008 Jun Reader, Admissions, Autobiographical Submission, year (1)

1999 Jul - 2001 Jun Student Advisor, student per year (2)

Undergraduate Medical Clerkship

2013 Jul - 2020 Jun Supervisor, Medical Subspecialties, rotation (8)

Postgraduate Teaching

Family Medicine and its subspecialties

2013 Jul - 2017 Jun Supervisor, Outpatient, clinic (22)

Internal Medicine and its subspecialties

2007 Jul - 2009 Jun Examiner, Observed Structured Clinical Examination, half-day (2)

2003 Jul - 2004 Jun Presenter, Rounds, occasion (12)

2003 Jul - 2004 Jun Supervisor, Clinical, Out-patient/Ambulatory Care, half-day (48)

2003 Jul - 2004 Jun Supervisor, Clinical, Inpatient, day (10)

1999 Jul - 2000 Jun Advisor/Mentor, resident per year (1)

1999 Jul - 2000 Jun Presenter, Academic Half-Day, occasion (3)

1999 Jul - 2000 Jun Presenter, Clinical Teaching Unit, occasion (1)

1999 Jul - 2000 Jun Presenter, Journal Club, occasion (1)

1999 Jul - 2000 Jun Supervisor, Block Elective, half-day (12)

Oncology and its subspecialties

2014 Jul - 2020 Jun Supervisor, Clinical, Inpatient, (4 weeks), month (4 weeks) (5)

2014 Jul - 2020 Jun Supervisor, Outpatient, clinic (1042)

2014 Jul - 2018 Jun Supervisor Block Elective, week (6)

2016 Jul - 2017 Jun Presenter, Academic Half Day/Core Curriculum, presentation (1)

2012 Jul - 2014 Jun Presenter, Academic Half-Day, occasion (2)

2012 Jul - 2014 Jun Supervisor, Clinical, Out-patient/Ambulatory Care, half-day (204)

2012 Jul - 2014 Jun Supervisor, Clinical, Inpatient, day (62)

2006 Jul - 2014 Jun Supervisor, Block Elective, half-day (178)

2012 Jul - 2013 Jun Supervisor, Research, Laboratory-based, week (104)

2011 Jul - 2012 Jun Supervisor, Clinical, Out-patient/Ambulatory Care, 131 half-days x 16 residents (131)

2010 Jul - 2011 Jun Supervisor, Clinical, Inpatient, 17 days
Jayson Potts/Laura Harild, December 13 - 23
Rachel VanderMeer, July 1 - 9, 2010 (17)

2010 Jul - 2011 Jun Supervisor, Clinical, Out-patient/Ambulatory Care, 70 half-days
Maria Bagovich, May 16 - 19, 2011
Jason Yu, April 11 - May 4, 2011
Jason Cheung, April 1 - May 1, 2011
Arthur Lau, March 1 - 31, 2011
Aisling O'Meara, February 1 - 28, 2011
Jayson Potts, September 1 - October 31, 2010
Amin Kay, August 24 - September 19, 2010
Karen Lumsden, July 27 - August 23, 2010
Mahraz Anjum, July 5 - 25, 2010
Elena Elimova, July 2 - August 31, 2010
Brandon Meyers, July 1 - August 31, 2010 (70)

2009 Jul - 2010 Jun Supervisor, Clinical, Inpatient, 14 days
Brandon Meyers, September 2 - 8, 2009
Brian Lee, September 2 - 8, 2009
Asma Ali, August 24 - August 31, 2009 (14)

2009 Jul - 2010 Jun Supervisor, Clinical, Out-patient/Ambulatory Care, 111 half-days
Humaid Al-Shamsi
Puja Sahni
Bryan Lee
Kosta Ioannou
Vikaash Kumar
Sadiya Kukaswadia
Raheb Elzuway
Abir Nawara
Dawn Armstrong
Sergey Pozdnyako
Dean Raso
Ravi Ramjeesingh
Blair Leonard
Aalok Kumar
Miranda Schell (111)

2008 Jul - 2009 Jun Presenter, Academic Half-Day, 2 occasions
Metastatic Colorectal Cancer, December 17, 2008
Esophageal and Gastric Cancer, November 19, 2008 (2)

2008 Jul - 2009 Jun Supervisor, Clinical, Elective (Block), 73 half-day clinics
Brandon Meyers, May 1 - 17, 2009
Rachel VanderMeer, May 8 - 31, 2009
Katalin Koller, April 1 - 30, 2009
Kimmen Quan, April 1 - 30, 2009
Lindsay Crabbe, March 1 - 31, 2009
N. Popat, March - April 2009
Waseem Sharieff, February 2 - March 1, 2009
Adrienne Penderell, February 2 - March 1, 2009
Puja Kumar, January 1 - February 1, 2009
A. Lau, January 2009
M. Mathivanan, September - October 2008 (73)

2008 Jul - 2009 Jun Supervisor, Clinical, Out-patient/Ambulatory Care, 99 half day clinics
Sabrina Allegro, May 1 - June 30, 2009
Abdullah Al-Zahrani, Oct 1 - Nov 30, 2008, Feb 2 - March 31, 2009
Sara Rask, February - March 2009
Sayeh Lavasani, December 1 - February 1, 2009
Khalid Al-Saleh, November 3 - January 1, 2009
Asma Ali, July 1 - November 2, 2008
Radhika Yelamanchilli, July 1 - September 20, 2008 (99)

2008 Jul - 2009 Jun Supervisor, Clinical, Inpatient, 20 days
Khalid Al-Saleh, March 23 - April 3, 2009
Rania Lingas, July 28 - August 8, 2008
Vikash Kumar, July 28 - August 8, 2008 (20)

2007 Jul - 2008 Jun Presenter, Academic Half-Day, 1 occasion
GI - Review of Anal and Rectal Cancer, March 12, 2008 (1)

2007 Jul - 2008 Jun Presenter, Regional Oncology Rounds, 2 occasions
Boen Markers in Cancer Metastatic to Bone, February 7, 2008
Geriatric Oncology, June 7, 2007 (2)

2007 Jul - 2008 Jun Supervisor, Clinical, Inpatient, 20 days
Aswaq Alolayan, January 28 - February 8, 2008
Radhika Yelamanchilli, August 13 - 26, 2007
V. Pavlova, August 13 - 26, 2007 (20)

2007 Jul - 2008 Jun Supervisor, Clinical, Out-patient/Ambulatory Care, 100 half day clinics
Sara Taylor, April 8 - May 7, 2008
Rania Lingas, January 2 - March 2, 2008
Sara Kuruvilla, November 1 - January 1, 2008
Sayeh Lavasani, September 4 - October 31, 2007
Ashwaq Alolayan, July 1 - September 3, 2007 (100)

2007 Jul - 2008 Jun Supervisor, Clinical, Elective (Block) 64 half-day clinics
Khuloud Nuri, June 2 - 30, 2008
Ioanna Papoutsi, May 1 - 31, 2008
Daniela Leto, April 1- 30, 2008
Vincent Tam, April 2008
I. MacDougall, March - April 2008
Bryan Lee, February 13 - March 10, 2008
K. D'Silva, January - February 2008
F. Bacchus, November - December 2007
Vikaash Kumar, September 4 - 30, 2007
Sue Richter, September 4 - 14, 2007 (64)

2005 Jul - 2007 Jun Examiner, Observed Structured Clinical Examination, half-day (2)

2006 Jul - 2007 Jun Presenter, Rounds, occasion (1)

2006 Jul - 2007 Jun Reader, Admissions, candidate (60)

2006 Jul - 2007 Jun Resource Person, Clinical Teaching Unit, occasion (4)

Other

Continuing Education

2005 Jul - 2006 Jun Speaker, occasion (5)

Additional Educational Contributions

McMaster teaching outside FHS

1986 - 1987	Pharmacology 549-221-M. Pharmacology of anti-tumour agents. McGill Medical School curriculum. (1)
1985 - 1986	Pharmacology 549-221-M. Pharmacolgoy of anti-tumour agents. McGill Medical School curriculum. (1)
1985 - 1986	Pharmacology 549-7028 (Graduate Course). Biochemical Pharmacology of anti-tumour drugs. Lectures: 10 hours Seminars: 20 hours McGill Medical School curriculum. (1)
1984 - 1985	Pharmacology 549-221-M. Pharmacologyof anti-tumour agents. McGill Medical School curriculum. (1)

SUPERVISORSHIPS

Supervisory Committees

Medical Sciences

2019 Jul - 2020 Jun Member, Supervisory, Committee, MSc, student per year (1)

RESEARCH FUNDING

Grants (Primary Investigator's name is the first name listed)

2018 Sep - 2021 Sep	Damu Tang, M. Bonert, A. Kapoor, P. Major, N. Seidah, G. Werstuck, PCSK9, a novel contributor to the development of castration resistant prostate cancer, Grant, Canadian Institute of Health Research, Research - New Project, $57,574.00
2003 Jan - present	Major, P, A randomized, double-blind, placebo-controlled, phase III study in patients with metastatic adenocarcinoma of the colon or rectum who are receiving first-line chemotherapy with oxaliplatin/5-flkuorourcil/leucovorin and PTK787/ZK 222584 or placebo, Grant, Novartis Oncology US, Clinical Trial, $350,000.00
2010 - 2014	Foley, R, Major, P, Fradet, Y, Dendritic Cell Vaccine for Prostate Cancer, Grant, OICR, Research - New Project, $484,000.00

2006 - 2010	Foely, R, Major, P, Fradet, Y, Dendritic Cell Vaccine for Prostate Cancer, Grant, CANVAC, Research - New Project, $300,000.00
2003 Jan - 2007	Major, P, A randomized, double-blind, placebo-controlled, phase III study of oxaliplatin/5-fluorouracil/leucovorin with PTK 787/ZK 222584 or placebo in patients with previously treated metastatic adenocarcinoma of the colon or rectum, Grant, Novartis Oncology US, Clinical Trial, $125,000.00
2001 Jan - 2006 Dec	Major, P, Phase II contract for early phase with emphasis on phase II studies awarded to Princess Margaret/Hamilton Regional Cancer Centre/London Regional Cancer Centre consortium., Grant, NCI-US, Clinical Trial, $5,500,000.00
2000 Jan - 2003 Dec	Major, P, The pharmacokinetics and pharmacodynamics of Zoledronic Acid in cancer patients with varying degrees of renal function, Grant, Novartis Oncology US, Clinical Trial, $104,256.00
2000 Jan - 2001 Dec	Major, P, R.Cook, Assessing the Therapeutic Effect of Aredia in Randomized Trials of Patients with Breast Cancer Metastatic to Bone. Request for funds to develop a mathematical model describing the natural history of breast cancer metastatic to bone and to analyse the effect of Aredia on the course of the disease using recently developed statistical techniques for the analysis of recurrent events, Grant, Novartis, Clinical Trial, $17,000.00
2000 Jan - 2001 Dec	Major, P, Extension Trial . An open label multicentre clinical study to evaluate the long term safety of intravenous Zometa (Zoledronate)8 mgm. in patients with metastatic bone lesions due to breast cancer or multiple myeloma, Grant, Novartis Oncology US, Clinical Trial, $24,900.00
2000 Jan - 2000 Dec	Major, P, A. Arnold, E. Chouinard,H. Hirte,R. Tozer, Extension-Zoledronate l0EA A randomized, double-blind, multicentre, comparative trial of iv Zoledronate (4mg or 8 mg) versus iv Aredia© (90mg), as an adjunct to standard therapies, in the treatment of multiple myeloma and breast cancer patients with cancer-related bone lesions, Grant, Novartis Oncology US, Clinical Trial, $58,000.00
2000 Jan - 2000 Dec	Major, P, J. Sathya, M. Patel, J Wu, H. Lukka, T. Corbett, A. Neville, A randomized double-blind placebo controlled phase III trial evaluating zoledronate plus standard therapy vs placebo & standard therapy in patients with recurrent carcinoma of the prostate who are asymptomatic with castrate levels of testosterone and have rising PSA levels without radiologically-evident metastatic disease, Grant, Novartis Oncology US, Clinical Trial, $180,000.00
1999 Jan - 2000 Dec	Major, P, E. Chouinard, P. McCulloch, A. Figueredo, SCH 766336: A Phase II Randomized, Open-Label Study of SCH 66336 and an Active Reference Agent Gemcitabine in Patients with Metastatic Adenocarcinoma of the Pancreas, Grant, Schering-Plough Research Institute, Clinical Trial, $10,000.00
1999 Jan - 2000 Dec	Major, P, E. Chouinard, P. McCulloch, A. Figueredo, SCH 766336: A Phase II Randomized, Open-Label Study of SCH 66336 and an Active Reference Agent Gemcitabine in Patients with Metastatic Adenocarcinoma of the Pancreas, Grant, Schering-Plough Research Institute, Clinical Trial, $10,000.00

1999 Jan - 2000 Dec	Major, P, H. Hirte, E. Chouinard, R. Tozer, A Arnold, D. Marcellus, R.Meyer, A. Benger, R. Foley, An open label, randomized, multicenter clinical study to investigate the efficacy and tolerability of intravenous Zometa (Zoledronate) 40 mg in patients with metastatic bone lesions due to breast cancer or multiple myeloma, Grant, Novartis Oncology US, Clinical Trial, $46,400.00
1998 Jan - 2000 Dec	Major, P, P. McCulloch, A. Figueredo, E. Chouinard, A double-blind, placebo-controlled, minimized phase III study comparing Marimistat to Placebo as adjuvant therapy in patients with resectable pancreatic cancer, Grant, British Biotech, Clinical Trial, $10,000.00
1998 Jan - 2000 Dec	Major, P, H. Hirte, R. Tozer, A randomized, double-blind, multicentre, comparative trial of Zoledronate (4 and 8 mgm. i.v.) versus Aredia (90 mgm. i.v.) as an adjunct to chemotherapy, in the treatment of multiple myeloma and breast cancer patients with osteolytic lesions, Grant, Novartis, Clinical Trial, $50,000.00
1997 Jan - 1999 Dec	Major, P, H. Hirte, R. Tozer, An open label, randomized multicentre evaluation of the safety and tolerability of Pamidronate (90mgm) administered as an intravenous infusion over 4, 2 or 1 hour., Grant, INT, Clinical Trial, $60,000.00
1997 Jan - 1999 Dec	Major, P, H. Hirte, L. Reyno, R. Tozer, A randomized double-blind study of two doses of Zoledronate and Aredia 90 mgm. in the treatment of tumour induced hypercalcemia., Grant, Novartis, Clinical Trial, $60,000.00
1996 Jan - 1998 Dec	Hirte, H, Major, P (Local Investigator), Phase I Trial of the Matrix Metallo Proteinase Inhibitor BAY 12-9566, Grant, NCIC Clinical Trial IND Group, Clinical Trial, $38,000.00
1985 Jan - 1989 Dec	Dion, A, Major, P, Human epithelial membrane antigens, Grant, NIH, Research - New Project, $336,000.00
1987 Jan - 1988 Dec	Major, P, G. Prud'Homme, L. Rosenthall, Monoclonal antibodies for diagnosis and therapy of human breast cancer, Grant, NCI, Research - New Project, $39,000.00
1987 Jan - 1988 Dec	Major, P, Regulation of expression of breast tumour markers, Grant, CRS, Research - New Project, $37,000.00
1985 Jan - 1988 Dec	Major, P, D. Ecobichon, K. Ogilvie, Clinical pharmacology of novel antivirals, Grant, MRC, Research - New Project, $234,000.00
1985 Jan - 1987 Dec	Major, P, Group grant for developing new approaches to treating breast cancer, Grant, FRSQ, Research - New Project, $119,000.00
1985 Jan - 1987 Dec	Major, P, G. Prud'Homme, L. Rosenthall, Monclonal antibodies for diagnosis and therapy of human breast cancer, Grant, NCI, Research - New Project, $96,000.00
1985 Jan - 1985 Dec	Major, P, G. Prud'Homme, L. Rosenthall, Rat model of breast cancer, Grant, CRS, Research - New Project, $20,000.00
1983 Jan - 1985 Dec	Major, P, Monclonal antibodies for diagnosis and therapy of human breast cancer, Grant, NCI, Research - New Project, $76,000.00
1983 Jan - 1984 Dec	Major, P, Monoclonal antibodies for diagnosis and therapy of human breast cancer, Grant, CRS, Research - New Project, $10,000.00

1983 Jan - 1984 Dec	Major, P, Monoclonal antibodies for diagnosis and therapy of human breast cancer, Grant, FRSQ, Research - New Project, $20,000.00
1981 Jan - 1984 Dec	Kufe, D, Major, P, Molecular modulations of ARA-C therapy in man, Grant, NIH, Research - New Project, $211,000.00
1982 Jan - 1983 Dec	Major, P, Biomedical research support grant - Monoclonal antibodies for diagnosis and therapy of breast cancer, Grant, NIH, Research - New Project, $15,000.00
1981 Jan - 1983 Dec	Kufe, D, Major, P, Molecular enhancement of Ara-A therapy, Grant, ACS, Research - New Project, $191,000.00
1980 Jan - 1981 Dec	Major, P, Pharmacology of ARA-C (Biomedical research grant), Grant, NIH, Research - New Project, $12,000.00

PATENTS AND COPYRIGHTS

2003 Treating Carcinoid Neoplasms with Therapeutic Viruses, Robert Lorence and Pierre Major

LIFETIME PUBLICATIONS (Principal Author is the first name on each of the entries below)

Peer Reviewed Contributions to Books

1. Major, P, MacKenzie, M. The role of bisphosphonates in bone metastasis. Bone Metastasis and Molecular Mechanisms, Pathophysiology, Kluwer Academic Publishers, Chapter 13, pp 277-301. (2004).

2. Major, P, Cook, RJ. Challenges and strategies in the analysis of multiple events in oncology. BoneMetastasis: Experimental And Clinical Aspects. Humana Press (2004).

3. Cook, RJ, Chen, B, Major, P. Marginal Analysis of Point Processes with Competing Risks. Handbook of Statistics, Vol 23, chapter 19, pp349-361 Elsevier Science BV (2004).

4. Lorence, RM, Hotte, SJ, Major, PP, Hirte, HW, Polawski S, Rheaume, N, Groene WS, Roberts, MS, Bamat, MK. Slow Infusion of PV701, an Oncolytic Virus: A Pahse I Study in Cancer Patients using Intravenous Administration. Scientific & Medical Publications, Pro ED COMMUNICATIONS Inc. (2004).

5. MacKenzie MJ, Major PP. "Mechanisms of Bisphosphonates". Chapter in Cancer Metastasis: Biology and Treatment, Kluwer Academic Publishers, 2003.

6. Weihrauch, TR, Kuhlmann, J, Maruhn, D, MacCarthy, P, Meyborg, H, Spilles, C; (Editorial Board) Arcieri G, Major, P, Wheywell, R, Phillip, E, (International Review Board). Manual of Clinical Drug Development. 2nd International Edition, Bayer 1994.

7. Thompson, DMP, Major, P, Shuster, J, Gold, P. Tumour immunology. In: Immunological Diseases, M. Samter (ed.) Little, Brown and Company, Boston. pp. 521-551, 1988.

8. Dion AS, Major P, Ishida M. Characterization of cross-related antigens of human milk fat globule membrane and breast tumours detected by a new monoclonal antibody panel. Monoclonal Antibodies and Breast Cancer. R. L. Ceriani (ed.), Kluever Academic Publishers, Dordrecht, The Netherlands 1987.

9. Major, P, Kufe, DW, Frei, E, III. Role of the kidney in the pharmacokinetic of anticancer agents. In: Cancer and the Kidney. Rieselbach, R.E., Garnick, M.B., eds. Lea and Febinger (1982).

Peer Reviewed Journal Articles

1. David Rodriguez, Marc Ramkairsingh, Ziaozeng Lin, Anil Kapoor, Pierre Major and Damu Tang. The central contributions of breast cancer stem cells in developing resistance to endocrine therapy in ER-positive breast cancer. Cancers 11, 1028, 2019.

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Peer Reviewed Journal Abstracts

1. Moore MJ, Tang P, Renouf D, Major P, Hedley D, Paterson V, Wnag L, Dhesy-Thind B, Southwood B, doyle L. A phase II study of Halchondrin B analog eribulin mesylate (E7389) as second-line therapy for patients with advanced panceatic cancer. J Clin Oncol 27 (suppl; abstr e15634). 2009.

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10. Major, P, Cook, R, Chen, BL, Zheng, M, Hohneker, J. Multiple event analysis of zoledronic acid in trials in patients with cancer metastatic to bone. ASCO 2003.

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12. Hotte, SJ, Major, P, Hirte HW, Polawski S, Bamat MK, Rhéaume N, Lorence RM. Phase I study of the Newcastle diseases virus, PV-701, in patients with advanced cancer: preliminary results with early evidence of efficacy. Submitted for presentation/publication at the American Society of Clinical Oncology (ASCO) annual meeting. May 2003, Chicago, Illinois, USA.

13. Rosen, L, Gordon, DH, Dugan Jr, W, Major, P, Eisenberg, P, Provencher ,L, Kaminski, M, Coleman, RE, Seaman, J, Chen ,BL. Zoledronic Acid (4mg) is more effective than pamidronate (90mg) for treating bone metastases in breast cancer patients with at least one osteolytic lesion. ESMO Abstract, 2002.

14. Coleman, RE, Rosen, LS, Gordon, D, Major, P, Kaminski, M, Apffelstaedt, J, Howell, A, Chen, BL, Seaman, JJ. Zoledronic acid (4mg) significantly reduces the relative risk of developing a skeletal-related event compared with pamidronate (90mg) in patients with breast cancer and bone metastasis. San Antonio Brst Ca Symposium, 2002.

15. Townsley, C, Major, P, Siu, LL, Dancey, J, Vincent, M, Pond, G, Maclean, M, Moore, MJ, Oza, AM. Phase II study of OSI-774 in patients with metastatic colorectal cancer. Euro J. Cancer 2002:38; 57.

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23. Figueredo, AT, Major, P, paper presentation. Follow-up of patients with colorectal cancer resected with curative intent: A meta-analysis of published data. Canadian Association of Medical Oncologists, Toronto April 23-25, 1999.

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Miscellaneous

1. Major P. Malignancy in the Peutz-Jeghers syndrome. J. Am. Med. Assoc. 1978;240:2155(letter).

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Accepted for Publication

Journal Article

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2. Elizabeth Sheid, Pierre Major, Alain Bergeron, et al. Tn-MUC1 Dendritic Cell Vaccination: A preclinical Study in Rhesus Macaques and Phase I/II Trial in Castrate Resistant Non-Metastatic Prostate Cancer Patients. Cancer Immunology. Apr 2016.

3. Xiaozeng Lin, Fenxiang Wei, Anil Kapoor, Pierre Major, Minxing Zheng, Peter Whyte, Damu Tang. BMI1 reduces ATR activation and signalling caused by hydroxyurea. Mar 2016.

4. Al-Shamsi HO, Al Farsi A, Mahraz A, Hua S, Zbuk K, Cook RJ, Linkins LA, Major P. Thrombotic events in metastatic colorectal cancer patients treated with leucovorin, fluorouracil and irinotican (FOLFIRI) plus bevacizumab. Journal of Gastrointestinal Oncology. Jan 2015.

5. Major P, Cook RJ, Chen BL, Sheng M. Survival-adjusted multipe-event analysis for the evaluation of treatment effects of Zoledronic Acid in patients with bone metastases from solid tumors. Supportive Cancer Therapy, 2005, Vol. 2 No. 4 234-240.

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1. Hirte, H, Miller, W, Major, P, Goss, G, Stewart, D, Batist, G, Douglas, L, Matthews, S, Lorimer, I, Seymour, L. Initial results of part 2 of a phase I/II pharmacokinetics (PK), pharmacodynamic (PD) and biological activity study of ZD18939 (Iressa™): NCIC CTG IND 122. NCIC CTG IND Program, Canada and AstraZeneca, Canada. In Press 2001.

Submitted for Publication

Journal Article

1. Warner BM, Santry LA, Leacy A, Chan M, Pham J, Vendramelli R, Pei Y, Tailor N, Valcourt E, Leung A, He S, Griffin BD, Audet J, Hustins M, Tierney K, Albietz A, Frost KL, Yates JG, Mould R, Chan L, Mehrani Y, Knapp J, Minott J, Banadyga L, Sanfronetz D, wood H, Booth S, Major P, Bridle B, Susta L, Kobasa D, Wootton S. Intranasal vaccination with a Newcastle disease virus vectored vaccine protects Syrian hamsters from SARS-CoV-2 infection and disease. Cell Reports. Apr 2021.

2. M. Zhao, J. Domm, T. McAusland, Y. Shang, P. Major*, J. Stout, S. Wootton*. Interference Chromatography: A novel approach to optimizing chromatographic selectivity and separation performance for virus purification. submitted to BMG Biotechnology. Jan 2020.

3. Scheid L, Major P, Gergeron A, Finn OJ, Salter RD, Landry C, Eady R, Dekaban G, Mukherjee S, Hotte S, Gariepy J, Sekaly RP, Lacombe l, Fradet Y, Foley R. Vaccination with autologous dendritic cells presenting Tn-MUC1 glycopeptide: Preclinical study in rhesus macaque and phase I/II clinical trial in castrate resistant non-metastatic prostate cancer patients. Cancer Immunology Research. 2015.

4. Major P, Cook R. Natural History of Bone Metastases. Submitted 2008.

5. Major P, Cook R. Statistical methods to analyze non-independent and recurrent complications from bone metastases. submitted 2008.

6. Hotte SJ, Lorence RM, Hirte HW, Bamat MK, O'Neil JD, Roberts MS, William S Groene WS, and Major PP. A Phase 1 Study of Slow Intravenous Administration of PV701, an Oncolytic Virus, in Patients with Advanced or Recurrent Solid Cancers. (submitted to JCO March 2006).

7. Major P, Cook R. Statisical methods to analyze non-independent and recurrent complications from bone metastases.

PRESENTATIONS AT MEETINGS

Invited Presentations

1. Coleman R, Cook R, Hirsh V, Major P, Lipton A Zoledronic Acid Use in Cancer Patients Cancer 2011 vol.117

2. Costa L, Major P Effect of Bisphosphonates on Pain and Quality of Life in Patients With Bone Metastases Nature Clinical Practice Oncology Vol. 6 2009

3. Major P Preserving functional independence in elderly patients with cancer-associated bone disease: the role of zoledronic acid Aging Health (2009)5(2)

4. Major, Pierre. Abstract selected for presentation: "Optimizing PV701 Clinical IV Dosing". Oncolytic Viruses as Cancer Therapeutics, Banff, Alberta March 2005.

5. Major, Pierre. Presenter, Oncology Rounds, Kingston Cancer Centre, Kingston, Ontario. 2004.

6. Major, Pierre. Debate with R Ladouceur, Use of Bisphosphonates in Palliative Care. 15th International Congress on Care of the Terminally Ill, Montreal, Quebec, September 2004.

7. Major, Pierre. Presenter, Physiotherapy 2004 National Congress, Quebec City, Quebec. May 2004.

8. Major, Pierre. Presenter, Oncology Rounds, Cancer Care Manitoba, Winnipeg, Manitoba. November 2003.

9. Major, Pierre. Presenter, Oncology Rounds, Alberta Cancer Centre. November 2003.

10. Major, Pierre. Presenter, Rounds, Hamilton Regional Cancer Centre, Hamilton, Ontario. October 2003.

11. Major, Pierre. Presenter, Rounds, Windsor Regional Cancer Centre, Windsor, Ontario. June 2003.

12. Major, Pierre. Presenter, Regional Oncology Rounds, Hamilton Regional Cancer Centre. Hamilton, Ontario, January 2003.

13. Major, Pierre. Presenter, Rounds, Hotel Dieu Hospital. St.Catharines, Ontario. January 2003.

14. Major, Pierre. Presenter, Hematology Rounds, Centre Hospitalier Universitaire de Quebec. Quebec City, Quebec, October 2002.

15. Major, Pierre. Presenter, Grand Rounds, Grand River Regional Cancer Centre. Kitchener, Ontario, May, 2002.

16. Major, Pierre. Presenter, Grand Rounds, Toronto-Sunnybrook Regional Cancer Centre. Toronto, Ontario, June 2001.

17. Major, Pierre. Presenter, Rounds, Ottawa Regional Cancer Centre. Ottawa, Ontario, May 2001.

18. Major, Pierre. Presenter, Grand Rounds, Queen Elizabeth II Health Sciences Corporation. Halifax, Nova Scotia, May 2001.

19. Major, Pierre. Tumour Osteolysis: The Clinical Problem. Toronto-Sunnybrook Regional Cancer Centre, June 2000.

20. Major, Pierre. Clinical Trial Design Issues in Bisphosphonate Trials. McGill University, Department of Oncology, December, 1999.

21. Major, Pierre. Bisphosphonates: Clinical Trial Design Issues and Implications for Their Clinical Use. Clinical Oncology Study Evaluation Program. British Columbia Cancer Agency, November, 1999.

22. Major, Pierre. The Role of Bisphosphonates in the Treatment of Breast Cancer: Emerging Trends in Breast Cancer. Princess Margaret Hospital, Toronto, Canada, November, 1999.

23. Major, Pierre. Chairman: Workshop on design and analysis of trials with bisphosphonates in cancer Second North American Symposium on Skeletal Complications of Malignancy. Montreal, Oct. 15-16, 1999.

24. Major, Pierre. Bisphosphonates. L'Hotel Dieu de Quebec, Oncology Rounds, October , 1999.

25. Major, Pierre. Bisphosphonates: Clinical Trial Design Issues and Implications for Their Clinical Use. Novartis Mtg. Washington, DC – September 1999.

26. Major, Pierre. Bisphosphonates: Clinical Trial Design Issues and Implications for Their Clinical Use. Oncology Grand Rounds, London Regional Cancer Centre, London, Canada – September 1999.

27. Major, Pierre. Aredia: 1 hour infusion / Prostate Cancer (oral presentation) Cancer Induced Bone Disease. Second International Conference, Davos, March 1999.

28. Major, Pierre. Revue des biphosphonates dans le cancer du sein "Meet the Professor". Societe des Hemato-oncologues du Quebec Chateau Mont-Tremblant (June 5, 1998).

29. Major, Pierre. Bisphosphonates: Clinical Trial Design Issues and Implications for Their Clinical Use. Saskatoon Cancer Centre (April 29, 1998).

30. Major, Pierre. Bisphosphonates: Clinical Trial Design Issues and Implications for their Clinical Use. Regional Oncology Rounds, Hamilton Regional Cancer Centre (April 30, 1998).

31. Major, Pierre. The future of cancer drug development and pharmaco politics. Division of Medical Oncology, Royal Victoria Hospital, Montreal, 1996 - 97.

32. Major, Pierre. Drug Development - The Impact of Government, Politicians, Industry and Advocacy Groups. Medical Grand Rounds, St.Joseph's Hospital, Hamilton, 1996 - 97.

33. Major, Pierre. Bisphosphonates for use in everything from Osteoporosis to Metastatic Cancer. Cambridge Memorial Hospital (Cambridge Academy of Medicine Clinic Day) 1996 - 97.

34. Major, Pierre. Drug Development - The Impact of Government, Politicians, Industry and Advocacy Groups. Medical Grand Rounds, Department of Medicine, McGill University/Royal Victoria Hospital, Montreal. 1996 - 97.

35. Major, Pierre. Angiogenesis and Cancer Treatment. Regional Rounds, Hamilton Regional Cancer Centre (in collaboration with Drs. H. Hirte and J. Rusthoven). 1996 - 97.

36. Major, Pierre. Cancer, Broken Bones and Politics. Regional Rounds, Hamilton Regional Cancer Centre 1996 - 97.

37. Major, Pierre. The future of cancer drug development and pharmaco politics. Regional Rounds, Hamilton Regional Cancer Centre, 1995 - 96.

38. Major, Pierre. Monoclonal antibodies and breast cancer. Oncology Rounds, Princess Margaret Hospital, 1994 - 95 .

39. Major, Pierre. Monoclonal antibodies and breast cancer. Institute for Molecular Medicine & Immunology, University of New Jersey School of Medicine & Dentistry, 1986 - 87.

40. Major, Pierre. Monoclonal antibodies and breast cancer. McGill Cancer Centre Seminar, 1986 - 87.

41. Major, Pierre. Monoclonal Antibodies and Breast Cancer. ACFAS, Montréal, 1985 - 86.

42. Major, Pierre. Molecular pharmacology of Ara-C. Ara-C Symposium, Ste-Justine Hospital Research Institute, 1985 - 86.

43. Major, Pierre. Monoclonal Antibodies and Breast Cancer. Institut du Cancer de Montréal, 1984 - 85.

44. Major, Pierre. Anticorps Monoclonaux et Cancer du Sein. Department of Pharmacology, University of Montréal, 1984 - 85.

45. Major, Pierre. Monoclonal Antibodies and Breast Cancer, Institut du Cancer de Montréal. 1984 - 85.

46. Major, Pierre. Joint Immunology Rounds. McGill University. 1984 - 85.

47. Major, Pierre. Oncology Conferences. Montréal General Hospital. 1984 - 85.

48. Major, Pierre. Joint Oncology Conferences. Royal Victoria Hospital, 1984 - 85.

49. Major, Pierre. Seminar: Repair of ara-C induced DNA damage. McGill Cancer Centre, McGill Department of Pharmacology, 1983 - 84.

50. Major, Pierre. Oncology Conference. Dana-Farber Cancer Institute, 1983 - 84.

51. Major, Pierre. Effect of Ara-C on DNA Structure. Ara-C Symposium, Upjohn Pharmaceutical, Kalamazoo, Michigan 1981 - 82.

52. Major, Pierre. Clinical Pharmacology of Deoxycoformycin. Deoxycoformycin Symposium, Warner Lambert Pharmaceutical, Ann Arbor, Michigan 1981 - 82.

53. Major, Pierre. Effect of 5 FU on DNA and RNA Structure. Biochemical Modulation Conference, Division of Cancer Treatment, NIH, USA. 1980 - 81.

Contributed Peer Reviewed Presentations

1. Coleman RE, Costa I, Saad F, Cook R, Hakji P, Terpos E, Carnero P, Brown J, Body JJ, Smith M, Lee KA, Major P, Dimopoulos M, Lipton A Consensus on the Utility of Bone Markers in the Malignant Bone Disease Setting Critical Reviews in Oncology Hematology (2011)

2. Coleman R, Brown J, Terpos E, Lipton A, Smith MR, Cook R, Major P Bone Markers and Their Prognostic Value in Metastatic Bone Disease: Clinical Evidence and Future Directions. Cancer Treatment Reviews Vol.34 2008

ADMINISTRATIVE RESPONSIBILITIES

External

1999 Apr - present	Member, Medical Advisory Board, Canadian Colorectal Cancer Association
1996 - 2000	Member, Member Grant Review Panel B, Cancer Research Society
1998 Feb - 2000 Dec	Chair, Chairman - International Safety Committee for the Pamidronate INT-03 Study
1996 Oct - 1998 Oct	Member, Systemic Therapy Program Committee, Cancer Care Ontario
1997 Sep - 1998 Apr	Member, Policy Advisory Committee for Colorectal Cancer Screening, Cancer Care Ontario
1995 Jun - 1996 Aug	Member, Member, Development Operating Committee responsible for selecting candidate drugs for development by Bayer North America and approving the clinical development plan and budgets.
1992 May - 1996 Aug	Member, Operating Committee, Bayer Pharmaceutical Division
1990 Jan - 1992 May	Member, Operating Committee, Syntex Inc.
1990 Jan - 1992 May	Member, Member of the Board, Syntex Inc

Hospital

2001 - present	Member, Disease Site Team Council, Juravinski Cancer Centre
2008	Treasurer, Medical Staff Accociation
1997 Sep - 2001 Jan	Member, Cancer Prevention Committee, Juravinski Cancer Centre, Hamilton, Ontario

University

2000	Member, Chair of Medicine Selection Committee, McMaster University

This is Exhibit "B" to the Affidavit of
Dr. Pierre Major, sworn before me on
this 29th day of November 2023

A Commissioner for Taking Affidavits
Rocco Galati, , B.A., LL.B., LL.M.

i. Stegelmeier AA, Santry LA, Guilleman MM, Matuszewska K, Minott JA, Yates JGE, Stevens BAY, Thomas SP, Vanderkamp S, Hanada K, Pei Y, Rghei AD, van Vloten JP, Pereira M, Thompson B, **Major PP**, Petrik JJ, **Bridle BW**, Wootton SK. AAV-Vectored Expression of the Vascular Normalizing Agents 3TSR and Fc3TSR, and the Anti-Angiogenic Bevacizumab Extends Survival in a Murine Model of End-Stage Epithelial Ovarian Carcinoma. *Biomedicines* 2022 Feb 2;10(2):362. doi: 10.3390/biomedicines10020362. PMID: 35203573; PMCID: PMC8962366.

ii. Warner BM, Santry LA, Leacy A, Chan M, Pham PH, Vendramelli R, Pei Y, Tailor N, Valcourt E, Leung A, He S, Griffin BD, Audet J, Willman M, Tierney K, Albietz A, Frost KL, Yates JGE, Mould RC, Chan L, Mehrani Y, Knapp JP, Minott JA, Banadyga L, Safronetz D, Wood H, Booth S, **Major PP***, **Bridle BW***, Susta L*, Kobasa D*, Wootton SK*. Intranasal vaccination with a Newcastle disease virus-vectored vaccine protects hamsters from SARS-CoV-2 infection and disease. *iScience* 2021 Nov 19;24(11):103219. doi: 10.1016/j.isci.2021.103219. Epub 2021 Oct 6. PMID: 34632328; PMCID: PMC8492382.

*equal contributions as senior authors

iii. McAusland TM, van Vloten JP, Santry LA, Guilleman MM, Rghei AD, Ferreira EM, Ingrao JC, Arulanandam R, **Major PP**, Susta L, Karimi K, Diallo JS, **Bridle BW**, Wootton SK. Combining vanadyl sulfate with Newcastle disease virus potentiates rapid innate immune-mediated regression with curative potential in

murine cancer models. *Molecular Therapy Oncolytics* 2021 Jan 21;20:306-324. doi: 10.1016/j.omto.2021.01.009. PMID: 33614913; PMCID: PMC7868934.

iv. Santry LA, van Vloten JP, Knapp JP, Matuszewska K, McAusland TM, Minott JA, Mould RC, Stegelmeier AA, **Major PP**, Wootton SK, Petrik JJ, **Bridle BW**. Tumour vasculature: Friend or foe of oncolytic viruses? *Cytokine Growth Factor Reviews* 2020 Dec;56:69-82. doi: 10.1016/j.cytogfr.2020.07.007. Epub 2020 Sep 1. PMID: 32893095.

v. Matuszewska K, Santry LA, van Vloten JP, AuYeung AWK, **Major PP**, Lawler J, Wootton SK, **Bridle BW**, Petrik J. Combining Vascular Normalization with an Oncolytic Virus Enhances Immunotherapy in a Preclinical Model of Advanced-Stage Ovarian Cancer. *Clinical Cancer Research* 2019 Mar 1;25(5):1624-1638. doi: 10.1158/1078-0432.CCR-18-0220. Epub 2018 Sep 11. PMID: 30206160.

vi. Santry LA, McAusland TM, Susta L, Wood GA, **Major PP**, Petrik JJ, **Bridle BW**, Wootton SK. Production and Purification of High-Titer Newcastle Disease Virus for Use in Preclinical Mouse Models of Cancer. *Molecular Therapy Methods and Clinical Development* 2017 Oct 16;9:181-191. doi: 10.1016/j.omtm.2017.10.004. PMID: 29556508; PMCID: PMC5854916.

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No.: **CV-22-0069-1880-0000**

Dr. BYRAM BRIDLE -and- David Fisman et al

Plaintiffs Defendants

.

ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDING COMMENCED AT TORONTO

AFFIDAVIT OF DR. PIERRE MAJOR

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Lawyer for the Plaintiff

TAB 10

Court File #: CV-22-0069-1880-0000

ONTARIO

SUPERIOR COURT OF JUSTICE

B E T W E E N:

DR. BYRAM BRIDLE

Plaintiffs

- and -

UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST

Defendants

AFFIDAVIT OF DR. NIEL KARROW

I, Dr. Niel Karrow, of the City of Guelph, in the Country of Canada, MAKE OATH AND SAY:

1. I am a professor of Immunotoxicology and Immunogenetics at the University of Guelph and an academic and professional colleague of Dr. Bridle, and as such, have knowledge of the matters contained in this Affidavit.

Professional, Academic and Research Association with Dr. Bridle

2. I am a senior immunologist and have collaborated for over 23 years with Dr. Bridle at the University of Guelph. Attached as **Exhibit A** is my CV.
3. Drs. Bridle, Bonnie Mallard, Shayan Sharif, and I, are the four (4) senior immunologists at the University of Guelph. This means that we have advanced training and expertise in immunology. Of the four of us, Dr. Bridle is the most knowledgeable about the immunological mechanisms by which a natural immune response is elicited by the SARS-CoV-2, the causative agent of COVID-19, and the immunity afforded by COVID-19

vaccines due to his combined qualifications, insights and critical thinking skills, in, not just immunology, but also vaccinology (a sub-discipline of immunology) and virology.

4. In addition to working closely with Dr. Bridle on campus, all three of us have collaborated on research and published peer-reviewed publications with Dr. Bridle in immunology, including on COVID-19.

5. For example, Dr. Bridle published five lay articles on the topic of COVID-19 in the academic publication known as "*The Conversation*", with Dr. Sharif, one of which was also published in French, attached as **Exhibit B** to this affidavit. Dr. Sharif has also co-authored six published peer-reviewed scientific papers with Dr. Bridle over the past three years, on the topics of antiviral immune responses and avian influenza, including one paper focused on a vaccine against avian influenza. Citations of the peer-reviewed papers are attached as **Exhibit C** to this affidavit.

6. I have published four (4) peer-reviewed publications with Dr. Bridle. Attached as **Exhibit D** is a list of citations of our peer-reviewed papers.

7. Dr. Mallard has ten peer-reviewed publications with Dr. Bridle. She is providing her own affidavit evidence in this Motion.

8. In recognition of the fact that Dr. Bridle is the *most* qualified immunologist on the topic of COVID-19 at the University of Guelph he was recruited to give a lecture on the subject in the new course "Pandemics" designated as UNIV*2020.

9. I can confidently speak on behalf of all three of the University's senior immunologists that Dr. Bridle is an extremely reliable, meticulous, and excellent researcher. He has received multiple top-tier honours in recognition of this fact by the Canadian Institutes of Health Research, and is a member of their prestigious college of reviewers, and has served by

invitation on their Virology and Viral Pathogenesis and Cancer Biology and Therapeutics grant review panels.

10. I know Dr. Bridle to be a person of unwavering integrity and conviction. In all the 23 years I have worked with him I know Dr. Bridle has never provided wrong or misleading information, let alone deliberately disseminated false information in his field of expertise.

11. On a personal level I know Dr. Bridle is a dedicated Christian with excellent character, and a strong moral imperative to speak the truth, even if it is contrary to the prevalent discourse.

"Misinformation" allegations and smear campaign against Dr. Bridle

12. I have read the affidavit of Dr. Fisman, filed in the within motion and listened to the Global "On Point" radio interview of Dr. Bridle on May 27, 2021, with journalist Alex Pierson (hereinafter "On Point interview").

13. On May 30, 2021, I was copied on an email from Dr. Bridle to Dr. Glen Pyle, titled "smear campaign", attached as **Exhibit E**. (Dr. Pyle is professor of biophysics and biomedical sciences, at the University of Guelph.) The email included a screenshot of Dr. Pyle's posts along with Dr. Fisman's social media post on Twitter, dated May 29, 2021, at 5:40 PM after the On Point radio interview, Dr. Fisman stated:

> "I've had questions over the past 48h about vaccine safety concerns aired Dr Bryam Bridle at @UofGuelphOAC in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here: byrambridle.com"

14. Dr. Bridle's email to Dr. Pyle stated:

> "Glen,
> I do not use social media. So, yes, it has been happening without my knowledge. If I ever have a problem with someone's science on campus, I take it up with them. This would have been the respectful thing to do. The major problem here was the fact that you did not condemn an egregious act against a colleague when you had the opportunity.

Sincerely,
Byram"

15. In his May 29, 2021, post, above, Dr. Fisman references and promotes a website set up to discredit Dr. Bridle. I viewed the website that bore Dr. Bridle's name. It gives the false impression it is his website. There is an image of a duck and comments that demean, mock, and belittle Dr. Bridle that imply to the reader that he is a "quack". I know the fact that a website was set up only to impersonate Dr. Bridle to discredit him as a viral immunologist terrified him and caused him anxiety. On May 29, 2021, I received an email from Dr. Bridle at 11:17 PM, attached as **Exhibit F** after the above radio interview aired and Dr. Fisman's tweet, stating:

> "Hi all,
> I have to admit that I am starting to get a bit scared. A website was made within the last 48 hours to discredit me…
> http://byrambridle.com/
> This has gotten very ugly very fast.
> Sincerely,
> Byram"

16. On May 31, 2021, I was copied on an email from Dr. Bridle to Dr. Scott Weese titled "misinformation", attached as **Exhibit G**. (Dr. Weese is a professor of pathobiology and a veterinary internist at the University of Guelph). The email included a screenshot of Dr. Weese's Twitter post of May 30, 2021, at 11:49 AM replying to Dr. Pyle and Dr. Fisman.

17. Dr. Weese's post was:

> "Its's tough but misinformation has to be challenged. More misinformation and confusion during a pandemic are dangerous and causing harm.

18. Dr. Bridle's email to Dr. Weese states, in part:

> "Like it or not, I'm not going to conform to your way of thinking about the pandemic and I have scientifically valid reasons for it. I am allowed to be an independent critical thinker."

19. Dr. Pyle and Dr. Weese's objections to Dr. Bridle expressing countervailing views to the government narrative were apparent. Their vehement opposition to Dr. Bridle's expressions was publicly announced in an Open letter they wrote with two other University of Guelph faculty members dated July 6, 2021.

Dr. Fisman's claims of Dr. Bridle spreading "misinformation" & "disinformation" are false

20. The claims made by Dr. Fisman, in his affidavit, that Dr. Bridle misrepresented the science regarding COVID-19 vaccines, and are not supported by evidence in scientific literature, are false. Therefore, the assumption that Dr. Bridle's statements are "dangerous" or "caused harm" is not supported by any evidence, and, is also false.

21. Although Dr. Fisman did not identify which of Dr. Bridle's claims were misinformed, based on my knowledge of immunology and peer-reviewed publications, all the points made by Dr. Bridle during the On Point interview ***are*** supported by scientific evidence and, in fact, have been borne out to be verified to be true:

    a. The vaccine components do not stay in the arm, they biodistributed throughout the body.[1]

    b. Spike protein has been detected in heart tissue and has been detected in blood and exosomes, which can distribute throughout the body and can be shed in bodily fluids.[2]

[1] Ogata, A.F., Cheng, C.A., Desjardins, M., Senussi, Y., Sherman, A.C., *et al.* (2022) Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccine antigen detected in the plasma of mRNA-1273 vaccine recipients. Clin Infect Dis. 74(4):715-718. doi:10.1093/cid/ciab465

[2] Di, J., Du, Z., Wu, K., Jin, S., Wang, X., Li, T., Xu, Y. (2022) Biodistribution and non-linear gene expression of mRNA LNPs affected by delivery route and particle size. Pharm Res. 39(1):105-114. doi: 10.1007/s11095-022-03166-5

c. Vaccine mRNA and antibodies have been detected in mother's milk which poses risk to nursing infants.[3]

d. Concern about targeting reproductive tissues has also been confirmed.[4]

e. The COVID-19 vaccines also contribute to increased risk of blood clotting, stroke, neurological complications, anaphylaxis, myopericarditis and heart attack.[5]

22. Dr. Bridle had the above insights in May 2021 due to his expertise. This is now indisputably evident in the most current scientific data.

23. I had the same genuine concerns as Dr. Bridle about the production, testing, efficacy and safety of the COVID-19 genetic vaccines, which Dr. Fisman labels as "misinformation" and "disinformation". I know Dr. Bonnie Mallard, the most senior immunologist at the university, also had the same concerns. On July 6, 2021, I sent an email to five of my personal acquaintance co-faculty members at the University, who are not immunologists, but signed the letter drafted by Drs. Weese and Pyle and two others. I set out the scientific rational which supported Dr. Byram's answers in the On Point interview, attached as **Exhibit H**. My email states, in part:

> "Byram is an expert in his field, and I share many of his concerns regarding vaccinating children, and also pregnant women.
> ….
> It is surprising to me that someone like Byram, who is expressing concerns about vaccine safety is shut down after providing evidence of their potential risk, when it is supposed to be the vaccine makers who should be providing the evidence of their safety!"

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[3] Yeo, K.T., Chia, W.N., Tan, C.W., Ong, C., Yeo, J.G., *et al.* (2022) Neutralizing activity and SARS-CoV-2 vaccine mRNA persistence in serum and breastmilk after BNT162b2 vaccination in lactating women. Front Immunol. 12:783975. doi:10.3389/fimmu.2021.783975

[4] Al Kadri HM, Al Sudairy AA, Alangari AS, Al Khateeb BF, El-Metwally AA. COVID-19 vaccination and menstrual disorders among women: Findings from a meta-analysis study. J Infect Public Health. 2023 May;16(5):697-704. doi: 10.1016/j.jiph.2023.02.019. Epub 2023 Mar 2. PMID: 36934644; PMCID: PMC9979695.

[5] "Inflammation after COVID19 Vaccination: An Endomyocardial Biopsy-Proven Case Series" *International Journal of Molecular Sciences*, 2022, 23, 6940 http://doi.org/10.3390/ijms23136940

24. With respect, in my opinion, Dr. Fisman does not have the scientific expertise required to understand Dr. Bridle's assertions of the science. His expertise as an epidemiologist is in the study of the distribution and determinants of disease. His work focuses on mathematical modelling, not on SARS-CoV-2 immunity or long-term safety of COVID-19 vaccines.
25. Dr. Fisman also asserts in his affidavit that Dr. Bridle's scientific assertions are "misinformation" because they "were contrary to the overwhelming majority of scientific opinion". This itself is a questionable statement. But, even if true, expressing dissenting opinions was never a problem for scientists – questioning and challenging conventional thinking is what we do as scientists daily. This is not a basis to accuse a scientist who offers his opinions in his area of expertise based on peer-reviewed science, of "spreading misinformation" and "disinformation".
26. I can confirm that Dr. Bridle's scientific assertions, whether contrary to the opinion of other scientists, are neither wrong (misinformation), nor deliberately falsified (disinformation). I know that such a claim by a scientist is tantamount to an allegation of fraud. It can destroy the academic and research career of a scientist.
27. With respect to his speech mannerisms during the interview, I know Dr. Bridle has Tourette Syndrome. He exhibits tics and stutters. This is apparent and exacerbated when he is stressed. I know he does not like public speaking and would not willingly participate in public events or media interviews unless he was 100% certain of his message and concerns.

Background and context at the University of Guelph

28. Since March 2020, to the present, given our respective interest and expertise in immunology, Dr. Bridle, Dr. Mallard, and I meet weekly to discuss the emerging science and data related to COVID-19. Dr. Bridle followed that scientific literature closely due to

his expertise in both immunology and virology. I have personal knowledge of his untiring efforts to remain apprised of all COVID-19 related publications in his field of expertise.

29. On March 3, 5, 16, and 23, 2021, I co-authored several “Open Letters” to Public Health and the Premier of Ontario to warn against mandating experimental “vaccines" to the public at large setting out the safety concerns, which Dr. Fisman claims are “misinformation”, attached as **Exhibit I.**

30. The same scientific information referenced in the open letters were also discussed in a meeting the three of us had with the Vice-President, Academics, Dr. Cate Dewey, at the University of Guelph on March 11, 2021. Dr. Dewey stated our concerns were valid and no member of the university should be coerced or pressured to take a COVID19 vaccine. During the meeting Dr. Dewey also said to us that she would not support a mandate.

31. Dr. Dewey appointed me, and Drs. Mallard and Bridle, as points of contact for student or staff who experienced pressure to take a COVID-19 vaccine. As a result, I was contacted confidentially by students and faculty and became aware of increasing pressure on campus regarding COVID-19 vaccines within the university community and faculty who disapproved of any criticism of Public Health policies.

32. Because Dr. Bridle is the most authoritative of all the senior immunologists at the University, he was sought after for media interviews and public speaking engagements to provide information and insights on SARS-CoV-2 and COVID-19 vaccines. He gained a reputation as a scientist who provided plain, easy-to-understand and truthful answers to complex questions. His expertise garnered both national and international media interviews.

33. However, Dr. Weese disliked Dr. Bridle's media appearances and pushed for censorship of his expressions on COVID-19 with the University administration. On April 15, 2021, Drs. Mallard and Bridle informed me and I believe they were "warned" by Dr. Weese to stop making statements contrary to public health at a Departmental meeting. News travels fast within the university and it was no secret that Dr. Weese disliked the public attention Dr. Bridle's public speaking and media interviews garnered.
34. Dr. Fisman added fuel to the fire here with his May 29th, 2021, post. Dr. Fisman's allegation against Dr. Bridle renewed Dr. Weese's campaign to discredit and censor Dr. Bridle.

On-line personal harassment is not scientific debate or disagreement.

35. I do not have a Twitter account and I am not on social media. I became aware of Dr. Fisman's social media posts when I received emails with screenshots from Dr. Bridle or immunology students and research assistants who fear reprisals from Drs. Weese and Pyle to disclose their name. This is how I learned that Dr. Weese was posting comments about Dr. Bridle that had nothing to do with science.
36. On June 24th, 2021, Dr. Bridle sent an email including tweets for Dr. Weese and Dr. Fisman. The email is attached as **Exhibit J**. Dr. Weese made disparaging references to Dr. Bridle, "spreading manure", after Dr. Bridle published a scientific paper on COVID-19 vaccines and children**.** This post is improper for an academic colleague. It is insulting and abusive.
37. In another, Dr. Weese, re-tweeted an earlier post by Dr. Fisman which had nothing to do with science, referring to Dr. Bridle as an "anti-vaxxer", "white supremist", "neo-Nazi". With Dr. Fisman's post, dated May 10, 2021, retweeted by Dr. Weese on November 10, 2021, with a link that goes directly to Dr. Bridle's photo, name and where he works.

38. These posts vilify and malign Dr. Bridle's character and are not about science.

39. I was also the subject of Dr. Weese's Tweet hate after the publication of my 2021 paper, which I co-authored with Dr. Bridle and others on "Maternal COVID-19 Vaccination and Its Potential Impact on Fetal and Neonatal Development".

40. I could not respond or defend myself as I am not on Twitter. Drs. Weese and Fisman know that I am not on Twitter. They also know Dr. Bridle is not on Twitter. It is unprofessional and unscholarly for academics to post personal insults and hateful comments about an academic colleague. On September 8, 2021, I requested the University to intervene and mediate or curtail the abusive posts by Drs. Weese and Pyle by email, attached as **Exhibit K**, which in part states:

> "I came across a Tweet that I find very disturbing (attached). I don't know Weese, nor do I care to, but his tweets are very immature and unprofessional. I believe as colleagues, we should be able to listen to and respect each other, and hopefully learn together. …I am embarrassed by Weese's childish behaviour, and I am ashamed to be affiliated with the same university that he attends. Since when did we learn to stoop so low?...If he disagrees with Bridle, then why doesn't he just sit down with him and discuss his concerns? Why the public slandering? This kind of caddy behaviour makes us all look bad and it says so much more about Weese's character than what Bridle stands for. Moving forward I think a mediator should be considered. In the short-term please show how curtail these Tweets."

41. The University did nothing to stop or curtail the personal nature of Dr. Weese's Tweets and re-tweeting of Dr. Fisman against Dr. Bridle.

42. I know Dr. Bridle invited scientific discussions and debates in person, as is the practice in academia by email until he was prohibited by the Dean. The June 24th, 2021 email is one example under Exhibit J above.

43. Dr. Bridle's request for a scientific conversation was not accepted by Drs. Fisman, Pyle or Weese because I believe it was not their intention to discuss or debate, but rather silence Dr. Bridle.

Harms for alleging Dr. Bridle is "an immunologist spreading misinformation"

44. After qualifications, reputation of a scientist is the most valuable asset.

45. Dr. Bridle being referred to spreading "misinformation" or "making claims that are not data or evidence-based" by Dr. Fisman, together with Dr. Weese, referring to him as "neo-Nazi" and "white supremist" has destroyed Dr. Bridle's reputation.

46. It has instilled fear amongst Dr. Bridle's university colleagues and students that they too will be subject to malicious and personal attack on social media for expressing scientific views that are countervailing to the dominant government discourse. It has set a deep chill at our university.

47. The website "byrambridle.com" is clearly a smear campaign against Dr. Bridle. Dr. Fisman's reference to it is underhanded for an academic.

48. Allegations of "misinformation" about vaccines and the derogatory term "anti-vaxxer" for a vaccinologist are fatal to an academic and research career. As immunologists, we advocate for effective and safe vaccines as an important tool to control endemic diseases and prevent emerging diseases. These labels alone immediately result in lost credibility by the immunology community and research funding agencies.

49. Reputation impacts students. It is difficult to recruit and retain immunology graduate students without a solid reputation. I know Dr. Bridle lost two graduate students because they were also adversely affected by the attack against him and feared the disclosure of their names. Without graduate students, it is extremely difficult to convince granting agencies that you have the ability to train highly qualified personnel. This is one criterion used to assess research grant applications.

50. Reputation impacts research funding. Consequently, Dr. Bridle's funding has come to an end, and he will have a very difficult time soliciting funds because "misinformation" and "disinformation" labels by Dr. Fisman, a former member of the Ontario Science Table, will carry weight. It will also be very difficult to get external reviewers for his proposed research projects because of the misinformation spread about Dr. Bridle.

51. Reputation impacts publication. It will be very difficult to find objective reviewers to peer review Dr. Bridle's publications. I have also noted over the past three years it has been very difficult publishing on topics in high-quality journals that do not conform with the non-questionable and non-critical narrative that the COVID-19 vaccines are "safe and effective" no matter what, even though concessions from public health officials, the scientific community, or data, tell a different story. Without high quality publications, this will also negatively impact professional credibility and funding opportunities.

52. The duty of a scientist in university is to question orthodoxy and Dr. Bridle's concerns have come to fruition, yet he has been punished for doing his job. This is a great injustice for a highly and uniquely qualified scientist in research and development of vaccines.

AFFIRMED BEFORE ME by Niel)
Karrow in the City of Guelph, in)
Canada, on this 15th day of December)
2023, in accordance with)
O. Reg. 431/20 Administering Oath or)
Declaration Remotely)

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

Dr. Niel Karrow

This is Exhibit " A " to the Affidavit of
Dr. Neil Karrow, affirmed before me on
this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

CURRICULUM VITAE

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November, 2023

PERSONAL

Mailing Address: Department of Animal Biosciences
University of Guelph
Guelph, Ontario, Canada
N1G2W1
(519)-760-2468

Born: December 17, 1965

Marital Status: Married to Yan Hua Zhu
Daughters: Jordan and Sarah

EDUCATION:

1989 B. Sc. Biology
Minors in Biomedical Science and Animal Biosciences, University of Guelph, ON Canada.

1995 M. Sc. Biology
Area of specialization: Aquatic Toxicology, Advisors: D.G. Dixon and C. Neville (Ontario Ministry of Environment and Energy), Thesis title; "Sensitivity of rainbow trout sacfry and swim-up stages to sublethal concentrations of 3,4-dicholoraniline, 1,2-dichlorobenzene, and 2,4,5-trichlorophenol." University of Waterloo, ON, Canada

1999 Ph. D. Biology
Area of specialization: Immunotoxicology, Advisors: D.G. Dixon and N.C. Bols, and H.J. Boermans (University of Guelph), Thesis title; "Chemical mixture immunotoxicity to rainbow trout". University of Waterloo, ON, Canada

OTHER EDUCATION:

-Vanto Group Workshop, 2019. Rewriting the future of your organization and life. October 17-19, Guelph.
-Visiting scientist on sabbatical leave, 2016. College of Animal Science and Technology, Huazhong Agricultural University, Wuhan, Hubei, 430070, P.R. China
-Visiting scientist on sabbatical leave, 2015. Aquatic Ecosystem and Aquaculture Lab. Ocean College, Zhejiang University, E201, Agriculture-Life-Environment Building, Zijingand Campus, 866 Yuhangtand Road, Hangzhou 310058, P.R. China.
-Course Re-design, 2006. Teaching Support Services, University of Guelph, May 23-26.
-19th Annual Teaching and Learning Innovations Conference, 2006. Pedagogies that challenge, University of Guelph, May 16th.
-Introduction to SELDI-TOF-MS, 2005. Ciphergen Biosystems, Inc. Woburn, MA, August 16-19.

-In-gel Protein Digestion and Identification by Mass Spectrometry, 2005. Department of Molecular Genetics and Biology, University of Guelph.
-Ontario Cancer Institute Microarray Tutorial: August 28, 2001, Toronto.
-Graduate Courses: Ecotoxicological Risk Characterization, Immunobiology, Modelling Environmental Pathways, Advanced Topics in Environmental Toxicology, Statistics and Experimental Design, and Special Topics in Research.
-1999 Society of Toxicology: Continuing education courses; Detecting and Quantifying Apoptosis, and Chemical Hypersensitivity

EDUCATIONAL AWARDS:

1999	Young Investigator Grant supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Grant# 1R13 AR 45962-01)
1997-1994	University of Waterloo Graduate Scholarship (UWGS)
1983	Headmaster's Award, St. John's Kilmarnock School First in Division in Waterloo Wellington Science and Engineering Fair
1982	Headmaster's Award, St. John's Kilmarnock School History and Geography Scholarship Third in Category in Canada Wide Science and Engineering Fair

EMPLOYMENT EXPERIENCE:

2023-2025	Adjunct Professor, Graduate School of Agricultural Science, Tohoku University, Sendai, Japan.
2018-2023	Adjunct Professor, Department of Animal Nutrition and Feed Science, Sichuan Agricultural University, 211 Hulmin Rd., Wenjiang District, Chengdu, Sichuan, 611130, P.R. China.
2017-2018	Chair Professor, College of Animal Science and Technology, Yangzhou University, Yangzhou, China.
2017	Full Professor, Department of Animal Biosciences, University of Guelph, Ontario, Canada
2016	Visiting Scholar, College of Animal Science and Technology, Yangzhou University, Yangzhou, China.
2011-17	Adjunct faculty appointment with Departments of Biomedical Science and Animal Biosciences, University of Guelph, Ontario, Canada
2008	Associate Professor, Department of Animal Biosciences, University of Guelph, Ontario, Canada
2002-2007	Assistant Professor, Department of Animal Biosciences, University of Guelph, Ontario, Canada

2007 Granted tenure 2007

Graduate Students/PDFs:

-Shadi Mamaghani (M.Sc. by coursework) Animal Biosciences, supervisor, 2004 (Program Manager, National Science Foundation, U of Toronto, Toronto)
-Leah Kabaroff (M.Sc. Toxicology) Animal Biosciences, supervisor, 2005 (Safety Specialist at Mount Sinai Hospital, Toronto, Ontario)
-Qiumei You (M.Sc.) Animal Biosciences, supervisor, 2006 (University of Guelph Animal Health Laboratory technician, Guelph, Ontario)
-Karen Phillips (M.Sc. Toxicology by coursework) Food Sciences, co-supervisor, 2006 (Senior Scientist, Intrinsik Environmental Science Inc., Calgary, Alberta)
-Jeremy Mount (M.Sc. Toxicology) Animal Biosciences, supervisor, 2007 (Veterinarian)
-Ivan Leyva (Ph.D.) Animal Biosciences, supervisor, 2007 (Product Manager at Thermo Fisher Scientific, Austin, Texas)
-James Godsmark (M. Sc. by coursework) Animal Biosciences, supervisor, 2008
-Rebecca Fisher (M.Sc. Toxicology) Animal Biosciences, co-supervisor, 2008
-Dr. Honghe Cao (post-doctoral fellowship) Animal Biosciences, co-supervisor, 2008 (University of Guelph Laboratory Services Division, Guelph, Ontario)
-Alicia Skelding (M.Sc. by coursework) Animal Biosciences, supervisor, 2009 (Veterinary Specialist in Anesthesia and Analgesia at Toronto Animal Health Partners Emergency and Specialty Hospital, Toronto)
-Yunee Kim (M.Sc. Toxicology) Animal Biosciences, supervisor, 2009 (Regulatory Affairs Associate at Gilead Sciences, U of Toronto, Toronto)
-Jennifer Ravin (M.Sc. course work) Animal Biosciences, supervisor, 2009
-Melissa Marshman (M.Sc. course work) Animal Biosciences, co-supervisor, 2009 (Veterinarian)
-Mainul Husain (Ph.D.) Animal Biosciences, co-supervisor, 2010 (Air Quality and Health Specialist, Regulatory Operations and Enforcement Branch at Health Canada).
-Eric Sauerteig (M.Sc. course work) Animal Biosciences, supervisor, 2010 (Manager, Project Office- Office of Campus Infrastructure and Sustainability, OntarioTech University-U of Waterloo)
-Chris Verschoor (Ph.D.) Animal Biosciences, supervisor, 2010 (Program Lead in Healthy Aging at Health Sciences North Research Institute)
-Sameer Pant (Ph.D.) Animal Biosciences, supervisor, 2010 (Assistant Professor Charles Sturt University, Wagga Wagga, New South Wales, Australia)
-Judy Stryker (M.Sc.) Animal Biosciences, supervisor, 2010
-Laura (Cain) Toms (M.Sc.) Animal Biosciences, supervisor, 2011 (Territory manager at Nestle Purina North America)
-Nancy Stonos (M.Sc. course work) Animal Biosciences, supervisor, 2012 (Technical and Regulatory Analyst at Animal Nutrition Association of Canada)
-Dr. Bhawani S. Sharma (post-doctoral fellowship/ research associate) Animal Biosciences, supervisor 2008-2012 (recovering from cancer)

-Philip Mead (M.Sc. Toxicology) Animal Biosciences, supervisor, 2013 (Chief Resident of Internal Medicine at OSF HealthCare)
-Rebecca Fisher (Ph.D. Toxicology) Animal Biosciences, supervisor, 2013
-Nitish Boodhoo (M.Sc. course work) Animal Biosciences, supervisor, 2013 (PDF, Pathobiology, U of Guelph, Ontario)
-Sanjay Mallikarjunappa (M.Sc. Toxicology) Animal Biosciences, supervisor 2013 (Ph.D. student University of Guelph, Guelph, Ontario)
-Dr. Rebecca Fisher-Heffernan (post-doctoral fellowship) Animal Biosciences, supervisor 2014-2015 (Research and Strategic Initiatives Facilitator, Lakehead University, Orillia)
-Heng Kang (M.Sc. coursework) Animal Biosciences, supervisor 2015 (Ph.D. student, Guelph)
-Steven Oh (Ph.D. Toxicology) Animal Biosciences, supervisor 2015
-Ziwei Li (M.Sc. Toxicology) Animal Biosciences, supervisor, 2015
-Qiumei You (Technician) Animal Biosciences 2006-15 (University of Guelph Animal Health Laboratory technician, Guelph, Ontario)
-Sarah Buttle (M.Sc. coursework Toxicology) Animal Biosciences, co-supervisor, 2017 (Veterinary Pharmaceutical Rep at NovaVive Inc.)
-Yunyun Guo (M.Sc. coursework Toxicology) Animal Biosciences, co-supervisor, 2017
-Lan You (M.Sc. Toxicology) Animal Biosciences, co-supervisor 2017 (GTA Regional manager at Robotique Zone 01 Robotics)
-Dr. Heba Attala (Research Associate) Animal Biosciences, co-supervisor 2017 (Research Associate, Pathobiology, U of Guelph, Ontario)
-Steven Oh (post-doctoral fellowship) Animal Biosciences, supervisor 2017 (Research Professor at Ewha Womans University, South Korea)
-Ziwei Li (Technician) Animal Biosciences 2015-2019 (University of Guelph Animal Health Laboratory technician, Guelph, Ontario)
-Alison Lee (Ph.D. Toxicology) Animal Biosciences, supervisor 2019 (Swine Researcher at Conestoga Meats)
-Samantha Dixon (M.Sc.) Animal Biosciences, co-supervisor 2019 (Buck Animal Hospital)
-Philip Mak (M.Sc. coursework Toxicology) Animal Biosciences, supervisor 2019 (Ph.D. student, Guelph)
-Sanjay Mallikarjunappa (Ph.D.) Animal Biosciences, supervisor 2019
-Emma Borkowski (Ph.D.) Pathobiology, co-supervisor 2019, (Assistant Professor, University of Surrey, Guildford, Surrey UK)
-Daniel Rothschild (M.Sc.) Animal Biosciences, co-supervisor 2019
-Danielle Naylor (M.Sc.) Animal Biosciences, supervisor 2020
-Nicole Moran (M.Sc. Toxicology) Animal Biosciences, supervisor 2021
-Ankita Sharma (Post-doctoral fellowship) Animal Biosciences, supervisor 2018-2021
-Misha McCaughan (M.Sc. coursework Toxicology) Animal Biosciences, supervisor 2021
-Ran Xu (Ph.D.) Animal Biosciences, supervisor 2023
-Kristen Lamers (Technician) Animal Biosciences 2019-2022
-Umesh Kumar Shandilya (Research Associate) Animal Biosciences, supervisor 2018-2022
-Caitlin McAllister (M.Sc. coursework) Animal Biosciences 2022
-Michael Ling (M.Sc. coursework) Animal Biosciences 2022
-Xiang Wu (M.Sc. coursework) Animal Biosciences 2022
-Tianna Sullivan (M.Sc.) Animal Biosciences, supervisor 2023

-Runzi Wang (M.Sc.) Animal Biosciences, supervisor 2023
-Yuancheng Liu (M.Sc. coursework Toxicology) Animal Biosciences, supervisor 2023
-Nicole Moran (Ph.D.) Animal Biosciences, supervisor
-Kristen Lamers (Ph.D.) Animal Biosciences, supervisor
-Nancy Gao (M.Sc. Toxicology) Animal Biosciences, supervisor
-Nieve Komadan (M.Sc. Toxicology) Animal Biosciences, supervisor
-Samantha Randle (M.Sc. coursework) Animal Biosciences, supervisor
-Spencer Leuschner (M.Sc. coursework) Animal Biosciences, supervisor
-Rebecka Sadler (M.Sc. Toxicology) Animal Biosciences, supervisor
-Samantha Dixon (Technician) Animal Biosciences 2023-2024

Graduate Student Committees:

-Zhumei Kang (M.Sc.) Animal Biosciences, committee member, 2005
-Maxwell Leung (M.Sc. Toxicology) Animal Biosciences, committee member, 2007
-Wendy Pearson (Ph.D.) Biomedical Sciences, committee member, 2007
-Corrine Hamilton (Ph.D.) Pathobiology, committee member, 2008
-Spencer Russell (Ph.D.) Pathobiology, committee member, 2008
-Mohsen Jafarikia (Ph.D.) Animal Biosciences, committee member, 2008
-Gordon Mitchell (Ph.D.) Pathobiology, committee member, 2008
-George Girgis (Ph.D.) Animal Biosciences, committee member, 2009
-Katja Linher (M.Sc.) Animal Biosciences, committee member, 2009
-Girish Channarayapatnak (Ph.D.) Animal Biosciences, committee member, 2009
-Mamun Or-Rashid (Postdoctoral fellowship) Animal Biosciences, co-supervisor, 2009
-Paulina Wiercinska (M.Sc.) Animal Biosciences, committee member, 2009
-Shannon Cartwright (M.Sc.) Pathobiology, committee member, 2010
-Michael Steele (Ph.D.) Animal Biosciences, committee member, 2011
-Meghan Hewitt (M.Sc.) Animal Biosciences, committee member, 2011
-Anooshrokh Rakhshandeh (Ph.D.) Animal Biosciences, committee member, 2011
-John Doelman (Ph.D.) Animal Biosciences, committee member, 2012
-Jason Baley (M.Sc.) Animal Biosciences, committee member, 2012
-Brandon Walters (M.Sc. Toxicology) Animal Biosciences, committee member, 2012
-Melissa Mortson (M.Sc.) Animal Biosciences, committee member, 2012
-Kathleen Thompson (Ph.D.) Pathobiology, committee member, 2012
-Louis Dionissopoulos, (Ph.D.) Animal Biosciences, committee member 2013
-Liu Hong Chen (Ph.D.) Animal Biosciences, co-supervisor 2013
-Lyle Shepherd (M.Sc.) Animal Biosciences, committee member 2013
-Lesley Berghuis (M.Sc.) Pathobiology, committee member 2013
-Mauren Crump (M.Sc.) Animal Biosciences, committee member 2015
-Bing Liu (M.Sc.) Animal Biosciences, committee member 2016
-Marlene Paibomesai (Ph.D.) Pathobiology, committee member 2016
-Shanmugasundaram Karuppuswamy (Ph.D.) Biomedical Science, committee member 2016
-Jamie Hooft (Ph.D.) Animal Biosciences, committee member 2017
-Monica Baquero (Ph.D.) Pathobiology, committee member 2017
-Luis Pena Ortega (Ph.D.) Animal Biosciences, committee member 2016

-Bo Pan (Ph.D.) Animal Biosciences, committee member 2018
-Hailey Hunter (M.Sc.) Integrative Biology, committee member 2018
-Kevin Stinson (Ph.D.) Pathobiology, committee member 2018
-Rebecca Egan (D.V.Sc.) Pathobiology, committee member 2019
-Kristen Lamers (M.Sc.) Clinical Studies, committee member 2019
-Mariana Roedel (M.Sc.) Animal Biosciences, committee member 2020
-Matthew Wong (M.Sc.) Animal Biosciences, committee member 2020
-Reza Akbari Moghaddam Kakhki, (Ph.D.) Animal Biosciences, committee member 2020
-Nasrin Setayesh (M.Sc.) Pathobiology, committee member 2020
-Michelina Crosbie (M.Sc.) Animal Biosciences, committee member 2020
-Lauren Hansen (M.Sc.) Animal Biosciences, committee member 2020
Mohaammed Boareki (Ph.D.) Animal Biosciences, committee member 2021
-George Hall (Ph.D.) Animal Biosciences, committee member 2021
-Chenchen Tang (M.Sc.) Animal Biosciences, committee member 2021
-Sudhanshu Sudan (Ph.D.) Animal Biosciences, committee member 2022
-Shannon Cartwright (Ph.D.) Pathobiology, committee member, 2022
-Emily Kim (Ph.D.) Animal Biosciences, committee member 2023
-Jiali Chen (Ph.D.) Animal Biosciences, committee member 2023
-Aileen MacLellan (Ph.D.) Animal Biosciences, committee member 2023
-Olivia Willoughby (Ph.D.) Animal Biosciences, committee member
-Alexandra Mick (M.Sc.) Animal Biosciences, committee member
-Kathryn Burns (M.Sc.) Animal Biosciences, committee member
-Amanda Mansz (D.V.Sc.) Pathobiology, committee member
-Kristin Wythe (M.Sc.) Pathobiology, committee member
-Raelyn McCurdy (M.Sc.) Animal Biosciences, committee member
-Tess Altvater-Hughes (Ph.D.) Pathobiology, committee member
-Julie Kim (Ph.D.) Population Medicine, committee member
-Wenyi Fan (Ph.D.) Animal Biosciences, committee member
-Lori Ogilvie (M.Sc.) Animal Biosciences, committee member
-Anna Garland (Ph.D.) Animal Biosciences, committee member
-Elise Lafleur Lariviere (M.Sc.) Animal Biosciences, committee member
-Linyi Tang (M.Sc.) Biological Engineering, committee member
-Carmon Co (D.V.Sc.) Pathobiology, committee member
-Linyi Tang (M.Sc.) School of Engineering, committee member
-Maddie Borland (M.Sc.) Animal Biosciences, committee member
-Tesa Kinasih (Ph.D.) Animal Biosciences, committee member

Visiting Scholars:

-Dr. Herman Boermans (Sabbatical) Biomedical Sciences, Univeristy of Guelph, 2009
-Dr. Yong Jun Li, (Sabbatical) College of Animal Science & Technology, Yangzhou University, Yangzhou, Jiangsu, China, 2011
-Laila Schnekel (M.Sc.), visiting graduate student, Universidade Federal Do Rio Grande Do Sul, Brazil, 2012
-Dr. Jialang Zhang (Sabbatical) West Campus, Animal Science Department, College of Animal Science, Yangtze University, Jingzhou, Hubei, China, 2013

-Yunyun Guo, visiting scholar, Hunlun Buir Center for Disease Control and Prevention, Hulun Buir City, Inner Mongolia, 2015
-Dr. Binglei Shen, visiting scholar, College of Animal Science and Veterinary Medicine, Heilongjiang Bayi Agricultural University, Daqing, 2015
-Dr. Yongjiang Mao, (Sabbatical) College of Animal Science & Technology, Yangzhou University, Yangzhou, Jiangsu, China, 2015
-Dr. Chunfang Wang, visiting scholar, College of Fisheries, Huazhong Agricultural University, Wuhan, Hubei, 430070, P.R. China 2018-21
-Cheng Ke (M.Sc.), visiting graduate student, College of Fisheries, Huazhong Agricultural University, Wuhan, Hubei, 430070, P.R. China 2019
-Dr. Umesh Kumar Shandilya, visiting scholar, Animal Biotechnology Division, National Bureau of Animal genetic Resources, Haryana, India 2019
-Jiahe Guo (M.Sc.), College of Animal Science & Technology, Yangzhou University, Yangzhou, Jiangsu, China, 2019
-Krishani Wijeshinghe (MSc.) Institute of Agriculture, University of Peradeniya, Sri Lanka
-Yan Liang (Ph.D.), College of Animal Science & Technology, Yangzhou University, Yangzhou, Jiangsu, China, 2023
-Yang Lui visiting scholar, Coldwater Fish Research Laboratory, Department of Aquaculture, Heilongjiang River Fisheries Research Institute, Chinese Academy of Fishery Sciences, Harbin.

Undergraduate Student Supervision:

-Elizabeth Courtney (Summer Student) Ontario Veterinary College, 2004 (Veterinarian)
-Jeremy Mount (Summer Student) Human Biology, 2004 (Veterinarian)
-Sergio Aguirre (Summer Student) Animal Biosciences, 2005 (Co-founder and CEO of Epineuron – Richard Ivey School of Business, Toronto)
-Yunee Kim (Summer Student) Animal Biosciences, 2005
-Robyn Slavinski (Summer Student) Animal Biosciences, 2005 (Veterinarian)
-Jessica Hartley (Hons. Thesis Project Student) Molecular Biology and Genetics, 2005 (Program Director for the MSc in Genetic Counselling at U of Manitoba, Manitoba)
-Carl McNicoll (Summer Student) Ontario Veterinary College, 2002-2005 (Veterinarian CFIA)
-Christian Sandrock (Hons. Thesis Project Student) Biomedical Sciences, 2006 (Laboratory Technician at University of Guelph Animal Health Laboratory)
-Julie Martin (Summer Student) Biomedical Sciences, 2006
-Tyler O'Neill (Summer Student) Animal Biosciences, 2006 (Veterinarian)
-Graham Biggar (Summer Student) Animal Biosciences, 2007-2008 (Veterinarian)
-Elise Shine (Hons. Thesis Project Student) Animal Biosciences, 2007
-Laura Cain (Hons. Thesis Project Student) Animal Biosciences, 2007
-Eric Sauerteig (Hons. Thesis Project Student) Animal Biosciences, 2009
-Sarah Taylor (Hons. Thesis Project Student) Animal Biosciences, 2009 (Veterinarian)
-Cara Yu (Summer Student) Biomedical Sciences, 2009 (Veterinarian)
-Trevor Giesler (Hons. Thesis Project Student) Animal Biosciences, 2010
-Rachael Nehir Oktem (Summer student) Animal Biosciences, 2010

-Caroline Balch (Hons. Thesis Project Student) Animal Biosciences, 2011 (Medical Laboratory Technologist in Kingston General Hospital clinical genetics lab, Kingston)
-Megan Whaley (Hons. Thesis Project Student) Animal Biosciences, 2011 (M.Sc. student at University of Guelph, Guelph)
-Samantha Medeiros (Hons. Thesis Project Student) Animal Biosciences, 2012 (Floridale Feed Mills, Floridale)
-Rachel Cliff (Hons. Thesis Project Student) Animal Biosciences, 2012 (M.Sc. student at University of British Columbia)
-Katherine Goliboski (Hons. Thesis Project Student) Animal Biosciences, 2012 (Veterinary Assistant, Brantford)
-Mikayla Ross (Hons. Thesis Project Student) Animal Biosciences, 2012 (Semex Alliance Inc.)
-Samantha Balthes (Hons. Thesis Project Student) Animal Biosciences, 2013
-Chris Hylands (Hons. Thesis Project Student) Biomedical Science, 2013 (QA Inspector, Novartis, Mississauga)
-Andrew Brereton (Hons. Thesis Project Student) Molecular Biology and Genetics, 2013 (M.Sc. student at Oregon State University, Oregon)
-Jillian Wegelin (Hons. Thesis Project Student) Animal Biosciences, 2013 (Veterinary technician)
-Mitra Jafari (Hons. Thesis Project Student) Animal Biosciences, 2013
-Vikram Bettadapura (Hons. Thesis Project Student) Animal Biosciences, 2013
-Katherina Welsh (Hons. Thesis Project Student) Nutrition, 2013 (Clinical nutritionist)
-Irene Lui (Summer student) Animal Biosciences, 2013 (Veterinarian)
-Alison Lee (Hons. Thesis Project Student) Animal Biosciences, 2014
-Julie Nadeau (Hons. Thesis Project Student) Animal Biosciences, 2014 (Veterinarian)
-Gabrielle Ene (Hons. Thesis Project Student) Animal Biosciences, 2014-2015
-Jasmine Carter (Hons. Thesis Project Student) Biomedical Science, 2014-2015
-Alisha Wornath-Vanhumbeck (Hons. Thesis Project Student) Animal Biosciences, 2014-2015
-Leighanna Yip (Hons. Thesis Project Student) Animal Biosciences, 2015
-Erin Syjueco (Summer student) Animal Biosciences, 2015 (Veterinarian)
-Kevin Barbosa (Summer student) Animal Biosciences, 2015
-Sean Roberts (Hons. Thesis Project Student) Animal Biosciences, 2016
-Philip Mak (Hons. Thesis Project Student) Animal Biosciences, 2016
-Kristen Lamers (Hons. Thesis Project Student) Animal Biosciences, 2016
-Michael Alcorn (Summer student) Animal Biosciences, 2016
-Alexandra Code (Hons. Thesis Project Student) Animal Biosciences, 2017-2018
-Oren Furmanov (Hons. Thesis Project Student) Animal Biosciences, 2017-2018
-Nicole Moran (Hons. Thesis Project Student) Animal Biosciences, 2018
-Theepan Tharumalingam (Summer student) Animal Biosciences, 2018-2019
-Tianna Sullivan (Hons. Thesis Project Student) Animal Biosciences 2018-2019
-Aisha Fong (Hons. Thesis Project Student) Animal Biosciences 2018
-Joey Ma (Hons. Thesis Project Student) Animal Biosciences 2018-2019
-Yieshna Bhujoo (Hons. Thesis Project Student) Biomedical Science 2019
-Tianna Sullivan (Summer student) Animal Biosciences 2019

-Yashi Zheng (Summer student, Hons. Thesis Project Student) Animal Biosciences 2019-2020
-Elizabeth Teel (Summer student) Animal Biosciences 2019
-Runzi Wang (Hons. Thesis Project Student) Animal Biosciences 2019-2020
-Victoria De Carvalho (Hons. Thesis Project Student) Animal Biosciences 2019-2020
-Ashley-Gail Lyons (Hons. Thesis Project Student) Animal Biosciences 2019-2020
-Gee-Zou J Wang (Hons. Thesis Project Student) Animal Biosciences 2020
-Giselle Kalnins (Hons. Thesis Project Student) Biomedical Sciences 2020
-Caitlin McAllister (Hons. Thesis Project Student) Animal Biosciences 2020
-Nancy Gao (Summer student & Hons. Thesis Project Student) Animal Biosciences 2021-2022
-Megan Woo (Hons. Thesis Project Student) Animal Biosciences 2021-2022
-Claudia Mercurio (Hons. Thesis Project Student) Biomedical Sciences 2022
-Sophie Tieu (Summer student) Animal Biosciences 2022
-Teeba Ismail (Hons. Thesis Project Student) Animal Biosciences 2022-2023
-Rebecka Sadler (Summer student) Animal Biosciences 2023
-Guyue Renke (Hons. Thesis Project Student) Animal Biosciences 2023-2024

High School Student Supervision:

-Alice Meng Gao, Guelph Collegiate Vocational Institute, Guelph, Ontario, 2009
-Stanley Lien, St. John's Kilmarnock, Breslau, Ontario, 2009
-Research project co-advisor with Dr. Louise Temple (James Madison Univerisity, Virginia) for students Joseph Burns and Benjamin Ghaemmaghami, Eastern Mennonite High School, Harrisonburg, Virginia, 2013

Course Lecturing:

-Graduate Course in Comparative Immunology, College of Animal Science and Technology, Huazhong Agricultural University, Wuhan, Hubei, 430070, P.R. China 2022 (32 hours) 2022
-Graduate Course in Nutritional Immunology, College of Animal Science and Technology, Huazhong Agricultural University, Wuhan, Hubei, 430070, P.R. China 2020 (30 hours)
-Graduate Course in Animal Health, College of Animal Science and Technology, Yangzhou University, Yangzhou, China 2019 (20 hours)
-Graduate Course in Animal Health, Department of Animal Nutrition and Feed Science, Sichuan Agricultural University, Chengdu, China 2018 (20 hours)
-Graduate Course in Animal Health, College of Animal Science and Technology, Yangzhou University, Yangzhou, China 2018 (20 hours)
-Graduate Course in Comparative Immunology, College of Animal Science and Technology, Huazhong Agricultural University, Wuhan, Hubei, 430070, P.R. China 2016-19 (32 hours)
-Graduate Course in Comparative Immunology, College of Animal Science and Technology, Yangzhou University, Yangzhou, China 2017 (20 hours)
-ANSC3270 Animal Disorders 2017-22 (60 hours)
-ANSC4650 Comparative Immunology 2006-22 (70 hours)

-ANSC 4080 Environmental Management and Animal Health 2004-5 (1 hour)
-AGR2350 Animal Production Systems and Industry 2004-6 (50 hours)
-AGR1250 Food System Trends and Issues 2003 (15 hours)
-ANSC4490 Applied Endocrinology 2003-10 (3 hour)
-TOX6200 Advanced Topics in Toxicology 2003-10 (1 hour)
-TOX4000 Medical Toxicology 2003-12 (3 hours)
-ANSC6330 Genomics and Proteomics for Animal Sciences 2004-6 (36 hours)
-ANSC4090 Applied Animal Behaviour 2005-10 (1 hour)
-ANSC4350 Experiments in Animal Biology 2009-12 (15 hour)
-POPM4230 Animal Health 2013 (70 hours)

Graduate Student Exam Committee Service:

-John Peacock (M.Sc.), Animal Biosciences, 2001
-Jennifer Beveridge (M.Sc.), Pathobiology, 2001
-H.V.L.N. Swamy (Ph.D.), Animal Biosciences, 2001
-Mamiko Shimizu (M.Sc.), Animal Biosciences, 2002
-Jennifer Stewart (M.Sc.), Animal Biosciences, 2002
-Paul Dyce (M.Sc.), Animal Biosciences, 2003
-Shankar Chowdhury (Ph.D.), External Examiner Representative, Animal Biosciences, 2003
- Muthafar Al-Haddawi (D.V.Sc.), Pathobiology, 2006
-Sergey Duvanov (M.Sc.) Animal Biosciences, 2008
-Gordon Mitchell (Ph.D.), Pathobiology, 2008
-Katja Linher (Ph.D.), Animal Biosciences, 2009
-Paulina Wiercinska (M.Sc.) Animal Biosciences, 2009
-Sabrina Greenwood (Ph.D.) Animal Biosciences, 2009
-Sarah Scapinello, (M.Sc.) Pathobiology, 2009
-Ontario Graduate Scholarship Evaluation Committee, 2010
-Kathleen Thompson (Ph.D.) Pathobiology, 2010
-Fariba Izadi Shavakand (Ph.D.) External Examiner, Animal Science, University of British Columbia, 2010
-Jamie Hooft (M.Sc.) Animal Biosciences, 2010
-Meghan Hewitt (M.Sc.) Animal Biosciences, 2011
-Anooshrokh Rakhshandeh (Ph.D.), Animal Biosciences, 2011
-Jason Baley (M.Sc.), Animal Biosciences, 2012
-Joel David (M.Sc.) External Examiner, Department of Medical Science, University of Calgary, July 17, 2013
-Caroline Gonano (M.Sc.) Examining Chair, Animal Biosciences, 2013
-Matthew Gray (Ph.D.) Examining Chair, Animal Biosciences, 2013
-Lesley Berghuis (M.Sc.) Exam Committee, Pathobiology, Committee member 2013
-Janelle Kelly (M.Sc.) Examining Chair, Animal Biosciences 2014
-Morgan Overvest (M.Sc.) Examining Chair, Animal Biosciences 2015
-Bing Liu (M.Sc.) Animal Biosciences, 2016
-Marko Rudar (Ph.D.), Animal Biosciences, 2016
-Victoria Asselstine (M.Sc.), Animal Biosciences, 2018
-Kristen Wight (M.Sc.), Animal Biosciences, 2018

-Kevin Stinson (Ph.D.) Pathobiology, 2018
-Rebecca Egan (D.V.Sc.) Pathobiology, 2019
-Kristen Lamers (M.Sc.) Clinical Studies 2019
-Seyedmehdi Emam (PhD) Pathobiology, 2019
-Nasrin Setayesh (M.Sc.) Pathobiology, 2020
-Yiru Sheng (M.Sc.) Integrative Biology, 2020
-Shannon Cartwright (Ph.D.) Pathobiology 2022
-Shannon Beard (Ph.D.) Pathobiology, 2023
-Aileen MacLellan (Ph.D.) Animal Biosciences, 2023

Graduate Student Qualifying Exam Committee Service:

-Wendy Pearson (Ph.D.), Biomedical Science, 2005
-Gordon Mitchell (Ph.D.), Pathobiology, 2005
-Anooshrokh Rakhshandeh (Ph.D.), Animal Biosciences 2006
-George Girgis (Ph.D.), Animal Biosciences, 2006
- Milton Daley (Ph.D.), Animal Biosciences, 2007
-Girish Channarayapanak (Ph.D.), Animal Biosciences, 2007
-John Doelman (Ph.D.), Animal Biosciences, 2008
-Melkaye Melka (Ph.D.), Animal Biosciences, 2008
-Chandrika Senthilkumaran's (Ph.D.), Pathobiology, 2011
-Krishna Yekkala (D.V. SC.), Pathobiology, 2011
-Jamie Hooft (Ph.D), Animal Biosciences, 2011
-Marlene Paibomesai (Ph.D.), Pathobiology, 2012
-Louis Dionissopoulos, (Ph.D.), Animal Biosciences, 2012
-Lauri Wagter Lesperance (Ph.D.), Pathobiology, 2012
-Shanmugasundaram Karuppuswamy (Ph.D.), Biomedical Science, 2012
-Amanda Mansz (D.V.Sc.), Pathobiology, 2013
-Shirene Singh (Ph.D.), Pathobiology, 2013
-Marko Rudar (Ph.D.), Animal Biosciences, 2013
-Monica Baquero (Ph.D.), Pathobiology, 2014
-Emily Miller (Ph.D.), Animal Biosciences, 2014
-Teresa Casey (Ph.D.), Animal Biosciences, 2014
-Wilfredo Mansilla (Ph.D.) Examining Chair, Animal Biosciences, 2014
-Alison Flemming (Ph.D.), Animal Biosciences, 2015
-Walter Sanchez-Suarez (Ph.D.), Examining Chair, Animal Biosciences, 2015
-Christopher Powel (Ph. D.), Examining Chair, Animal Biosciences, 2016
-Laura Bassel (Ph.D.), Examining Committee, Pathobiology, 2016
-Seyedmehdi Emam (Ph.D.), Pathobiology, 2016
-Flavia Damasceno (Ph.D.), Examining Chair, Animal Biosciences, 2016
-Emma Borkowski (Ph.D.), Examining Committee, Pathobiology, 2017
-Mariana Roedell (Ph.D.), Examining Committee, Animal Biosciences, 2018
-Stephanie Lam (Ph.D.), Examining Committee, Animal Biosciences, 2018
-Reza Akbari Moghaddam Kakhki (Ph.D.), Animal Biosciences, 2018
-Xindi Yin (Ph.D.), Examining Chair, Animal Biosciences, 2019
-Michelle Lavery (Ph.D.), Examining Chair, Animal Biosciences, 2019

-Alison Lee (Ph.D.), Examining Committee, Animal Biosciences, 2019
-Emma Borkowski (Ph.D.), Examining Committee, Pathobiology, 2019
-Victoria Asselstine (Ph.D.), Examining Committee, Pathobiology, 2019
-Sudhanshu Sudan (Ph.D.), Examining Committee, Animal Biosciences, 2020
-Shannon Beard (Ph.D.), Examining Committee, Pathobiology, 2020
-Ran Xu (Ph.D.), Examining Committee, Animal Biosciences, 2020
-Jia Li Chen (Ph.D.), Examining Committee, Animal Biosciences, 2020
-Emily Kim (Ph.D.), Examining Committee, Animal Biosciences, 2020
-Aileen MacLellan (Ph.D.), Examining Committee, Integrative Biology, 2020
-Anna Garland (Ph.D.), Examining Committee, Animal Biosciences, 2021
-Xiaoshu Zhan (Ph.D.), Examining Chair, Animal Biosciences, 2021
-Nooshin Nikmararam (Ph.D.), Examining Committee, School of Engineering, 2021
-Nicole Moran (Ph.D.), Examining Committee, Animal Biosciences, 2023

Administrative Service:

-Office of Research contact for the Department of Animal Biosciences, 2002-4
-Ontario Agriculture College Communications Committee, 2002-4
-Co-chaired the Disease Resistance Symposium at the 7th World Congress on Genetics Applied to Livestock Production, Montpellier, France, Aug. 19-23, 2002
-Council member for the University of Guelph Faculty Association, 2003-2005
-Member of the University of Guelph Salary Negations Committee, 2003-2005
-Member of the Department of Animal Biosciences Undergraduate Teaching Committee, 2004-2012
-Judged Molecular Biology and Genetics undergraduate thesis project student's posters, 2005
-OAC representative of the University of Guelph Mass Spectrometry Committee, 2005-2010
-Undergraduate Ontario Universities Fair, September 28-30, 2007
-Member of OAC delegation to Northwestern A&F University, April 13-17, 2009, Yangling, Shaanxi, China
-Chaired Animal Proteins (Section 5.3) at the 5th Anniversary of Protein and Peptide Conference (PepCon-2012) March 23-25, 2012, Beijing, China
-Departmental Graduate Teaching Committee member, 2012-present
-Departmental Research Committee, 2012-present
-Promotion and Tenure Committee, 2012-2016
-Mycotoxin detection and risk assessment panel member at the Alltech Symposium, Lexington Kentucky, May 19-21, 2013
-Chaired Veterinary Medicine and Treatment, Animal Models and Testing, and Animal Ecology (Sections 6, 7, and 8) at the 1st International OMICS Group Conference on Animal & Dairy Sciences, July 23-24, 2013, Las Vegas, Nevada
-Participated in the Research Strategy Workshop for Stakeholders in the Ontario Goat Sector, Guelph, On. Oct. 3, 2013
-Participated in the Ontario Veal Research Strategy Development Meeting, Guelph, On. Oct. 2, 2013
-Planning committee for ASAS-ADSA-CSAS Joint Annual Meeting section titled "Small

Ruminant: Sustainable Small Ruminant Production Strategies to Meet Global Demands" July 23, 2014, Kansas City, MO
-Client reviewer of the services and functions of U of G Animal Care Services 2014
-Judge at the Waterloo Wellington Science and Engineering Fair, Waterloo, April 8, 2014
-Hosted visiting scientist Dr. Kieran Meade & Bioscience Research Department, Animal & Grassland Research and Innovation Centre, Teagasc, Grange, Co. Meath, Ireland, April 25-26, 2014
-Animal Biosciences Poultry Nutrition Faculty Search Committee, 2014
-Chaired CSAS Graduate Student Oral Presentation Competition at the ADSA-ASAS-CSAS Joint Annual Meeting, 2014, Kansas City, Missouri, July 20-24
-Immunotoxicology consultant for the Safety Evaluation Centre of Shenyang Research Institute of Chemical Industry (SYRICI), 2014, Shanyang, China, August 2-5
-Animal Biosciences representative hosted dairy science delegation from Guyana September 18, 2014
-Animal Biosciences Beef Nutrition Faculty Search Committee 2015
-Animal Biosciences Graduate Student Committee, 2016-2021
-University of Guelph Genomics Facility User Committee, 2014-2018
-Faculty member of the University of Guelph's undergraduate and graduate program in Toxicology, 2004-present.
-Faculty member of the University of Guelph's graduate program in Bioinformatics, 2011-Present
-Animal Biosciences Animal Physiology Faculty Search Committee 2017-18
-Editorial board of Revista de la Facultad de Medicina Veterinariay de Zootecnia, which publishes case reports as well as original articles, reviews, and opinion articles in all areas of veterinary medicine and animal science 2018
-External Ph.D. defence examiner for graduate students (Q. Zhao, S.H. Qamar, B. He, E. Kuang Yi Wen) at Sichuan Agricultural University, Chengdu, Sichuan, P.R. China, 2018
-Animal Biosciences Graduate Student Coordinator, 2019-2020
-Animal Biosciences Aquaculture Faculty Search Committee, 2019
-Animal Biosciences Acting Department Chair 2019-2020
-Animal Biosciences Graduate Program Assistant Search Committee, 2020
-Faculty member of the University of Guelph's graduate program in One Health, 2020-Present
-Promotion and Tenure Committee, 2020-Present
-Guest editor for special Toxins issue on Remediation Strategies for Mycotoxin in Animal Feed of Toxins 2021
-Canadian COVID Care Alliance (CCCA) Science and Medical Advisory Committee 2021-2022
-Chief Scientific Officer of ImmunoCeutica Inc., Cambridge, ON, PO Box 27069 Clair Rd. Guelph, ON N1L0A6, 2022

2002-2000 Postdoctoral Fellowship with Dr. B. Mallard, Department of Pathobiology, University of Guelph, Guelph, Ontario, Canada
Supervised two graduate students research projects and initiated the development of a bovine endocrine-immune microarray chip.

2000 Fall Sessional Lectures
Undergraduate Biomedical Toxicology 4000. Sessions included respiratory, renal, hepatic, dermal toxicology and immunotoxicology.

2000-1999 Research Associate with Dr. K.L. White, Jr., Department of Pharmacology and Toxicology, Medical College of Virginia- Virginia Commonwealth University, Richmond, VA, USA
Principal Investigator for contact hypersensitivity studies, and Study Director for several immunotoxicity studies conducted for the National Institute of Health Sciences (NIEHS).

Course Lecturing:
Supervised two graduate students' rotational projects. I was also involved in lecturing graduate courses in immunotoxicology, chemical hypersensitivity and endocrinology.

PHTX/ENVS 691 Environmental Toxicology: Endocrine disruptors in immunotoxicology
PMC536 Principles of Pharmacology and Toxicology: Dermal toxicology
PMC 535 Introduction to Toxicology: Endocrine toxicology, Immunotoxicology

1999 Immunotox Inc., Richmond, VA, USA
Contracted to develop a holistic cell-mediated immune model for evaluating antisense oligonucleotide anti-inflammatory properties in mice.

1998 Post Doctorate Fellowship with Dr. K.L. White, Jr., Department of Pharmacology and Toxicology, Medical College of Virginia- Virginia Commonwealth University, Richmond, VA, USA
Supervised a graduate student rotational project titled, "Evaluating lymphocyte subsets and cytokine mRNA expression in draining lymph nodes following cinnamaldehyde exposure." A travel grant to the Experimental Contact Dermatitis Research Group was awarded to us for this research.
1998-1997 Consulting Scientist for Environment Canada, Burlington, ON, Canada
Evaluated the immunotoxicity of PAH contaminated sediments and sewage treatment plant effluents in the Hamilton Harbour using caged rainbow trout.

1996-1995 Study Director, University of Guelph, Guelph, ON, Canada
Directed several sublethal creosote microcosm exposure studies. This involved planning, training personnel, and supervising two microcosm field studies to evaluate creosote sublethal toxicity to rainbow trout. Biomarkers of exposure included immune parameters, growth, EROD activity, endocrine response, bile metabolites and DNA adduct formation.

1998-1991 Teaching Assistant, Department of Biology, University of Waterloo, Waterloo, ON, Canada
Demonstrated in numerous undergraduate laboratories including, animal physiology, genetics, toxicology, and immunology. Co-supervised three undergraduate special project students.

1993-1991 Laboratory Technician, BAR Environmental Inc. Guelph, ON, Canada

Technical duties: sediment toxicity testing; benthos taxonomy; spottail shiner collection along Lake Superior; toxicity testing using rainbow trout, Chinook salmon, fathead minnows, *D. magna*, *C. dubia*, *D. pulex*, Lemna, and Rotifers; and Trent River environmental impact assessment.

1990 Fisheries Biologist, Environmental Advisory Services, Guelph, ON, Canada
1990 Great Lakes Fish Collection of Young of the Year Spottail Shiners for the Ministry of the Environment, and brook trout habitat assessment for the Uxbridge and Beaverton Rivers.

1989-1990 Research Assistant, Integrated Explorations Environmental Consultants, Guelph, ON, Canada
Train laboratory personnel to conduct *D. magna* and rainbow trout bioassays and data entry for MISA program.

Technical duties: Saltwater bioassays using mysid shrimp and sheepshead minnows; brook trout stomach content taxonomy; taxonomic identification of benthos from Bass Lake, Misema River, Sir Adam Beck Reservoir and St. Lawrence River (Cornwall) projects; establish quality assurance/quality control monitoring program for laboratory invertebrate, vertebrate and microphyte stocks; analytical and microbiological water quality analysis.

Field work: 1989 Lake Simcoe Whitefish Spawning Shoal Survey; Kincardine sewage treatment plant outflow repair; installation of a destratifier on Guelph Lake; Lakeview water intake inspection; 1991 St. Lawrence benthological Survey in Cornwall; and 1991 Lake Simcoe whitefish and lake trout spawning shoal survey.

1989 Contracted Fisheries Biologist, Ministry of Natural Resources, Owen Sound, ON, Canada
Access point creel survey along Lake Huron.
1988-1989 Research Assistant for Dr. P. Conlon, Department of Biomedical Sciences, University of Guelph, Guelph, ON
Conducted experiments to evaluate the effectiveness of the immunomodulating drug, levamisole, in treating dairy calves infected with IBR virus. Mechanisms of action were explored, using chemiluminescence to assess alveolar macrophage activity, and various therapeutic drugs to modulate respiratory burst.

1987 Research Assistant, Cambridge Horticulture Research Station, University of Guelph, Guelph, ON, Canada
Involved in crop and pesticide research.

1983-1986 **Camp Tawingo**- Counsellor
Cowdenknowles Farms- Swine and crop management
Stoltzlane Farms- Dairy and crop management
University of Waterloo- Usher in Humanities Theatre

Graduate Student Theses:

T. Sullivan (M.Sc.) 2023. Forming the basis for genetic selection of stress resilient dairy heifers: Characterization of the bovine stress response.

M. Wang (M.Sc.) 2023. An Investigation into the use of butyrate to reduce risk of endotoxemia during lethal bacterial lipopolysaccharide challenge in larval zebrafish.

R. Xu. (Ph.D.) 2023. In vitro toxicity assessment of mycotoxins using bovine mammary epithelial cells and their remediation using yeast-based adsorbents.

N. Moran (M.Sc.) 2021. An investigation into the potential use of 6-gingerol to combat endotoxemia and reduce inflammation during tissue trauma in larval zebrafish.

D. Naylor (M.Sc.) 2020. The ovine inflammatory response to lipopolysaccharide and association with the stress response phenotype.

S. Mallikarjunappa (Ph.D.) 2019. Johne's disease in dairy cattle: Validation of genetic markers and assessment of salivary gland transcriptome.

S. Dixon (M.Sc.) 2019. Identifying hepatic genes regulating the ovine response to gastrointestinal nematodes.

A. Lee (Ph.D.) 2019. Effect of microalgae or fish oil supplementation in late gestation sows on piglet health.

E. Borkowski (Ph.D.) 2019. Investigation of the immune response of sheep to gastrointestinal nematode infection under Ontario grazing conditions to identify genetically resistant animals.

L. You (M.Sc.) 2017. Effect of fish oil or algae meal supplementation on the fetal and neonatal endotoxin-induced stress response.

Z. Li (M.Sc.) 2015. In vitro assessment of Saccharomyces cerevisiae derivatives using bovine epithelial cells, macrophages, and Mycobacterium avium spp. paratuberculosis.

S. Oh (Ph.D.) 2014. Assessing immunomodulatory effect of Penicillium mycotoxins using a bovine macrophage cell line (BOMACs)

S. Mallikarjunappa (M.Sc.) 2013. Breed-specific cytokine expression in Holstein-Friesian and Jersey calves infected with Mycobacterium avium subsp. Paratuberculosis.

R. Fisher (Ph.D.) 2013. Maternal supplementation with fishmeal protects against late gestation endotoxin-induced fetal programming of the ovine hypothalamic-pituitary-adrenal axis.

P. Mead (M.Sc.) 2013. Infection of monocyte-derived macrophages with a reporter Mycobacterium avium spp. paratuberculosis (MAP) strain: validation of the susceptibility SNP (-298A>G) in the bovine MIF gene.

L. Cain (M.Sc.) 2011. Variation in the endotoxin-induced ovine cortisol response and its association with immune function.

J. Stryker (M.Sc.) 2010. Evaluation of dietary fish meal or soybean meal supplementation effects on ovine immune response during pregnancy and lactation

C. Verschoor (Ph.D.) 2010. Genetic variation in candidate inflammatory-related genes and its relation to infectious bovine disease.

S. Pant (Ph.D.) 2010. Identification of SNPs and chromosomal regions associated with inflammatory disease resistance in Holstein dairy cattle.

M. Hosain (Ph.D.) 2010. Using BALB/c mice as a model of food allergy to study gene expression profiles in response to common food allergens.

Y. Kim (M.Sc.) 2009. Evaluation of local and systemic bovine host defense protein profiles following intramammary challenge with various strains of *Staphylococcus aureus*.

A. Skelding (M.Sc.) 2009. Association of SNP in the IL-12 and IL-23 receptor genes with milk SCS and antibody response to MAP infection in dairy cattle.

R. Fisher (M.Sc.) 2008. Effect of maternal endotoxemia on the offspring hypothalamic-pituitary-adrenal axis and fever response later in life.

I. Leyva (Ph.D.) 2007. Association of SNPs in the CCL2, CXCL8, CCR2, and CXCR1 genes with health and production traits in Canadian Holsteins.

J. Mount (M.Sc.) 2007. Inflammation induced chemokine gene expression in bovine mammary gland explants.

Q. You (M.Sc.) 2006. Evaluation of immune responsiveness and hepatic gene expression in high, medium, and low endotoxin stress responsive sheep. M.Sc. Thesis. University of Guelph.

L.C. Kabaroff (M.Sc.) 2005. The acute phase response to *E. coli* LPS in pregnant and non-pregnant ewes. M.Sc. Thesis. University of Guelph.

Book Chapters:

S. Karuppusamy, L. Mutharia, D. Kelton, B. Plattner, S. Mallikarjunappa, **N. Karrow**, G. Kirby 2021. Detection of Mycobacterium avium Subspecies paratuberculosis (MAP) microorganisms using antigenic MAP cell envelope proteins. Advances in the Diagnosis

and Control of Johne's Disease. Eds. M. Alonso-Hearn, K. de Silva, M. Salgado. Frontiers Media SA. doi: 10.3389/fvets.2021.615029, Volume 8, Article 615029, pp. 70-83.

N.A. Karrow, Z. Li, S. Oh. Endotoxin tolerance: fishing for answers 2016. Advances in Medicine and Biology Vol. 99, Ed. L.V. Berhardt. Nova Science Publishers, ISBN 978-1-63485-098-8. Chapter 1.

S. Oh, R.E. Fisher, H.V.L.N. Swamy, H.J. Boermans, A. Yiannikouris, **N.A. Karrow** 2015. Silage *Penicillium* Mycotoxins: Hidden Modulators of the Immune System. Mycotoxins: Occurrence, Toxicology and Management Strategies, Ed. C. Rios. Nova Science Publishers, ISBN 978-1-63483-544-2. Chapter 1.

M. Ross, S. Oh, A. Yiannikouris, **N.A. Karrow** 2015. The Effects of the Trichothecenes: T-2, Deoxynivalenol, Diacetoxyscirpenol, Fusarenon-x, Nivalenol and Neosolaniol, on Livestock Health and Production with Emphasis on Ruminants. Mycotoxins: Occurrence, Toxicology and Management Strategies, Ed. C. Rios. Nova Science Publishers, ISBN 978-1-63483-544-2. Chapter 2.

N.A. Karrow, B. Sharma, R. Fisher, B.A. Mallard, 2011. Epigenetics and Animal Health, Comprehensive Biotechnology, 2nd Edn. Editor-in-Chief: M. Moo-Young. Elsevier. ISBN: 978-0-08-088504-9. pp. 381-394.

C. P. Verschoor, S. D. Pant, and **N.A. Karrow**, 2010. Unraveling the genetics of bovine Johne's disease: Lessons learned from human inflammatory bowel disease. Veterinary Immunology and Immunopathology. Eds. L. Neumann and S. Meier. NOVA Science Publishers, ISBN 978-1-61761-656-3.

N.A. Karrow and E. J. Squires, 2005. Novel Discoveries & Technologies in Neuroendocrine-Immune Research. Animal production and animal science worldwide, World Association for Animal Production book of the year. Wageningen Academic Publishers, The Netherlands, pp 99-108.

Magazine/WEB Articles:

K. Wijesinghe, A. Sharma, N.A. Karrow 2021. Stress resilience of sheep to climate change. Ontario Sheep News 39:1:10

Ariana Longley 2018. Combatting Johne's disease. Milk Producer 94:12:38.

N. Stonos 2017. Johne's and Maedi-Visna – More to the story. Ontario Sheep News 36:1: 22.

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J.J. Whyte, **N.A. Karrow**, H. Boermans, D.G. Dixon and N.C. Bols 2000. Combined methodologies for measuring exposure of rainbow trout to polycyclic aromatic hydrocarbons (PAHs) in creosote contaminated microcosms. Polycyclic and Aromatic Compounds 18, 71-98.

N.A. Karrow, H.J. Boermans, N.C. Bols, D.G. Dixon, K.R. Solomon and J.J. Whyte 1999. Characterizing the immunotoxicity of creosote to rainbow trout *Oncorhynchus mykiss*: a microcosm study. Aquatic Toxicology 45, 223-239.

D. Percy, **N.A. Karrow** and J. Bhasin 1988. Incidence of Pasteurella and Bordetella infections in fryer rabbits: an abattoir survey. Journal of Applied Rabbit Research 11, 245-256.

KTT Articles, Workshops or Symposiums:

B.D. De Wolf, C. Bauman, P.I. Menzies, E.A. Borkowski, **N.A. Karrow**, A.S. Peregrine 2023. Evaluating the CARLA Saliva Test ® in Ontario: is saliva the key to parasite resistant sheep? Ontario Sheep Convention, Alliston, Ontario, October 26-27th.

N. Moran, K. Lamers, S. Dixon, R. Sadler, **N.A. Karrow** 2023. Supplementation with organic versus inorganic selenium during pregnancy to support ewe and lamb health. Ontario Sheep Convention, Alliston, Ontario, October 26-27th.

S. Randle, S. Dixon, L. Wagter-Lesperance, B. Mallard. **N.A. Karrow** 2023. The role of Vitamin D in the stress response of sheep. Ontario Sheep Convention, Alliston, Ontario, October 26-27th.

Do No Harm: Protect Pregnancy & Breastfeeding Do no Harm 2023. https://www.canadiancovidcarealliance.org/wp-content/uploads/2023/07/Protect-

Pregnancy-Do-No-Harm-CCCA-Resource-Guide-Jul-26-2023.pdf / https://rumble.com/v32thny-are-the-covid-19-mrna-vaccines-safe-for-pregnant-and-breastfeeding-women.html

N.A. Karrow et al. 2022. PAXLOVID™ - Making an Informed Decision https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/07/PAXLOVID-Making-an-Informed-Decision-20220727.pdf

E. Bastian, **N.A. Karrow**, O. Halgas, K. Nakatsu 2021. Early treatment of the inflammatory stage of COVID-19 and its rationale. https://zenodo.org/record/5033246#.YNZt4vKSleU

N.P. Moran, K. Lamers, **N.A. Karrow** 2020. The effect of parental age on larval zebrafish survival following LPS challenge. University of Guelph GSA Virtual Conference. Guelph, ON, August 26th.

N.A. Karrow, E. Borkowski, A. Peregrine, P. Menzies, J. Avula, B. Lillie, D. Kennedy, J. MacTavish, A. Canovas, S. Dixon, B. Lillie 2019. Immune Response of Sheep to GIN Infection Under Ontario Grazing Conditions to Identify Genetically Resistant Animals, Ontario Sheep Farmers Board Meeting, December 5th.

A. Suárez-Vega, E.A. Borkowski, S. Dixon, **N.A. Karrow**, A.S. Peregrine, P. Menzies, B. A. Mallard, M. N. Boareki, F. S. Schenkel, A. Cánovas. 2019. Identification of novel transcripts associated with parasite resistance in sheep. Ontario Sheep Convention, Alliston, Ontario, October 24-25th.

U.K. Shandilya, S. Mallikarjunappa, A. Sharma, J. Guo, Y. Mao, **N.A. Karrow** 2019. Toll-like receptor 4 (TLR4) and its association with bovine mastitis and Johne's disease. International Symposium on new insights on animal nutrition, breeding and reproduction. Yangzhou, China, September 26-27th.

E. Borkowski, **N.A. Karrow**, P. Menzies, J. Avula, B. Lillie, A.S. Peregrine 2018. Searching for superewes: Can CarLA help select sheep with immunity to nematodes? Ontario Sheep Convention. Alliston, Ontario, November 1-2.

D. Naylor, Z. Li, B.A. Mallard, A. Cánovas, C. Baes, **N.A. Karrow** (2018). Breeding sheep resistant to climate change. Arrell Food Summit. May 22, Guelph.

S. Dixon, **N.A. Karrow**, P. Menzies, P. Fonseca, D. Kennedy, A. Suárez-Vega, E. Borkowski, B.A. Mallard, A. Cánovas 2018. Genetic selection of sheep resistant to gastrointestinal nematodes in a changing climate. Arrell Food Summit. May 22, Guelph.

E. Borkowski, **N.A. Karrow**, P. Menzies, J. Avula, B. Lillie, A.S. Peregrine 2018. Correlation of CarLA® salivary antibody with parasitism in sheep under Ontario grazing conditions. Small Ruminant Research Forum, May 14, Guelph.

E. Borkowski, **N.A. Karrow**, B.A. Mallard, P. Menzies, J. Avula, B. Lillie, A.S. Peregrine 2018. Immunity to gastrointestinal nematodes in sheep with variable stress responses. Small Ruminant Research Forum, May 14, Guelph.

S. Dixon, **N.A. Karrow**, P. Menzies, M. Boareki, P. Fonseca, A. Suarez-Vega, D. Kennedy, A. Peregrine, E. Borkowski, B.A. Mallard, A. Cánovas 2018. Identifying key regulator genes associated with resistance of sheep to parasites and their climate change effects. Small Ruminant Research Forum, May 14, Guelph.

D. Naylor, Z. Li, N.A. Karrow, B.A. Mallard, A. Cánovas 2018. In-vitro characterisation of resilience of stress-phenotyped sheep to climate-associated stressors. Small Ruminant Research Forum, May 14, Guelph.

A.V. Lee, L. You, S. Oh, Z. Li, M. Alcorn, J. Zhu, R.E. Fisher-Heffernan, T. Regnault, L. Huber, C.F.M. de Lange, **N.A. Karrow** 2018. Effect of dietary supplementation with fish oil or microalgae on nursery pig growth and acute-phase response. University of Guelph Swine Research Day, Guelph, May 16.

E. Borkowski, **N.A. Karrow**, P. Menzies, J. Avula, B. Lillie, A. Peregrine 2018. Investigation of the immune and stress responses of sheep to gastrointestinal nematodes under Ontario grazing conditions. Small Ruminant Veterinarians of Ontario AGM 2018. Guelph, Ontario, February 7.

S. Dixon, A. Livernois, S. Cartwright, N. Husseini, M. McKechnie, V. Asselstine, P. Menzies, B.A. Mallard, A. Cánovas, **N.A. Karrow** 2018. Understanding the genes and metabolic pathways associated with the resistance of sheep to gastrointestinal nematodes and its climate change effects. Food from Thought Research Integrated Symposium, Guelph, Ontario, January 10.

A. Livernois, S. Cartwright, N. Husseini, M. McKechnie, S. Dixon, V. Asselstine, **N.A. Karrow**, A. Cánovas, B.A. Mallard 2018. Sustaining robust livestock production and health during climate change. Food from Thought Research Integrated Symposium, Guelph, Ontario, January 10.

V. Asselstine, F. Miglior, A. Livernois, S. Cartwright, N. Husseini, M. McKechnie, S. Dixon, S. Lam, **N.A. Karrow**, B.A. Mallard, A. Cánovas 2018. Genetic mechanism of mucus plug formation and immune response to infection. Food from Thought Research Integrated Symposium, Guelph, Ontario, January 10.

S. Dixon, **N.A. Karrow**, P. Menzies, D. Kennedy, A. Peregrine, L. Brito, A. Suarez-Vega, E. Borkowski, B.A. Mallard, A. Canovas 2017. Leveraging genomic data to understand the genes and metabolic pathways with resistance of sheep to gastrointestinal nematodes. OSMA Annual Meeting, Nottawasaga, Ontario, October 26-27.

E. Borkowski, S. Bourgon, A. Peregrine, **N. Karrow**, B. Lillie, P. Menzies 2017. Correlation of pre-breeding CarLA® with periparturient and late lactation fecal

gastrointestinal nematode egg count and hematocrit in Ontario sheep. OSMA Annual Meeting, Nottawasaga, Ontario, October 26-27.

N.A. Karrow 2017. Improving resilience of sheep to stress. Annual GenOvis Meeting, Guelph, Ontario, May 17.

A.V. Lee, L. You, S. Oh, R.E. Fisher-Heffferman, C.F.M. de Lange, **N.A. Karrow** 2017. Maternal dietary omega-3 supplementation in late gestation and effects on piglet health. University of Guelph Swine Research Day, Guelph, Ontario, May 17.

N.Stonos, **N.A. Karrow** 2016. Effect of small ruminant lentiviruses and Johne's disease on Ontario Goats. Ontario Goat Annual Group Meeting, Guelph, Ontario, October 22.

N. Stonos, C. Baiman, P. Menzies, S.K. Wootton, **N.A. Karrow** 2016. Prevalence of small ruminant lentivirus and Mycobacterium avium subsp. paratuberculosis co-infection in Ontario dairy sheep and dairy goats. OSMA Annual Meeting, Alliston, Ontario, October 27-28.

E. Borkowski, A. Peregrine, **N.A. Karrow**, P. Menzies 2016. Investigation of the immune response of sheep to gastrointestinal nematodes under Ontario grazing conditions. OSMA Annual Meeting, Alliston, Ontario, October 27-28.

A.V. Lee, R.E. Fisher-Heffferman, L. You, S. Oh, J. Zhu, D. Wey, C.F.M. de Lange, **N.A. Karrow** 2016. Benefits of algae meal supplementation in nursery pigs. University of Guelph Swine Research Day, Guelph, Ontario, May 4.

A.V. Lee, R.E. Fisher-Heffferman, J. Zhu, D. Wey, C.F.M. de Lange, **N.A. Karrow** 2015. Evaluation of algae meal as an omega-3 supplement in nursery pigs. University of Guelph Mike Wilson Swine Research Day, Guelph, Ontario, June 3.

S. Hooda, N. Richmond, D. Wey, J. Zhu, **N. A. Karrow**, C.F.M. de Lange 2014. Impact of nursery diet protein quality and fish oil supplementation on immune response of pigs. 33rd Centralia Swine Research Update, Kirkton, Ontario, January 29.

N.A. Karrow 2013. Mycotoxins and Dairy Health, Alltech sponsored Dairy Twilight Meeting, Thorndale Ontario, August 22.

N. Stonos, **N.A. Karrow** 2013. Caprine arthritis encephalitis in Ontario goats. OMAFRA Small Ruminant Research Day, Guelph, Ontario, January 31.

N.A. Karrow, Q. You, L. Cain, N. Stonos, B. Sharma, Y. Li, L. Schenkel, F. Schenkel, G. Vandervoort, J. Wilton, M. Marshman, S. Medeiros 2012. Genetics of how sheep respond to stress and disease. OMAFRA Productions Systems Animals Research Expo, Guelph, Ontario, June 26.

R. Fisher, H. Boermans, B. McBride, **N.A. Karrow** 2012. Fishmeal supplementation during gestation protects against endotoxin induced fetal programming of the hypothalamic-pituitary-adrenal axis in sheep. OMAFRA Productions Systems Animals Research Expo, Guelph, Ontario, June 26.

N.A. Karrow 2012. Genetics of how sheep respond to stress and disease. Journey of research in ovine production, CEPOQ meeting, La Pocatiere, Quebec, June 7.

P. Mead, **N.A. Karrow** 2012. Genetic selection of Johne's disease resistance. University of Guelph Dairy Research Communication & Extension Event, Guelph, Ontario, February 21.

R.E. Fisher, M. Or'Rashid, B.W. McBride, H.J. Boermans, **N.A. Karrow** 2011. Maternal Omega-3 Supplementation of the Ewe During Pregnancy and the Impact on the Offspring's Stress Response. OMAFRA Beef and Sheep Research Update, Guelph, Ontario, December 5.

S. Oh, H.J. Boermans, S. Haladi, B.S. Sharma, **N.A. Karrow** 2010. The immunomodulatory effects of *Penicillium* mycotoxins; citrinin, ochratoxin A, patulin, mycophenolic acid, and penicillic acid on a bovine macrophage cell line (BOMACs), OMAFRA Beef and Sheep Research Update, Guelph, Ontario, December 9.

R.E. Fisher, M. Or'Rashid, B.W. McBride, H.J. Boermans, **N.A. Karrow** 2010. Omega-3 fatty acid supplementation during ovine pregnancy and offspring health. OMAFRA Beef and Sheep Research Update, Guelph, Ontario, December 9.

L. Cain, Q. You, J. Wilton, **N.A. Karrow** 2010. The influence of endotoxin exposure on how sheep respond to stress and disease. OMAFRA Beef and Sheep Research Update, Guelph, Ontario, December 9.

R.E. Fisher, M. Or'Rashid, B.W. McBride, H.J. Boermans, **N.A. Karrow** 2010. Omega-3 fatty acid supplementation during ovine pregnancy and offspring health. 2nd Annual Sheep Research Day, Ontario Sheep, Guelph, Ontario, October 28.

Q. You, L. Cain, Y.J. Li, B. Sharma, M. Marshman, **N.A. Karrow** 2010. Genetics of how sheep respond to stress and disease. 2nd Annual Sheep Research Day, Ontario Sheep, Guelph, Ontario, October 28.

M. Marshman, C. You, I. Duncan, **N.A. Karrow** 2009. Variable adrenal responding sheep, which were selected on the basis of their cortisol response to systemic Escherichia coli lipopolysaccharide (LPS) endotoxin challenge, have unique behavior and pituitary responses to psychological stress. 1st Annual Sheep Research Day, Ontario Sheep, Cambridge, Ontario, November 27.

J.A. Stryker, R. Fisher, M. Quinton, B. McBride, **N.A. Karrow** 2009. Effects of dietary fishmeal and soybean meal on ovine innate and acquired immunity during pregnancy and lactation. 1st Annual Sheep Research Day, Ontario Sheep, Cambridge, Ontario, November

27.

Invited speaker at the Beef and Sheep Research Communication and Extension Event, Oct. 2, 2008. Guelph, Ont. "Variation on the ovine stress response to bacterial endotoxin is predominantly determined by signalling within the HPAA".

Invited speaker at the Canadian-Brazil Symposium on Bovine Genomics, April 4-6, 2005, Guelph, Ont. "Review and discussions of the bovine genetics program in Houston".

Invited participant at the Bovine Genome Project: The next phase International Workshop, March 29-31, 2005, Houston, TX.

Invited speaker at the Dairy Research Communication and Extension Event, Feb. 19-20, 2004. Guelph, Ont. "Genetic regulation of mammary inflammation".

Invited participant at the International Workshop on Bovine Genomics June 17-19, 2003 Montreal, QC.

Invited speaker at the Dairy Research Communication and Extension Event, Feb. 20-21, 2003. Guelph, Ont. "Immunogenetic research on dairy cattle: future directions".

Articles in Conference Proceedings:

N.A. Karrow 2023. miRNA Signalling and stress resilience, and its implications for disease resistance. Animal- Science Proceedings 14: 8. PL-6

M.R.L.V. Peixoto, M. Edwards, **N.A. Karrow**, A.E.M. Newman, T.M. Widowski 2018. Susceptibility to pre-natal stress in laying hens: Effects of genetic strain and maternal age on growth rate of the offspring. 11th World Congress on Genetics Applied to Livestock Production. Auckland, New Zealand, February 11-16.

N.A. Karrow, S. Oh, A. Lee, Z. Li, L. You, R.E. Fisher-Hefferman, K. de Lange. 2017. Pre-programming of the immune system to enhance immunological capacity of offspring. 50th ASAS Midwest Section/ADSA Midwest Branch Joint Meeting, Omaha, Nebraska, March 13, Journal of Animal Science 95 Suppl. 2/Journal of Dairy Science 100: Suppl. 1# 144.

N.A. Karrow, A. Lee, M.M. Or-Rashid, O. AlZahal, M. Quinton, B.W. McBride, R.E. Fisher-Hefferman 2015. Maternal nutrition to promote offspring health: Fishing for answers using the bacterial endotoxemia model (Invited). 1st International Animal Intestinal Ecology and Health in China Summit Forum (IAIEH), Changsha, China, November 14th.

Q. You, P, Mead, S. Oh, S. Mallikarjunappa, L. Mutheria, and **N.A. Karrow** 2014. Construction of a reporter *Mycobacterium avium* subsp. *paratuberculosis* (Map) strain and infection of monocyte-derived macrophages from cows homozygous for SNP -298 A>G in

the macrophage migration inhibitory factor (MIF) gene. 10th World Congress on Genetics Applied to Livestock Production. Vancouver, B.C. August 17-22.

S. Mallikarjunappa, B.L. Plattner, P. Mead, L.M. Mutharia, M. Quinton, and **N.A. Karrow** 2014. Cytokine gene expression in Holstein and Jersey calves infected with *Mycobacterium avium* subsp. *paratuberculosis*. 10th World Congress on Genetics Applied to Livestock Production. Vancouver, B.C. August 17-22.

R.E. Fisher, M.M. Or-Rashid, O. AlZahal, M. Quinton, B.W. McBride, H.J. Boermans, and **N.A. Karrow** 2014. Expression of the ovine hippocampal glucocorticoid receptor (GR) and mineralcorticoid receptor, and adrenal melanocortin 2 receptor and GR genes in offspring born to ewes supplemented with fishmeal and stress challenged with bacterial endotoxin during late pregnancy. 10th World Congress on Genetics Applied to Livestock Production. Vancouver, B.C. August 17-22.

N.A. Karrow 2013. Fishmeal supplementation during pregnancy may help protect against maternal stress-induced programming of the ovine fetal neuroendocrine-immune system. Proceedings of the 1st International Conference on Animal & Dairy Sciences, Las Vegas, Nevada, July 23-24, Journal of Veterinary Science & Technology, 4:48.

N.A. Karrow, R. Fisher, J. Stryker, B. McBride 2012. Fishmeal supplementation during ruminant pregnancy and lactation: implications for maternal and neonatal health. Conference proceedings of the 48th Eastern Nutrition Conference, Kitchener, Ontario, May 9-10.

S. Cartwright, N. Begley, L.R. Schaeffer, E.B. Burnside, **N. Karrow,** B. A. Mallard 2010. Variation in Immune Response Between Canadian Purebred Holstein and Crossbred Norwegian Red Calves and First Calf Heifers. 9th World Congress on Genetics Applied to Livestock, August 1-6, Leipzig, Germany.

B.S. Sharma, I. Leyva, F. Schenkel, and **N.A. Karrow** 2006. Polymorphisms in the bovine *TLR4* gene and associations with milk somatic cell score and other health related traits in Canadian Holstein cows. 8th World Congress on Genetics Applied to Livestock, August 13-18, Brazil.

H. Cao, L.C. Kabaroff, Q. You, A. Rodriguez, B.A. Mallard, M. Quinton and **N.A. Karrow** 2006. Ovine hepatic gene expression profiles following systemic challenge with *Escherichia coli* lipopolysaccharide. 8th World Congress on Genetics Applied to Livestock, August 13-18, Brazil.

I. Leyva, F. Schenkel, B.S. Sharma, G.B. Jansen, and **N. A. Karrow** 2006. Evaluation of DNA pooling for low frequency SNP detection, and the association of *CXCR1+777* SNP with health and production traits in Canadian Holstein bulls. 8th World Congress on Genetics Applied to Livestock, August 13-18, Brazil.

A. Hernandez, **N.A. Karrow**, B.N. Wilkie, and B.A. Mallard 2002. Evaluation of immune responses of cattle as a means to identify high or low responders and use of a human microarray to differentiate gene expression. 7th World Congress on Genetics Applied to Livestock Production, August 16-18, Montpellier, France.

Conference Oral Presentations:

N. A. Karrow 2023. Using bacterial endotoxin to assess genetic and epigenetic contributions to the ovine stress response phenotype. International Symposium on Domestic Ruminants' Welfare and Sustainable Production. Yangzhou, China, November 19-22. (Invited)

N.A. Karrow 2023. miRNA Signalling and Stress Resilience, and its Implications for Disease Resistance. 10th International Sheep Veterinary Congress. Seville, Spain, March 6-10.

N.A. Karrow, U.K. Shandilya, C. McAllister, Xiang Wu, A. Sharma 2022. Characterizing the function of Bovine TLR4. Yangzhou International Conference on Agriculture and Agri-Product Safety-Germplasm Innovation Agri-Product Safety in Yangzhou, China, November 30.

N.A. Karrow, U.K. Shandilya, C. McAllister, Xiang Wu, A. Sharma 2022. Functional Characterization of the Bovine TLR4 Gene. International Symposium on Welfare and Health of Farm Animals. Yangzhou, China, August 17.

R. Xu, U.K. Shandilya, A. Yiannikouris, **N.A. Karrow** 2021. Emerging Fusarium mycotoxins disrupt homeostasis of bovine mammary cells by altering cell permeability and innate immune function. Young Scientist Pitch at the 13th World Mycotoxin Forum (virtual), November 30.

R. Xu, U.K. Shandiya, **N.A. Karrow** 2021. Effects of Deoxynivalenol on Permeability of Bovine Mammary Epithelial Barrier. 23rd International Conference on Animal Science, Ruminant Animal Nutrition and Recent Development (Virtual), Toronto, June 15-16.

A. Sharma, T. Sullivan, K. Lamers, **N. A. Karrow** 2021. Variation in circulatory serum biomarkers in dairy heifers exposed to endotoxin indicate disparity in induced physiological responses. 38th International Society for Animal Genetics Conference (ISAG) virtual conference, Cape Town, South Africa, July 26-30th.

A. Sharma, U. K. Shandilya, T. Sullivan, D. Naylor, A. Canovas, B.A. Mallard, **N. A. Karrow** 2020. Screening ovine circulatory miRNAs as biomarkers of microbial stress. 3rd World Congress on Sheep virtual meeting. Beijing, Oct 16-18.

E.A. Borkowski, **N.A. Karrow**, P.I. Menzies, J. Avula, B.N. Lillie, A.S. Peregrine 2019. Salivary antibody to carbohydrate larval antigen: a promising tool for selection of Ontario sheep with superior gastrointestinal nematode immunity. British Association for Veterinary Parasitology (BAVP) Winter Meeting. Edinburgh, UK, December 5-6.

R.A.M. Kakhki, D.W.L. Ma, K. Price, J. Moats, **N.A. Karrow**, T.M. Widowski and E. Kiarie 2019. Impact of feeding dietary sources of docosahexaenoic acid and α-linolenic acid to ISA brown and Shaver white pullet breeders and/or progrny on tibia attributes of 18-wk pullets. Poultry Science Association Annual Meeting, Montreal, Quebec, July 15-18.

A. Sharma, D. Naylor, A. Canovas, B.A. Mallard, **N.A. Karrow** 2019. Identification of ovine serum biomarkers during bacterial endotoxin challenge to characterize stress resilience. 37th International Society for Animal Genetics Conference, Lleida, Spain, July 7-12.

S. Dixon, **N. Karrow**, P. Menzies, A. Suarez-Vega, D. Kennedy, A. Peregrine, E. Borkowski, B. Mallard, A. Cánovas 2019. Identifying potential candidate genes regulating host response to gastrointestinal nematodes in Ontario grazing sheep using transcriptomics. Ontario Small Ruminant Veterinary Conference, Guelph, ON, June 17-19.

D. Naylor, A. Sharma, A. Canovas, B.A. Mallard, **N.A. Karrow** 2019. Exploring the potential of increased stress resilience in sheep with a novel health phenotype. Ontario Small Ruminant Veterinary Conference, Guelph, ON, June 17-19.

E.A. Borkowski, **N.A. Karrow**, P.I. Menzies, J. Avula, B.N. Lillie, A.S. Peregrine 2019. Associations between gastrointestinal nematode parasitism, growth and reproduction in Ontario ewe lambs. Ontario Small Ruminant Veterinary Conference, Guelph, ON, June 17-19.

E.A. Borkowski, **N.A. Karrow**, P.I. Menzies, J. Avula, B.N. Lillie, A.S. Peregrine 2019. Correlation of salivary antibody to carbohydrate larval antigen (CarLA®) with parasitism in Ontario sheep. Ontario Small Ruminant Veterinary Conference, Guelph, ON, June 17-19.

E. Borkowski, **N.A. Karrow**, P. Menzies, J. Avula, B. Lillie, A.S. Peregrine 2018. Correlation of carbohydrate larval antigen (CarLA) antibody response with parasitism in Ontario sheep. American Association of Small Ruminant Practitioners Meeting. Phoenix, Arizona September 13-14.

N.A. Karrow (2018). Immunotoxicity of mycotoxins in food-producing monogastric species. 1st National Conference on Mycotoxins to Ensure the Safety of Feed. Wuhan, China, August 18-19.

M.R.L.V. Peixoto, **N.A. Karrow**, A.E.M. Newman, T.M. Widowski 2018. Effects of early-life stress on embryonic mortality, hatching weight and growth are dependent on stress model, maternal age and genetic line. Poultry Science Association Annual Meeting, San Antonio, Texas. July 23-26.

N.A. Karrow, S. Mallikarjunappa, S.D. Pant, M. Sargolzaei, J. Chesnais, K. G. Meade 2017. Bovine Johne's disease and the search for genetic variants influencing host antibody response to the casuitive agent, *Mycobacterium avium* spp. *paratuberculosis*. 1st Multilateral Conference on Agriculture and Agri-product Safety, Yangzhou University, Yangzhou, China, Nov. 28-30.

S. Mallikarjunappa, M. Sargolzaei, K.G. Meade, **N.A. Karrow**, S.D. Pant 2017. QTLs associated with resistance to MAP infection (Johne's disease) in Holstein-Frisian cattle. Association for Veterinary Teaching and Research Work 51st Annual Scientific Meeting, AFBI, Hillsborough, North Ireland. October 6.

N.A. Karrow, S. Oh, A. Lee, Z. Li, L. You, R.E. Fisher-Hefferman, K. de Lange. 2017. Pre-programming of the immune system to enhance immunological capacity of offspring (Invited). 50th ASAS Midwest Section/ADSA Midwest Branch Joint Meeting, Omaha, Nebraska, March 13.

N.A. Karrow, S. Oh, N. Cedergreen, A. Yiannikouris, H.J. Boermans, T.K. Smith, H.V.L.N. Swamy 2016. Evaluating joint effects of binary mixtures of Penicillium mycotoxin (PMs) using bovine macrophage cell line (BoMacs) (Invited). Joint meeting of the 9th Conference of The World Mycotoxin Forum and the XIVth IUPAC International Symposium on Mycotoxins, Winnipeg, Manitoba, June 6-9.

N.A. Karrow, A. Lee, M.M. Or-Rashid, O. AlZahal, M. Quinton, B.W. McBride, R.E. Fisher-Hefferman 2015. Maternal nutrition to promote offspring health: Fishing for answers using the bacterial endotoxemia model (Invited). 1st International Animal Intestinal Ecology and Health in China Summit Forum (IAIEH), Changsha, China, November 14th.

N.A. Karrow, R.E. Fisher, A. Lee, M.M. Or-Rashid, O. AlZahal, M. Quinton, B.W. McBride, H.J. Boermans 2015. Maternal stress during pregnancy: implications for offspring health and disease (Invited). Japanese Society of Animal Science Annual Meeting, Utsunomiya City, Japan, March 29.

R.E. Fisher, M.M. Or-Rashid, O. AlZahal, M. Quinton, B.W. McBride, H.J. Boermans, and **N.A. Karrow** 2014. Expression of the ovine hippocampal glucocorticoid receptor (GR) and mineralcorticoid receptor, and adrenal melanocortin 2 receptor and GR genes in offspring born to ewes supplemented with fishmeal and stress challenged with bacterial endotoxin during late pregnancy. 10th World Congress on Genetics Applied to Livestock Production. Vancouver, B.C. August 17-22.

N.A. Karrow, S.D. Pant, Q. You, G. V. Voort, L. Schenkel, J. Wilton, L. Cain, F. Schenkel 2014. Identification of chromosomal regions influencing cortisol responses in sheep (Invited). 34 International Society for Animal Genetics Conference, Xi'an, China, July 28-August 1.

N.A. Karrow, S. Oh, 2013. Assessing the impact of Penicillium mycotoxins on immunity using in-vitro studies (Invited). Alltech Management Summit, Budapest, Hungary, November 12-13.

N.A. Karrow, R.E. Fisher, J. Stryker, B. McBride 2013. Nutritional epigenetics and ruminant health (Invited). Alltech Symposium, Lexington, Kentucky, May 19-21.

N.A. Karrow 2013. Developing novel strategies to enhance the health of neonatal ruminants (Invited). Lallemand Lower Gut Workshop, Guelph, Ontario, April 18-19.

N.A. Karrow, S. Oh, B.S. Sharma, R. Cliff, C.G. Balch, H.J. Boermans, H.V.L.N. Swamy 2012. The hidden risks in forages- Detoxifying the milk production killers. Alltech 28th Annual International Animal Health and Nutrition Symposium (Invited). Lexington, Kentucky, May 20-23.

N.A. Karrow, R. Fisher, J. Stryker, B. McBride 2012. Fish meal supplementation during ruminant pregnancy and lactation: implications for maternal and neonatal health (Invited). 48th Eastern Nutrition Conference, Kitchener, Ontario, May 9-10.

N.A. Karrow, B.S. Sharma, C. Verschoor, Q. You 2012. Implications of the genetic and epigenetic regulation of bovine MIF (Invited). 5th Anniversary of Protein and Peptide Conference (PepCon-2012), Beijing, China, March 23-25.

P. Mead, **N.A. Karrow** 2011. Bomac effector function and gene expression during infection with a reporter MAP strain. 4th Canadian MAP Researchers Meeting. Banff, Alberta, October 19-21.

N.A. Karrow 2011. Bovine MIF and Johne's disease: genetic variants, functional characterization, and epigenetic regulation (Invited Key Note Speaker). 4th Canadian MAP Researchers Meeting. Banff, Alberta, October 19-21.

N.A. Karrow, B.S. Sharma 2010. Epigenetics of Johne's disease, Banff, Alberta, October 27-28.

P. Mead, **N.A. Karrow** 2010. Monocyte-derived macrophage gene expression profiles during infection with several strains of *Mycobacterium avium subsp. paratuberculosis* from cows genotypes for the MIF susceptibility SNP -395A<G. 3rd Canadian MAP Researchers Meeting, Banff, Alberta, October 27-28.

N.A. Karrow B.A. Mallard, D. Kelton, K. Leslie, F. Malouin, P.Menzies, A. Potter, X. Zhao 2009. Integrative genomic and proteomic strategies to identify immunological profiles associated with enhanced host defense against mastitis pathogens. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Montreal, Qu., October 27-28.

M. Husain, H. Boermans, **N.A. Karrow** 2009. Mouse mesenteric lymph node gene expression profiles during sensitization, and ear-swelling, histamine, and immunoglobulin

response during elicitation in response to common food allergens. 48th Annual Society of Toxicology Meeting, Baltimore, Maryland, March 15-19.

N.A. Karrow, S. Pant, C. Verschoor, A. Skelding, F.S. Schenkel, B.S. Sharma 2008. Genetic selection of Johne's disease resistance in Canadian dairy cattle. Canadian MAP Researchers Meeting, Banff, Alberta, October 15-16.

A. Skelding, S. Pant, C. Verschoor, F.S. Schenkel, B.S. Sharma, **N.A. Karrow** 2008. Identification of SNPs in the bovine IL-12 receptor and IL-23 receptor genes and their association with susceptibility/ resistance to Johne's disease in dairy cattle. Canadian MAP Researchers Meeting, Banff, Alberta, October 15-16.

C. Verschoor, S. Pant, F.S. Schenkel, B.S. Sharma, **N.A. Karrow** 2008. Understanding the host response to chronic MAP infection using a candidate gene approach and comparative gene expression profiling. Canadian MAP Researchers Meeting, Banff, Alberta, October 15-16.

B. Sharma, C. Verschoor, S. Pant, F.S. Schenkel, **N.A. Karrow** 2008. Association of toll-like receptor 4 polymorphisms with MAP infection. Canadian MAP Researchers Meeting, Banff, Alberta, October 15-16.

N.A. Karrow B.A. Mallard, D. Kelton, K. Leslie, F. Malouin, P.Menzies, A. Potter, X. Zhao 2007. Integrative genomic and proteomic strategies to identify immunological profiles associated with enhanced host defense against mastitis pathogens. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Montreal, Qu., November 12-13.

N.A. Karrow, B.A. Mallard, F.S. Schenkel, B.S. Sharma, S.D. Pant, and H.D. Daetwyler 2007. Integrative immunogenomics and health of the dairy cow: SNPs and chips and latte to go (Invited). 13th International Conference on Production Diseases in Farm Animals, Leipzig, Germany, July 29- August 4.

B.A. Mallard, **N.A. Karrow**, D. Kelton, K. Leslie, F. Malouin, P.Menzies, A. Potter, X. Zhao 2006. Integrative genomic and proteomic strategies to identify immunological profiles associated with enhanced host defence against mastitis pathogens. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Mississauga, Ont., November 15-16.

B.S. Sharma, I. Levya, D. Kelton and **N.A. Karrow** 2005. Association of *TLR4* SNPs with Health Traits in Canadian Holsteins. Brian Kennedy Memorial Colloquium, Michigan State University, USA, May 9-10.

N.A. Karrow 2005. Ovine phenotypic responses to endotoxin-induced acute inflammatory stress during fetal, neonatal, and adult development (Invited). American Society of Animal Science/American Dairy Science Association Midwestern Meeting, Des Moines, Iowa, March 21-23.

L. Kabaroff, H.J. Boermans and **N.A. Karrrow** 2004. Responsiveness of the ovine hypothalamic-pituitary-adrenal axis during pregnancy and lactation following immunological challenge with *Escherichia coli* lipopolysaccharide. 7th International Veterinary Immunology Symposium, Quebec City, July 25-30.

N.A. Karrow 2003. Regulation of the mammary gland inflammatory response: a comparative species approach. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Mont Saint-Hilaire, QC, October 1-2.

N.A. Karrow, B.A. Mallard, S. Sharif, K. Leslie and D. Kelton 2002. Genetic regulation of immune response and resistance to Staphylococcus-induced mastitis in Canadian Holsteins (Invited). 10th International Symposium on Staphylococci and Staphylococcal Infections, Tsukuba City, Japan, October 16-19.

Z. Alizadeh, **N.A. Karrow**, S. Sharif, B.N. Wilkie and B.A. Mallard 2002. Biological effect of varying peptide binding affinity to BoLA-DRB3*2703 allele. 2nd International Symposium on Candidate Genes for Animal Health. Montpellier, France, August 16-18.

N.A. Karrow, T. Guo, B. Leffel and K.L. White, Jr. 1999. Evaluating lymphocyte subsets and cytokine mRNA expression in draining lymph nodes following cinnamaldehyde exposure. Experimental Contact Dermatitis Research Group, Cincinnati, OH, May 21-22.

N.A. Karrow, D. Bennie, H.J. Boermans, N.C. Bols, S. Brown, D.G. Dixon, A. Gamble, R. Ganassin, J. Parrott, K.R. Solomon and J. Sherry 1998. Comparison of innate immune parameters from *Oncorhynchus mykiss* caged at various sites in the Hamilton Harbour. SETAC 19th Annual Meeting, Charlotte, NC, Nov. 15-19.

J.J. Whyte, K.L. Herbert, **N.A. Karrow**, J.G. Sivak, D.G. Dixon and N.C. Bols 1997. Effect of creosote exposure on ocular damage and hepatic 7-ethoxyresorufin-*O*-deethylase activity in rainbow trout *Oncorhynchus mykiss*. Proceedings of the 24th Annual Aquatic Toxicity Workshop: Niagara Falls, ON, October 20-22.

N.A. Karrow, H.J. Boermans, N.C. Bols, D.G. Dixon, K.R. Solomon and J.J. Whyte 1997. Creosote immunotoxicity to rainbow trout *Oncorhynchus mykiss*. Proceedings of the 24th Annual Aquatic Toxicity Workshop: Niagara Falls, ON, October 20-22.

Oral Presentations:

N.A. Karrow 2023. Using bacterial endotoxin to assess genetic and epigenetic contributions to the ovine stress response phenotype. Seminar on the epigenetics of ruminant animals. Yangzhou University, China, November 23.

N.A. Karrow, R. Xu, U. Shandilya, K Lamers and S.Y. Oh 2023. In vitro Assessment of Mycotoxin Toxicity and Mitigation. CFAI Special Seminar organized by the International Education and Research Center of Food and Agricultural Immunology (CFAI), Graduate School of Agricultural Science, Tohoku University, Japan, November 28.

N.A. Karrow 2023. Assessing genetic and epigenetic contributions to the ovine stress response phenotype using bacterial endotoxin. CFAI Special Seminar organized by the International Education and Research Center of Food and Agricultural Immunology (CFAI), Graduate School of Agricultural Science, Tohoku University, Japan, October 30.

N.A. Karrow, U.K. Shandilya, C. McAllister, Xiang Wu, A. Sharma 2022. Characterizing the Function of Bovine TLR4 Gene. Huazhong Agricultural University, Wuhan, Hubei, China. September 12.

U.K. Shandilya, S. Mallikarjunappa, A. Sharma, J. Guo, Y. Mao, **N.A. Karrow** 2019. A Toll tale about bovine inflammatory diseases. Yangzhou University, Yangzhou, China, September 25th.

N.A. Karrow, D. Naylor, A. Sharma, Z. Li, E. Borkowski, S. Dixon 2018. Defining the Stress Response Phenotype in Ruminants and its Relation to Animal Health. Sichuan Agricultural University, Sichuan Agricultural University, Chengdu, China, November 26th.

N.A. Karrow, D. Naylor, A. Sharma, Z. Li, E. Borkowski, S. Dixon 2018. Characterizing Stress Responsiveness in Ruminants and its Relation to Animal Health. Yangzhou University, Yangzhou, China, November 19th.

N.A. Karrow, 2016. Toxicity of Penicillium mycotoxins to bovine macrophages (BoMacs). School of Agricultural Science, Tohoku University, Sendai, Japan, December 12.

N.A. Karrow, 2016. Implications of variable stress responsiveness on livestock health. College of Animal Science, Shaanxi University of Technology, Hangzhong, China, December 6.

N.A. Karrow, 2016. Animal Bioscience at University of Guelph, Northwest Plateau Institute of Biology, Xining, China, December 2.

N.A. Karrow, 2016. Assessment of the stress response phenotype in ruminants: Implications for health, longevity and fertility. College of Animal Science & Technology, Yangzhou, China, November 24.

N.A. Karrow, 2016. Ruminant innate defense at the gastrointestinal mucosal surface. College of Animal Science & Technology, Yangzhou University, Yangzhou, China, November 22.

N.A. Karrow, A. Lee, M.M. Or-Rashid, O. AlZahal, M. Quinton, B.W. McBride, R.E. Fisher-Hefferman 2015. Maternal bacterial endotoxemia, nutrition, and fetal programming of the ovine neuroendocrine-immune system, Huazhong Agricultural University, Wuhan, China, November 18.

N.A. Karrow, Z. Li, S. Oh 2015. Endotoxin tolerance: What can we learn from zebrafish? Zhejiang University, Hangzhou, China, December 3.

N.A. Karrow, Z. Li, and R.E. Fisher-Heffernan 2015. Endotoxin tolerance: fishing for answers. Huazhang Agricultural University, Wuhan, China, October 21.

N.A. Karrow, S. Oh, N. Cedergreen 2015. Assessing the immunomodulatory effects of Penicillium mycotoxins and binding efficacy of Mycosorb A+ using bovine macrophages. Alltech Webinar, May 8.

N.A. Karrow 2014. Research in immunogenetics and immunoregulation. College of Animal Science & Technology, Yangzhou, China, August 6th.

N.A. Karrow, Q. You, L. Cain, B.S. Sharma, Y.J. Li, L. Schenkel, G. Vander Voort, J. Wilton 2011. Genetics of the ovine stress response, College of Animal Science & Technology, Yangzhou, China, May 9th.

N.A. Karrow 2009. Ruminant Immunogenetics and Immunoregulation. Northwestern A&F University, Yangling, Shaanxi, China, April 13-17.

N.A. Karrow 2006. The impact of dietary fatty acids on inflammation during ovine pregnancy, lactation, and fetal development. Ontario Sheep Marketing Agency, Guelph, Ont., July 5.

N.A. Karrow 2006. Immunogenetics, immunomodulation and ruminant inflammatory diseases, Ontario Sheep Marketing Agency, Guelph, Ont., March 24.

N.A. Karrow 2003. Genetic programming and regulation of the neuroendocrine-immune axis in ruminants. Michigan State University, Michigan, USA, March 12.

N.A. Karrow 2001. Dairy genomics: what more can be done to increase productivity? University of Guelph, Guelph, ON, November 23.

N.A. Karrow 2001. Metal immunotoxicity: potential disruption of the neuroendocrine-immune axis during embryonic and post-natal development. University of Montana, Missoula, MT, October 12.

N.A. Karrow 2000. Dermal exposure to cinnamaldehyde alters lymphocyte sub-populations, the number of IFN-γ-producing cells, and the expression of B7 co-stimulatory molecules and cytokine mRNAs in the auricular lymph nodes of B6C3F1 mice. Atlantic Veterinary College, University of Prince Edward Island, Charlottetown, PEI, March 4.

N.A. Karrow 2000. A strategy to assess the effects of environmental stressors on fish immune systems and fish health in aquatic systems impacted by sewage effluent and industrial discharges. National Water Research Institute, Environment Canada, Burlington, ON, January 18.

N.A. Karrow 1999. Evaluating environmental and therapeutic agents for the potential to induce contact hypersensitivity. Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan, December 16.

N.A. Karrow 1998. Assessment of creosote immunotoxicity to fish innate immune parameters using a microcosm design. Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, August 19.

N.A. Karrow 1998. Assessment of polycyclic aromatic hydrocarbon (PAH) immunotoxicity to the fish immune system in microcosm and field studies. National Water Research Institute, Environment Canada, Burlington, ON, August 7.

N.A. Karrow 1998. Toxicity of liquid creosote to rainbow trout innate immune parameters. Department of Environmental Medicine, University of Rochester, Rochester, NY, July 17.

N.A. Karrow, G. Dixon and H. Boermans 1995. Application of fish immunological biomarkers as an indicator of stress in environmental impact assessment. University of Guelph-Michigan State University Colloquium, Michigan State University, Michigan, USA.

Conference Abstracts:

T.M. Sullivan, A. Sharma, K. Lamers, C. White, B. Mallard, A. Cánovas, **N.A. Karrow** 2022. Identifying phenotypes to enhance stress resilience of dairy cows. Proceedings of 12th World Congress on Genetics Applied to Livestock Production (WCGALP) 2855 DOI: 10.3920/978-90-8686-940-4_692, Rotterdam, The Netherlands, July 3-8.

O. Willoughby, E. Borkowski, S. Dixon, S.M. Cunha, V. Asselstine, A.S. Peregrine, P.I. Menzies, **N.A. Karrrow**, Á. Cánovas 2022. Differences in gene expression following natural exposure to gastrointestinal parasites between sheep selected for high cellular and high antibody adaptive immune responses. ASAS-CSAS-SSASAS Annual Meeting, Oklahoma City, Oklahoma, June 26-30.

E. Borkowski, **N.A. Karrow**, P. Menzies, J. Avula, B.N. Lillie, A.S. Peregrine 2021. Correlation of salivary antibody response to carbohydrate larval antigen (CarLA®) with parasitism in Ontario sheep. 70th IVSA Congress (Virtual). Utrecht, Netherlands, July 19-29.

A. Sharma, U. Shandilya, T. Sullivan, D. Naylor, A. Canovas, B. Mallard, **N.A. Karrow** 2021. Ovine circulatory markers regulating the acute-phase response of variable stress responding sheep to LPS challenge. ASAS-CSAS-SSASAS Annual Meeting (Virtual). Louisville, KY, July 14-18.

T.M. Sullivan, A. Sharma, K. Lamers, B.A. Mallard, A. Canovas, **N.A. Karrow** 2021. Immune tolerance of dairy heifers in response to repeated bacterial endotoxin exposure. ASAS-CSAS-SSASAS Annual Meeting (Virtual). Louisville, KY, July 14-18.

A. Sharma U. Shandilya, T. Sullivan, D. Naylor, A. Canovas, B.A. Mallard, **N.A. Karrow** 2020. Screening ovine circulatory miRNAs as biomarkers of microbial stress. 3rd World Conference on Sheep (Virtual), October 16-18.

T. M. Sullivan, A. Sharma, K. Lamers, A. Canovas, B. Mallard, **N. A. Karrow** 2020. The systemic inflammatory response to intramuscular endotoxin challenge in dairy heifers. American Dairy Science Association Annual Meeting (Virtual), Palm Beach, FL, June 22-24.

W. Fan, X. Yin, W. Wang, J. Zhang, L. Huber, **N.A. Karrow**, Y. Mine. M.Z. Fan 2020. Dietary Therapeutic Aureomycin Improves Ileal Lysine Digestibility Independent of Gut Terminal Protein Digestion and CAT-1 Expression in Weaning Pigs Fed Crystalline Lys Supplemented Low-Crude Protein Diets. Global Animal Nutrition Summit Guelph, Guelph, August 11-14th.

V. Asselstine, J.F. Medrano, S. Germani, F. Ceciliani, A. Suarez-Vega, B. Mallard, **N. Karrow**, A. Islas-Trejo, A. Cánovas 2020. Identification of novel lncRNA associated with mastitis disease in Holstein dairy cattle using an optimized RNA-Sequencing pipeline. 71st Annual Meeting of European Federation of Animal Science, Porto, Portugal August 31-September 4th.

A. Sharma, D. Naylor, T. Sullivan, Z. Li, K. Lamers, A. Canovas, B. Mallard, **N.A. Karrow** 2020. Cytokine/chemokine and microRNA profiles of variable stress responding sheep under bacterial endotoxin challenge. Plant & Animal Genome Conference XXVIII, San Diego, CA, January 11-15.

U.K. Shandilya, S. Mallikarjunappa, A. Sharma, J. Guo, K. Lamers, Y. Mao, K.G. Meade and **N.A. Karrow** 2020. Bovine Toll-like receptor 4 modulates the inflammatory response of mammary epithelial cells to Mycobacterium avium subsp. paratuberculosis cell lysate and Escherichia coli lipopolysaccharide. Plant & Animal Genome Conference XXVIII, San Diego, CA, January 11-15.

B.A. Mallard, N. Husseini, S. Cartwright, A. Livernois, D. Hodgins, T. Altvater-Hughes, S. Beard, **N.A. Karrow**, A. Canovas, J. Schmied 2020. Resilience of High Immune Response (HIR) Genetics in the context of climate change: Effects of heat stress on cattle with diverse immune response genotypes. Immunology. Honolulu, Hawaii, May 8-12.

E.A. Borkowski, **N.A. Karrow**, P.I. Menzies, J. Avula, B.N. Lillie, J.S. Gilleard, A.S. Peregrine 2019. Effects of gastrointestinal nematode parasitism on growth and reproductive performance in replacement ewe lambs in Ontario, Canada. 27th Conference of the World Association for the Advancement of Veterinary Parasitology, Madison, WI, July 7-11.

E.A. Borkowski, **N.A. Karrow**, P.I. Menzies, J. Avula, B.N. Lillie, A.S. Peregrine 2019. Correlation of salivary antibody to carbohydrate larval antigen with gastrointestinal nematode parasitism in sheep under Ontario grazing conditions. 27th Conference of the World Association for the Advancement of Veterinary Parasitology, Madison, WI, July 7-11.

D. Naylor, A. Sharma, Z. Li, A. Canovas, B.A. Mallard, **N.A. Karrow** 2019. Characterizing biomarkers of inflammation in variable stress responding sheep. International Veterinary Immunology Symposium, Seattle, Washington, August 13-16.

S. Dixon, **N.A. Karrow**, P. Menzies, A. Suarez-Vega, D. Kennedy, A. Peregrine, E. Borkowski, B.A. Mallard, A. Cánovas 2019. Identifying potential candidate genes regulating host response to gastrointestinal nematodes in grazing sheep using transcriptomics. International Veterinary Immunology Symposium, Seattle, Washington, August 13-16.

D. Naylor, A. Sharma, Z. Li, A. Canovas, B.A. Mallard, **N.A. Karrow** 2019. Characterizing cytokine and miRNA responses in variable stress-responding sheep. North American Comparative Immunology Workshop, Waterloo, June 3-5.

D. Rothschild, M. Nascimento dos Santos, T. M. Widowski, **N.A. Karrow**, L. Susta, E. Kiarie, I. Mandell, S. Torrey 2019. A comparison of organ size between conventional and slower growing broiler chickens. Poultry Science Association Annual Meeting, Montreal, July 15-18.

A.V. Lee, L. You, L.E. Harris, S.Y. Oh, R.E. Fisher-Heffernan, K.M. Brennan, L. Huber, C.F.M. De Lange **N.A. Karrow** 2019. Microalgae or fish oil supplementation and maternal stress in late gestation sows and effects on adrenal gland gene expression in male offspring fed a low-quality protein diet. Animal Nutrition Conference of Canada Niagara Falls, ON, May 15-16.

R.A.M. Kakhki, D.W.L. Ma, K. Price, J. Moats, **N.A. Karrow**, T.M. Widowski and E. Kiarie 2019. ISA brown and Shaver white egg-type pullet breeders fed algae or flaxseed products as sources of n-3 polyunsaturated fatty acids: Embryonic uptake of fatty acids. Poultry Science Association Annual Meeting, Montreal, Quebec, July 15-18.

A. Suárez-Vega, E.A. Borkowski, S. Dixon, **N.A. Karrow**, A.S. Peregrine, P. Menzies, B.A. Mallard, M.N. Boareki, F.S. Schenkel, P.A.S. Fonseca, J.J. Arranz, G. Tosser, C. Klopp A. Cánovas 2019. Identification of differentially expressed lncRNAs linked to Haemonchus contortus in variable stress-responder grazing sheep. 37th International Society for Animal Genetics Conference, Lleida, Spain, July 7-12.

S. Mallikarjunappa, M. Sargolzaei, F.S. Schenkel, L.F. Brito, N. Bissonnette, K.M. Meade, F. Miglior, J. Chesnais, M. Lohuis, **N.A. Karrow** 2019. Association of SNPs related to

Johne's disease with EBVs of Canadian Holstein bulls for milk ELISA test scores. 37th International Society for Animal Genetics Conference, Lleida, Spain, July 7-12.

E.A. Borkowski, **N.A. Karrow**, P.I. Menzies, J. Avula, B.N. Lillie, A.S. Peregrine 2019. Effects of gastrointestinal nematode parasitism on growth and reproductive performance in ewe lambs in Ontario, Canada. 27th Conference of the World Association for the Advancement of Veterinary Parasitology. Madison, Wisconsin, July 7-11.

E.A. Borkowski, **N.A. Karrow**, P.I. Menzies, J. Avula, B.N. Lillie, A.S. Peregrine 2019. Correlation of salivary antibody to carbohydrate larval antigen with gastrointestinal nematode parasitism in sheep under Ontario grazing conditions. 27th Conference of the World Association for the Advancement of Veterinary Parasitology. Madison, Wisconsin, July 7-11.

C.N. Reedman, T.F. Duffield, T.J. DeVries, K.D. Lissemore, N.A. Karrow, Z. Li, C.B. Winder 2019. Efficacy of pain control for caustic paste disbudding in very young calves. ADSA Annual Meeting, Cincinnati, Ohio, June 23-26.

K. Lamers, M. Baquero, **N.A. Karrow**, M. Hurtig 2019. Intra-articular cell therapy alters the immune profile in osteoarthritis. North American Veterinary Regenerative Medical Association Conference. Sacramento, California, September 6-9.

D. Rothschild, T. M. Widowski, **N.A. Karrow**, L. Susta, E. Kiarie, I. Mandell, S. Torrey 2018. The effects of a low-nutrient diet on the prevalence of right ventricle hypertrophy and bursal atrophy in two strains of fast-growing broilers. Poultry Science Association Annual Meeting, San Antonio, Texas. July 23-26.

A.V. Lee, L. You, S. Oh, Z. Li, M.D.M. Alcorn, C. Zhu, R.E. Fisher-Heffernan, T. Regnault, L. Huber, **N.A. Karrow** 2018. Effect of dietary microalgae and fish oil on nursery pig acute-phase response. ASAS-CSAS Annual Meeting and Trade Show, Vancouver, July 8-12.

S. Dixon, N. A. Karrow, P. Menzies, M. Boareki, P. Fonseca, A. Suarez-Vega, D. Kennedy, A. Peregrine, E. Borkowski, B.A. Mallard, A. Cánovas 2018. Identifying key regulator genes and metabolic pathways associated with parasite-resistant sheep. ASAS-CSAS Annual Meeting and Trade Show, Vancouver, July 8-12.

E. Borkowski, N.A. Karrow, B.A. Mallard, P. Menzies, J. Avula, B. Lillie, A.S. Peregrine 2018. Gastrointestinal nematode resistance in variable stress-responding sheep. ASAS-CSAS Annual Meeting and Trade Show, Vancouver, July 8-12.

E. Borkowski, E. Redman, R. Avramenko, R. Chant, J. Avula, **N. Karrow**, P. Menzies, B. Lillie, A. Peregrine, J. Gilleard 2017. Comparison of deep amplicon nemabiome sequencing with morphological identification to quantify species proportions of gastrointestinal larvae isolated from small ruminant feces. Canadian Animal Health Laboratician's Network, Guelph, June 4-7.

A.V. Lee, L. You, S. Oh, R.E. Fisher-Heffernan, C.F.M. de Lange and **N.A. Karrow** 2017. Maternal omega-3 supplementation and endotoxin challenge in late gestation and their effects on piglet health. 10th World Congress of Developmental Origins of Health and Disease, Rotterdam, Netherlands, Oct 15-18.

N.A. Karrow, S. Oh, A.V. Lee, L. You, R. E. Fisher-Heffernan, C. F.M. de Lange 2017. Maternal fish oil and algae meal supplementation and endotoxin challenge in late gestation sows and their effects on piglet health. 19th Animal Genetics and Breeding Conference, Nanjing, China, October 13-16.

E. Borkowski, E. Redman, R. Avramenko, R. Chant, J. Avula, **N.A. Karrow**, P. Menzies, B. Little, A. Peregrine, J. Gillard 2017. Comparison of deep amplicon nemabiome sequencing with morphological identification to quantify species proportions of gastrointestinal larvae isolated from small ruminant feces. Annual Conference Canadian Animal Health Laboratorian's Network, Guelph, June 4-7.

M.R.L.V. Peixoto, E.M. Newman, **N.A. Karrow**, T.M. Widowski 2017. Susceptibility to pre-natal stress in different stains of layers: Effects on early body weight and growth rate. European Symposium on Poultry Welfare, Ploufragan, France, June 19-22.

H. Leung, M. Neijat, R. Snyder, R. Patterson, J. Barta, **N.A. Karrow**, E. Kiarie 2017. Effect of feeding yeast nucleotides (Maxi-Gen Plus) to broiler chickens challenged with *Eimeria*. 2017. Poultry Science Association Annual Meeting, Orlando, Florida, July 17-20.

S. Mallikarjunappa, M. Sargolzaei, K.M. Meade, **N.A. Karrow**, S.D. Pant 2017. QTLs associated with resistance to MAP infection in Holstein-Friesian cattle. 36th International Society for Animal Genetics Conference, Dublin, Ireland, July 16-21.

H. Atalla, B.A. Mallard **N.A. Karrow** 2016. Characterization of exosomal immune-related microRNAs in colostrum and milk from average, low and high immune responder cows. 35th International Society for Animal Genetics Conference, Salt Lake City, Utah, July 23-27.

H. Atalla, M. Ross, E. Syjueco, **N.A. Karrow**, B.A. Mallard 2016. Bioactivity of exosomal microRNAs in high immune responser cow's colostrum and milk. Keystone Symposia on Exosomes/Microvesicles: Novel Mechanisms of Cell-Cell Communication, Keystone Resort, Keystone, Colorado, June 19-22.

S. Mallikarjunappa, **N.A. Karrow**, S.Y. Oh, J. Chesnais and K.G. Meade 2016. Genetic markers of resistance to Johne's disease: Their validation and functional assessment. XXIX World Buiatrics Congress, Dublin, Ireland, July 3-8.

A.V. Lee, R.E. Fisher-Heffernan, M. Quinton, **N.A. Karrow** 2015. Impact of maternal endotoxin challenge and omega-3 fatty acid supplementation on ovine placental and fetal

hippocampal gene expression. 9th World Congress on Developmental Origins of Health and Disease, Cape Town, South Africa, November 8-11.

R.E. Fisher-Heffernan, A.V. Lee, M. Quinton, T.R.H. Regnault, **N.A. Karrow** 2015. Alterations in hippocampal mRNA expression of lambs born to ewes supplemented with fishmeal and challenged with endotoxin. 9th World Congress on Developmental Origins of Health and Disease, Cape Town, South Africa, November 8-11.

E. Crane, A. Fontoura, N. Consôlo, R. Ventura, J. Munro, S. Bourgon, K. Swanson, A. Fredeen, **N. Karrow**, Y. Montanholi 2015. Metabolic profile and immune response of heifers relating to feed efficiency and genomic clusters. 66th European Federation of Animal Science Annual Meeting, Warshaw, Poland, August 31-September 4.

R.E. Fisher-Heffernan, A. Lee, M. Or'Rashid, O. AlZahal, M. Quinton, B.W. McBride, H.J. Boermans, and **N.A. Karrow** 2015. Hippocampal mRNA expression of lambs born to ewes supplemented with fishmeal and challenged with endotoxin. 35th Annual Meeting of the American Society For Reproductive Immunology. Kingston, Ontario, June 2-5.

A.V. Lee, R.E. Fisher-Heffernan, **N.A. Karrow** 2015. Gene expression in ovine placental and fetal hippocampal tissue following fishmeal supplementation and endotoxin challenge. 35th Annual Meeting of the American Society for Reproductive Immunology. Kingston, Ontario, June 2-5.

O. Ariel, N. Gévry, G. Fecteau, E.M. Ibeagha-Awemu, **N. A. Karrow**, and N. Bissonnette 2015. Genetic association of Johne's disease susceptible cows through transcriptome profiling of MAP infected macrophages. American Dairy Science Association and American Society of Animal Science, Orlando, Florida, July 12-16.

S. Hooda, H. Golightly, R.E. Fisher, **N.A. Karrow**, and C. F. M. de Lange 2015. Effects of reducing the dietary Omega-6 to Omega-3 fatty acid ratio in low protein quality nursery diets and *Escherichia coli* LPS-induced inflammation on nutrient digestibility and gut morphology in starter pigs. 13th Digestive Physiology of Pigs Symposium, Kliczkow, Poland, May 19-21.

S. Hooda, R.E. Fischer, **N.A. Karrow**, and C.F.M. de Lange 2014. Effects of reducing the Omega-6 and Omega-3 fatty acids ratios in low protein quality nursery diets on growth performance and immune response in starter pigs. Midwest Meeting of the American Dairy Science Association and American Society of Animal Science, Des Moines, IA March 15-18.

Q. You, P, Mead, S. Oh, S. Mallikarjunappa, L. Mutheria, and **N.A. Karrow** 2014. Construction of a reporter *Mycobacterium avium* subsp. *paratuberculosis* (Map) strain and infection of monocyte-derived macrophages from cows homozygous for SNP -298 A>G in the macrophage migration inhibitory factor (MIF) gene. 10th World Congress on Genetics Applied to Livestock Production. Vancouver, B.C. August 17-22.

S. Mallikarjunappa, B.L. Plattner, P. Mead, L.M. Mutharia, M. Quinton, and **N.A. Karrow** 2014. Cytokine gene expression in Holstein and Jersey calves infected with *Mycobacterium avium* subsp. *paratuberculosis*. 10th World Congress on Genetics Applied to Livestock Production. Vancouver, B.C. August 17-22.

N.A. Karrow, S.D. Pant, Q. You, G. V. Voort, L. Schenkel, J. Wilton, L. Cain, F. Schenkel 2014. Identification of chromosomal regions influencing cortisol responses in sheep. 34 International Society for Animal Genetics Conference, Xi'an, China, July 28-August 1.

S. Oh, H. Boermans, S. Haladi, **N.A. Karrow** 2014. Effect of *Penicillium* mycotoxins on bovine macrophage (BOMAC) function. ADSA-ASAS-CSAS Joint Annual Meeting, Kansas City, Missouri, July 20-24.

Z. Li, Q. You, F. Ossa, P. Mead, **N.A. Karrow** 2014. *In vitro* assessment of *Saccharomyces cerevisiae* cell wall components (CWC) using bovine epithelial cells and macrophages. ADSA-ASAS-CSAS Joint Annual Meeting, Kansas City, Missouri, July 20-24.

M. Kornya, S. Lam, **N. Karrow**, B.L. Plattner 2013. Ontogeny and cytokine gene expression of intestinal gamma-delta T cell subsets in uninfected and Mycobacterium avium subsp. paratuberculosis (MA)-infected calves. 64rd Annual Meeting of the American College of Veterinary Pathologists and 48th Annual Meeting of the American Society of Veterinary Clinical Pathology, Atlanta, Georgia, November 8-12.

S. Oh, R. Cliff, C.G. Balch, B.S. Sharma, H. Boermans, S. Haladi and **N.A. Karrow** 2013. Penicillium mycotoxins alter the expression of genes coding enzymes that regulate epigenetic programming in bovine macrophages." Society of Toxicology's 52nd Annual Meeting, San Antonio, Texas, March 13, Abstract 2081.

M. Kornya, S. Lam, **N. Karrow**, B.L. Plattner 2012. Distribution of intestinal gamma-delta T cell subsets in uninfected and Mycobacterium avium subsp. paratuberculosis (MA)-infected calves. 63rd Annual Meeting of the American College of Veterinary Pathologists and 47th Annual Meeting of the American Society of Veterinary Clinical Pathology, Seattle Washington, December 1-5.

R.E. Fisher, H.J. Boermans, B.W. McBride, **N.A. Karrow** 2012. Fishmeal supplementation during gestation protects against endotoxin induced fetal programming of the hypothalamic-pituitary-adrenal axis in sheep. Symposium on Functional Genomics of Early Development in Livestock, Banff, Alberta, July 24-26.

R.E. Fisher, H.J. Boermans, B.W. McBride, **N.A. Karrow** 2011. Fishmeal supplementation during gestation may lead to alterations in the cortisol response of the offspring following maternal endotoxin challenge. 7th World Congress on Developmental Origins of Health and Disease. Portland, Oregon, September 18-21. (Journal of Developmental Origins of Health and Disease S2:S64)

S. Oh, **N.A. Karrow**, H.J. Boermans, S. Haladi, B.S. Sharma 2011. Effects of the *Penicillium* Mycotoxins; Citrinin, Ochratoxin A, Patulin, Mycophenolic acid, and Penicillic acid on Macrophage Viability and Proliferation, EPPH, Wuhan, China, May 11-13.

L. Cain, Q. You, M. Quinton, **N.A. Karrow** 2011. Cortisol response to endotoxin-induced inflammatory stress is associated with aspects of the ovine immune system. CSAS/SCSA Annual Meeting, Halifax, May 4-5.

S. Oh, **N.A. Karrow**, H.J. Boermans, S. Haladi, B.S. Sharma 2011. The immunomodulatory effects of *Penicillium* mycotoxins; citrinin, ochratoxin A, patulin, mycophenolic acid, and penicillic acid on a bovine macrophage cell line (BOMACs). 50th Annual Meeting of the Society of Toxicology, Washington, D.C., March 6-10.

S. Oh, **N.A. Karrow**, H.J. Boermans, S. Haladi, B.S. Sharma 2010. The immunomodulatory effects of *Penicillium* mycotoxins; citrinin, ochratoxin A, patulin, mycophenolic acid, and penicillic acid on a bovine macrophage cell line (BOMACs). The 6th World Mycotoxin Forum, Noordwijkerhout, The Netherlands, 8-10 November.

H. V. L. N. Swamy, **N. A. Karrow** 2010. Detection of mycophenolic acid and roquefortine C mycotoxins in Canadian corn silage. Joint ADSA-PSA-AMPA-CSAS-ASAS meeting, Denver, Colorado, July 11-15.

A. Rakhshandeh, A. Holliss, **N. A. Karrow** and C.F.M de Lange 2010. Immune system stimulation and sulfur amino acid intake alter the pathways of glutathione metabolism at transcriptional level in pigs. Joint ADSA-PSA-AMPA-CSAS-ASAS meeting, Denver, Colorado, July 11-15.

A. Rakhshandeh, A. Holliss, **N. A. Karrow** and C.F.M de Lange 2010. Impact of sulfur amino acid intake and immune system stimulation on pathways of sulfur aminoacid metabolism at transcriptional level in growing pigs. Joint ADSA-PSA-AMPA-CSAS-ASAS meeting, Denver, Colorado, July 11-15.

G.N. Girgis, J.R. Barta, **N.A. Karrow**, H.J. Boermans, C.K. Girish, T.K. Smith 2010. Effects of feed-borne Fusarium mycotoxins and an organic mycotoxin absorbent on

immune cell dynamics in the jejunum of broiler breeder pullets infected with Eimeria maxima. Joint ADSA-PSA-AMPA-CSAS-ASAS meeting, Denver, Colorado, July 11-15.

J.A. Stryker, R. Fisher, Q. You, B, McBride and **N. A. Karrow** 2010. Effects of dietary fish meal and soybean meal on ovine innate and acquired immunity during pregnancy and lactation. The 23rd Annual Spring Meeting of the Canadian Society of Immunology, Niagara Falls, April 23 - 26.

L. Cain, Q. You, M. Quinton, **N. A. Karrow** 2010. The ovine immune response is not associated with individual variation in the cortisol response to acute endotoxin challenge. The 23rd Annual Spring Meeting of the Canadian Society of Immunology, Niagara Falls, April 23 - 26.

J. Ravin, B.S. Sharma, **N.A. Karrow** 2010. Identification of DNA methylation patterns in the putative promoter of *IL-10Rβ* using pooled DNA from the blood of high and low somatic cell score cows. The 5th IDF International Mastitis Conference, Christchurch, New Zealand, March 21-24.

R. E. Fisher, M. Or'Rashid, S. Pant, B.W. McBride, H.J. Boermans, **N.A. Karrow** 2009. Fishmeal supplementation during gestation protects against endotoxin-induced fetal programming of the dermal immune response in sheep. 6th World Congress on Developmental Origins of Health and Disease. Santiago, Chile, November 19-22. (Journal of Developmental Origins of Health and Disease, Vol.1, Suppl. 1, P-2C-70)

A. Rakhshandeh, **N.A. Karrow**, S.P. Miller, C.F.M. de Lange 2009. Impact of immune system stimulation and sulfur amino acid intake on urinary sulfur excretion and whole body nitrogen to sulfur balance ratio in pigs. Joint ADSA-CSAS-ASAS meeting, Montreal, Quebec, July 12-16. (Canadian Journal of Animal Science 89:153)

K. Thompson, **N.A. Karrow**, K. Leslie, M. Quinton, F. Miglior, B.A. Mallard 2009. Phenotypic and genotypic variation of bovine immune responses in cohort dairy herds across Canada. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Montreal, October 27-28.

C.P. Verschoor, S.D. Pant, B.S. Sharma, F. Schenkel, **N.A. Karrow** 2009. Genetic variation in candidate immunoregulatory cytokines and their association to chronic inflammatory diseases of the mucosa in Canadian dairy cattle 2nd European Congress of Immunology, Berlin, Germany, September 13-16.

K. Thompson, **N.A. Karrow**, K. Leslie, M. Quinton, F. Miglior, B.A. Mallard 2009. Phenotypic and genetic variation of bovine immune responses in cohort dairy herds across Canada. ADSA-CSAS-ASAS joint annual meeting, Montreal, Quebec, July 12-16.

S. Cartwright, E.B. Burnside, **N.A. Karrow**, L. Schaeffer, B.A. Mallard 2009. Variation in antibody and cell-mediated immune responses between Canadian Holsteins and Norwegian-Red crossbred calf heifers. ADSA-CSAS-ASAS Joint Annual Meeting, Montreal, Quebec, July 12-16.

Y. Kim, H. Atalla, B. Mallard, C. Robert, H. Boermans, **N.A. Karrow** 2009. Evaluation of local and systemic bovine defense protein responses to intramammary challenge with persistent and genetically characterized strains of *Staphylococcus aureus*. 22nd Annual Canadian Society for Immunology Conference, Whistler, BC, April 3-6.

S. Cartwright, E.B. Burnside, **N.A. Karrow**, L. Schaeffer, B.A. Mallard 2008. Variation in antibody and cell-mediated immune responses between Canadian Holsteins and Norwegian-red crossbred first calf heifers. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Toronto, November 3-6.

K.A. Thompson, **N.A. Karrow**, K. Leslie, F. Miglior, M. Quinton, B.A. Mallard 2008. Phenotypic and genotypic variation of bovine immune responses in cohort dairy herds across Canada. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Toronto, November 3-6.

A. Skelding, B.S. Sharma, C. Verschoor, S.D. Pant, F. Schenkel, H. Boermans, **N.A. Karrow** 2008. Association of single nucleotide polymorphisms in the interleukin-12 receptor and interleukin-23 receptor genes with health and production traits in dairy cows. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Toronto, November 3-6.

Y. Kim, H. Atalla, B.A. Mallard, C. Robert, H. Boermans, **N.A. Karrow** 2008. Evaluation of local and systemic bovine cytokine responses to intramammary challenge with persistent and genetically characterized strains of Staphylococcus aureus. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Toronto, November 3-6.

C. Verschoor, S.D. Pant, B.S. Sharma, F. Schenkel, **N.A. Karrow** 2008. Single nucleotide polymorphisms in type-1 and -2 cytokines are associated with health and production traits in Canadian dairy bulls. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Toronto, November 3-6.

M.M. Or-Rashid, R. Fisher, **N.A. Karrow**, O. AlZahal, B.W. McBride 2008. Fatty acid profile of colostrum and milk of ewes supplemented with docosahexaenoic acid and the subsequent plasma fatty acid status of their lambs. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

M.M. Or-Rashid, R. Fisher, **N.A. Karrow**, O. AlZahal, B.W. McBride 2008. Plasma fatty acid profile of gestating ewes supplemented with docosahexaenoic acid. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

S.D. Pant, C. Verschoor, F.S. Schenkel, B.S. Sharma, **N.A. Karrow** 2008. Identification of single nucleotide polymorphisms in bovine peptidoglycan recognition protein 1 and their association with inflammatory disease resistance in Canadian dairy cattle. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

K. Alain, **N.A. Karrow,** M. Lessard, B.A. Mallard N. Bissonnette 2008. Identification of the osteopontin transcript during the early phases of intramammary infection caused by Escherichia coli and Staphylococcus aureus using subtractive suppressive hybridization. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

S. Cartwright, E.B. Burnside, **N.A. Karrow**, L. Schaeffer, B.A. Mallard 2008. Variation in antibody and cell-mediated immune responses between Canadian Holsteins and Norwegian-Red first calf heifers. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

B.S. Sharma, S.D. Pant, C. Verschoor, F.S. Schenkel, **N.A. Karrow** 2008. Association of Toll-like receptor 4 polymorphisms with Johne's disease. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

A. Skelding, B.S. Sharma, C. Verschoor, S.D. Pant, F. Schenkel, H. Boermans, **N.A. Karrow** 2008. Association of single nucleotide polymorphisms in the interleukin-12 receptor β-2 gene with Johne's disease and production traits in dairy cattle. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

C.P. Verschoor, S.D. Pant, B.S. Sharma, F. Schenkel, and **N.A. Karrow** 2008. Single nucleotide polymorphisms (SNPs) in bovine IL-10, IL-10 receptor, and TGF-®, and their association with milk somatic cell score and susceptibility to *Mycobacterium avium paratuberculosis* (MAP) infection. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

A. Rakhshandeh, **N.A. Karrow**, S.P. Miller, and C.F.M. de Lange 2008. C.F.M. Impact of immune system stimulation and sulfur amino acid intake on urinary sulfur excretion and whole body nitrogen to sulfur balance ratio in pigs. Annual meeting of the Canadian Society of Animal Science. Guelph, Ont., August 11-14.

A. Rakhshandeh, **N.A. Karrow**, S.P. Miller, and C.F.M. de Lange 2008. Impact of immune system stimulation and sulfur amino acid intake on urinary sulfur excretion and whole-body nitrogen to sulfur balance ratio in pigs. Animal Nutrition Association of Canada 44th annual Eastern Nutrition Conference, Guelph, Ont., May 22-23.

S.D. Pant, F.S. Schenkel, C. Verschoor, I. Leyva, B.S. Sharma, **N.A. Karrow** 2007. Identification of polymorphisms in bovine PGRP and CARD15, and associations between

CARD15 polymorphisms and milk somatic cell score in Canadian Holsteins, and functional relevance of SNP c.3020A>T. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Montreal, November 12-13.

C. Verschoor, S. Pant, **N.A. Karrow** 2007. Single nucleotide polymorphisms in the Canadian Holstein IL-10, IL-10 receptor, and TGF-β1 genes. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Montreal, November 12-13.

B.S. Sharma, J. Mount, **N.A. Karrow** 2007. Functional relevance of a promoter single nucleotide polymorphism of the bovine Toll-like-4 receptor gene. International Symposium on Animal Genomics for Animal Health, Oct. 23-25, Paris, France, and Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Montreal, November 12-13.

S.D. Pant, F.S. Schenkel, I. Leyva, B.S. Sharma, **N.A. Karrow** 2007. Identification of polymorphisms in bovine *TLR-2* and *CARD15*, and associations between *CARD15* polymorphisms and milk somatic cell score in Canadian Holsteins. International Symposium on Animal Genomics for Animal Health, Oct. 23-25, Paris, France.

K.A. Phillipps, **N.A. Karrow**, C.M. McNicoll, E. Courtney, J. Hay, and H. Boermans 2007. Use of an ovine model to evaluate the effects of ageing on the acute-phase response. XIth International Congress of Toxicology, July 15-19, Montreal.

Doelman, J., N.G. Purdie, C. Hao, L.E. Wright, **N.A. Karrow**, J.P. Cant 2007. Hepatic gene expression profiling in fasted postpubertal Holstein dairy heifers. ADSA-PSA-AMPA-ASAS Joint Annual Meeting. San Antonio, TX, July 8-12.

Leung, M. C. K., T. K. Smith, **N. A. Karrow**, and H. J. Boermans 2007. Effects of feedborne Fusarium mycotoxins with and without a glucomannan mycotoxin adsorbent on body weight, feed intake, serum chemistry, and nutrient digestibility of mature beagles. ADSA-PSA-AMPA-ASAS Joint Annual Meeting. San Antonio, TX, July 8-12.

R. Fisher, H. Drake, E. Finegan, S. Miller, J. Atkinson, H. Boermans, **N.A. Karrow** 2007. Ovine maternal inflammatory stress during late pregnancy alters offspring febrile responsiveness to systemic endotoxin challenge later in life. 46th Annual Society of Toxicology Meeting, March 25-29, Charlotte, North Carolina.

K.A. Phillipps, **N.A. Karrow**, C.M. McNicoll, E. Courtney, J. Hay, and H. Boermans 2007. Age-related changes in adrenal responsiveness, granulocyte trafficking, and serum IL-6 concentrations in female sheep systemically challenged with *Escherichia coli* lipopolysaccharide. 46th Annual Society of Toxicology Meeting, March 25-29, Charlotte, North Carolina.

Leung, M.C.K., M. K. Brunt, **N.A. Karrow**, H.J. Boermans, S.T. Millman, and T.K. Smith (2006). Nutritional toxicity of feed-borne Fusarium mycotoxins on mature beagle dogs. 42nd Eastern Nutrition Conference, Animal Nutrition Association of Canada. Guelph, ON, Canada, May 11–12.

B.S. Sharma, F. Schenkel, **N.A. Karrow** 2006. Associations of bovine TLR4 with milk somatic cell score and other health traits in Canadian Holstein cows. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Mississauga, Ont., November 15-16.

S. Pant, F. Schenkel, I. Leyva, B.Sharma, **N.A. Karrow** 2006. Identification of single nucleotide polymorphisms in bovine *CARD15/NOD2* and its association with milk somatic cell score in Canadian Holsteins. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Mississauga, Ont., November 15-16.

J. Mount, Y. Kim, **N.A. Karrow** 2006. Assessment of chemokine gene expression in bovine mammary gland tissue explants in response to LPS, LTA+PTG, and CpG ODN2135. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Mississauga, Ont., November 15-16.

I. Leyva, F. Schenkel, B.S. Sharma, G.B. Jansen, **N.A. Karrow** 2006. Evaluation of DNA pooling for low frequency SNP detection, and the association of *CXCR1*+777 SNP with health and production traits in Canadian Holstein bulls. Annual Scientific Meeting of the Canadian Bovine Mastitis Research Network, Mississauga, Ont., November 15-16.

L. Kabaroff, A. Rodriguez, H. Boermans, **N.A. Karrow** 2006. Assessment of the ovine acute phase response to Escherichia coli endotoxin. 45th Annual Society of Toxicology Meeting, March 5-9, San Diego, California.

Q. You, A. Rodriguez, B.A. Mallard, **N.A. Karrow** 2006. Evaluation of immune responsiveness and hepatic gene expression in high (H), middle (M), and low (L) inflammatory stress responsive sheep. 45th Annual Society of Toxicology Meeting, March 5-9, San Diego, California.

H. Drake, H. Boermans, **N.A. Karrow** 2006. Fetal programming of the ovine neuroendocrine-immune system in response to an acute bacterial endotoxin challenge. 45th Annual Society of Toxicology Meeting, March 5-9, San Diego, California.

B.S. Sharma, I. Leyva, D. Kelton and **N. A. Karrow** 2005. Polymorphisms in *TLR4* and their association with health traits in Canadian Holsteins. 3rd International Symposium on Genetics of Animal Health, July 13-15, Ames, Iowa.

Q.M You, A. Rodriguez, B.A. Mallard, **N.A. Karrow** 2005. Evaluation of immune responsiveness in high and low stress responsive sheep. 3rd International Symposium on Genetics of Animal Health, July 13-15, Ames, Iowa.

I. Leyva, B. S. Sharma, G. B. Jansen, and **N. A. Karrow** 2005. Potential associations of single nucleotide polymorphisms located in *CCL2*, *CCR2*, *CXCL8* and *CXCR1* genes with health, production and conformation traits in Canadian Holsteins. 3rd International Symposium on Genetics of Animal Health, July 13-15, Ames, Iowa.

H. Drake, H. Boermans, and **N.A. Karrow** 2005. Fetal programming of the ovine neuroendocrine-immune system in response to an acute bacterial endotoxin challenge. 18th Annual Spring Meeting of the Canadian Society for Immunology, April 7-10, Whistler, BC.

L. Kabaroff, **N.A. Karrow**, and H.J. Boermans 2005. Changes in the ovine hypothalamic-pituitary-adrenal axis during pregnancy and lactation following challenge with *Escheriichia coli* lipopolysaccharide. 44th Society of Toxicology Meeting, March 6-10, New Orleans.

B.S. Sharma, G.B. Jansen, **N.A. Karrow**, and Z. Jiang 2004. Detection and mapping of an AFLP marker for clinical mastitis in Canadian Holsteins. 29th International Conference on Animal Genetics, September 11-16, Tokyo, Japan.

I. Leyva, B.S. Sharma, G.B. Jansen, and **N.A. Karrow** 2004. Association of the single nucleotide polymorphisms from the MCP-1 gene with milk somatic cell counts (SCC) in a Canadian Holstein cattle population. 29th International Conference on Animal Genetics, September 11-16, Tokyo, Japan.

L. Kabaroff, H.J. Boermans and **N.A. Karrow** 2004. Responsiveness of the ovine hypothalamic-pituitary-adrenal axis during pregnancy and lactation following immunological challenge with *Escherichia coli* lipopolysaccharide. 7th International Veterinary Immunology Symposium, July 25-30, Quebec City.

B.A. Mallard, Z. Alizadeh, **N.A. Karrow**. 2003. Biological effect of varying peptide binding affinity to BoLA-DRB3*2703 allele. IVVDC, July 13-18, Guelph, Ont..

B.A. Mallard, W. Tao, **N.A. Karrow**, and B. Bridle 2003. Construction and validation of a bovine immune-endocrine cDNA microarray. IVVDC, July 13-18, Guelph, Ont.
H. V. L. N. Swamy, T. K. Smith, **N.A. Karrow**, and H.J. Boermans. 2003. Effects of feeding blends of grains naturally-contaminated with *Fusarium* mycotoxins on immune parameters of broiler chickens. Poster presented at Annual Meeting of Poultry Science Association, July 6-9, Madison, WI.

H. V. L. N. Swamy, T. K. Smith, E.J. MacDonald, **N.A. Karrow**, and H.J. Boermans. 2003. Effects of feeding blends of grains naturally-contaminated with *Fusarium* mycotoxins on antibody titers and brain neurochemistry of starter pigs. Poster presented at Annual Joint Meeting of American Society of Animal Science and American Society of Dairy Science, June 21-26, Phoenix, AZ.

W. Tao, B.A. Mallard, **N.A. Karrow**, and B.Bridle 2003. Construction and validation of a bovine immune-endocrine cDNA microarray. International Symposium on Animal Functional Genomics. May 9-11, East Lansing, Michigan.

H.V.L.N. Swamy, T.K. Smith, E.J. MacDonald, H.J. Boermans, **N.A. Karrow** and W.D. Woodward. 2002. Effects of feeding blends of grains naturally-contaminated with Fusarium mycotoxins on growth, serum chemistry and haematology of starter pigs. Joint Meeting of the

American Dairy Science Association, American Society of Animal Science, and Canadian Society of Animal Science, July 21-25, Quebec City, Quebec.

B.A. Mallard, Z. Alizadeh, **N.A. Karrow**, B.N. Wilkie and S. Sharif. 2002. Varying peptide binding affinity to BoLA-DRB3*2703. 16th Spring Meeting of the Canadian Society for Immunology, April 5-8, Collingwood, ON.

A. Hernandez, **N.A. Karrow**, B.N. Wilkie and B.A. Mallard. 2002. Evaluation of DTH and antibody to OVA as a means to identify high (H) and low (L) immune responsiveness in cattle: Microarray analysis of gene expression associated with H and L immune response phenotypes. 16th Spring Meeting of the Canadian Society for Immunology, April 5-8, Collingwood, ON.

Z. Alzadeh, **N.A. Karrow** and B.A. Mallard. 2001. Biological effect of varying peptide binding affinity to BoLA-DRB3.2*2703 allele. 6th International Veterinary Immunology Symposium, July 15-20, Uppsala, Sweden.

N.A. Karrow, T.L. Guo, L.X. Zhang, J.A. McCay, V.L. Peachee, R.D. Brown, D.L. Musgrove, C.K. Washington, D.R. Germolec and K.L. White, Jr. 2001. The immunomodulatory effects of thalidomide in B6C3F1 mice after 28 days of treatment: A study of the macrophage phagocytic system and host resistance. 40th Annual Meeting of the Society of Toxicology, San Francisco, California, March 25-29. (The Toxicologist 60, 1)

T.L. Guo, J.A. McCay, L.X. Zhang, **N.A. Karrow**, R.D. Brown, D.R. Germolec and K.L. White, Jr. 2001. Genistein modulates immune responses and increases host resistance to B16F10 tumor model in adult female B6C3F1 mice. 40th Annual Meeting of the Society of Toxicology, San Francisco, California, March 25-29. (The Toxicologist 60, 1)

N.A. Karrow, J.A. McCay, T.L. Guo, G.W. Johnson, R.D. Brown, D.L. Musgrove, D.R. Germolec and K.L. White, Jr. 2000. Exposure to sodium chlorite in drinking water for 28 days produced minimal immunomodulatory effects in female B6C3F1 mice. 39th Annual Meeting of the Society of Toxicology, Philadelphia, Pennsylvania, March 19-23. (The Toxicologist, 54, 1, 157)

T.L. Guo, J.A. McCay, **N.A. Karrow**, G.W. Johnson, R.D. Brown, D.L. Musgrove, D.R. Germolec and K.L. White, Jr. 2000. Exposure to sodium bromate in drinking water for 28 days produced minimal immunotoxic effects in female B6C3F1 mice. 39th Annual Meeting of the Society of Toxicology, Philadelphia, Pennsylvania, March 19-23. (The Toxicologist, 54,1, 156)

J.A. McCay, D.L. Musgrove, R.D. Brown, G.W. Johnson, **N.A. Karrow**, T.L. Guo, D.R. Germolec and K.L. White, Jr. 2000. Exposure to the disinfection by-product dibromoacetic acid does not alter immune function or host resistance. 39th Annual Meeting of the Society of Toxicology, Philadelphia, Pennsylvania, March 19-23. (The Toxicologist, 54,1, 157)

N.A. Karrow, J.A. McCay, T.L. Guo, G.W. Johnson, R.D. Brown, D.L. Musgrove, D.R. Germolec and K.L. White, Jr. 1999. Immunotoxicity of sodium chlorite in female B6C3F1

mice: A 28-day drinking water study. Foundations of Immunotoxicology 14th Annual Conference, September 8-10, Morgantown, WV.

T. Guo, J.A. McCay, **N.A. Karrow**, G.W. Johnson, R.D. Brown, D.L. Musgrove, D.R. Germolec and K.L. White, Jr. 1999. Immunotoxicity of sodium bromate in female B6C3F1 mice: A 28-day drinking water study. Foundations of Immunotoxicology 14th Annual Conference, September 8-10, Morgantown, WV.

J. Sherry, **N.A. Karrow**, A. Gamble, J. Parrott, D. Bennie, R. Ganassin, S. Brown, M. McMaster, K. Solomon, G. Dixon and N. Bols. 1999. Caged fish as a health assessment tool: Immune, endocrine, and liver detoxification responses in trout Oncorhynchus mykiss and *Salmo trutta* caged in Hamilton Harbour. IAGLR Annual Meeting, May 24-28, Cleveland, OH.

A.V. Gamble, D. Bennie, S. Brown, P.V. Hodson, **N.A. Karrow**, J. Parrott, M. Servos, K.R. Solomon and J.P. Sherry. 1998. Use of rainbow trout *Oncorhynchus mykiss* and brown trout *Salmo trutta* to screen Hamilton Harbour water for estrogenic effects. SETAC 19th Annual Meeting, November 15-19, Charlotte, NC.

N.A. Karrow, H.J. Boermans, N.C. Bols, D.G. Dixon, K.R. Solomon and J.J. Whyte. 1997. Creosote immunotoxicity to rainbow trout Oncorhynchus mykiss. ISDCI, July 21-25, Williamsburg, VA.

N.A. Karrow, H.J. Boermans, N.C. Bols, D.G. Dixon, K.R. Solomon and J.J. Whyte. 1997. Characterizing the immunotoxicity of creosote to rainbow trout Oncorhynchus mykiss: a mesocosm study update. CNTC Meeting, March 23-25, Toronto, ON.

N.A. Karrow, H.J. Boermans, N.C. Bols, D.G. Dixon, K.R. Solomon and J.J. Whyte. 1996. Characterizing the immunotoxicity of creosote to rainbow trout Oncorhynchus mykiss: a mesocosm study. SETAC 17th Annual Meeting, November 17-21, Washington, DC.

J.J. Whyte, **N. Karrow**, S. Majdic, D.G. Dixon and N.C. Bols. 1996. Use of SPMDs and rainbow trout to examine CYP1A1 induction in creosote contaminated mesocosms. SETAC 17th Annual Meeting, November 17-21, Washington, DC.

N.A. Karrow, H.J. Boermans, N.C. Bols, D.G. Dixon, K.R. Solomon and J.J. Whyte. 1996. Characterizing the immunotoxicity of creosote to rainbow trout Oncorhynchus mykiss: a mesocosm study. CNTC Meeting, March 23-25, Toronto, ON.

SOCIETY MEMBERSHIPS:

Canadian Society for Animal Science
American Society of Animal Science
International Society for Developmental Origins of Health and Disease
International Society for Animal Genetics

RESEARCH FUNDING:

2023	Mitacs Globalink Research Awarded to Ran Xu $6,000 Role of Peyer's patches in mycotoxicity
2022-2025	$168,000 OMAFRA-Tier 1 Impact of maternal diet on small ruminant colostrum bioactives and postnatal health
2022-2023	$203,166 TrouwNutrition The effects of feeding gestating sows Fusarium mycotoxins and potential mitigation with mycotoxin binders
2021-2023	$210,000 NSERC-Alliance Impact of maternal diet on small ruminant colostrum bioactives and postnatal health
2022-2025	$124,960 The Canada First Research Excellence Fund Food from thought research program: Breeding livestock for climate resilience Co-Investigator Drs. B.A. Mallard, D. Tulpan, A. Canovas
2021-24	$60,000 Ontario Sheep Farmers The impact of maternal diet and stress on small ruminant colostrum bioactives and postnatal health Principal Investigator
2021-22	$22,000 Gartshore Memorial Sheep Research Fund Impact of maternal diet on sheep colostrum bioactives and postnatal health Principal Investigator

2019-2025 $198,000
NSERC-Discovery
Neuroendocrine-immune system programming of zebrafish embryos and larva: Implications for stress resilience, disease resistance and longevity
Principal Investigator

2019-2021 $434,700
The Canada First Research Excellence Fund
Food from thought research program: Breeding livestock for climate resilience
Co-Investigator
Drs. B.A. Mallard, C. Baes, A. Canovas, F. Schenkel

2019-22 $202,879
NSERC-CRD-Alltech
Penicillium and Fusarium mycotoxin assessment using bovine intestinal epithelial cells (IEC) and co-cultured IEC + macrophages, and remediation with yeast mycotoxin binders
Principal Investigator

2019-22 $403,100
NSERC-CRD- Semex
Assessment of genetics of stress resilience in dairy cattle
Principal Investigator

2018-19 $25,000
NSERC-Discovery
Pre- and post-natal programming of the neuroendocrine-immune system: Implications for stress resilience, disease resistance and longevity
Principal Investigator

2018-20 $120,000
MITACS Elevate Postdoctoral Fellowship-Semex awarded to Dr. Ankita Sharma
Assessment and genetics of stress resilience in dairy cattle
Principal Investigator

2017-2018 $50,000
Jiangsu Aomai Bio-tech Company
Effects of deoxynivalenol on the growth performance, immunity and intestinal microflora of weanling piglets
Co-Investigator
Dr. L. Sun, Huazhong Agricultural University, Wuhan, China.

2017-18 $34,600
OMAFRA-HQP awarded to Samantha Dixon
Leveraging transcriptomics and systems biology to understand the genes and metabolic pathways associated with ovine resistance to gastrointestinal nematodes
Co-Investigator
Dr. A. Canovas

2017-2019 $327,900
The Canada First Research Excellence Fund
Food from thought research program: Breeding livestock for climate resilience
Co-Investigator
Drs. B.A. Mallard, C. Baes, A. Canovas, F. Miglior, F. Schenkel

2016-18 $63,000
OMAFRA-HQP awarded to Emma Borkowski
Investigation of immune response of sheep to gastrointestinal nematode infection under Ontario grazing conditions for purposes of identifying genetically resistance animals
Co-Investigator
Drs. A. Peregrine, P. Menzies

2016-17 $149,850
NSERC-RTI
Zebrafish advanced life support system
Co-Investigator
Drs. T. Van Raay, N. Bernier, J. Dawson, G. Van Der Kraak, T. Gillis, S. Ryan

2016-19 $132,500
NSERC-CRD- Semex
Genetic markers and bovine Johne's disease
Principal Investigator

2016-19 $125,000
OMAFRA
Evaluation of immunonutrition in pigs: leucine and n-3 PUFAs
Co-investigator
Dr. L. Huber

2015-17 65,000 EU
Adisseo France
Assessment of nursing piglet and weaner pig health during selenium supplementation
Co-investigator

Drs. H. Liu and L. Sun, Huazhong Agricultural University, Wuhan, China.

2015-16 $149,900
NSERC-RTI
Purchase of an imaging multi-mode reader for Animal Biosciences research
Co-Investigator
Drs. J. Squires, J. Li, G. Bedecarrats, J. Cant

2015 $17,640 USD
Alltech Inc.
Risk assessment modeling of mycotoxin interactions based on assessment of biomarkers and mycotoxin metabolites, and evaluation of the impact of remediation strategies using zebrafish as an in vivo experimental model
Principal Investigator

2015-18 $332,644
OMAFRA/ OSMA-AAFC- Agri-innovation
Investigation of immune response of sheep to gastrointestinal nematode infection
Co-Investigator
Drs. P. Menzies, A. Peregrine

2015-19 $124,000
Teagasc Walsh Fellowship awarded to Sanjay Mallikarjunappa
Defining Innate Phenotypes Associated with Enhanced Immunity to Johne's Disease
Co-Investigator
Drs. K. Meade, B.A. Mallard, B. Plattner

2015-2019 $440,000
NSERC-CRD- Alltech Inc.
The benefits of algae meal supplementation during pregnancy on piglet and weaner pig health
Principal Investigator

2014-17 $175,000
OMAFRA
Assessing the bioactivity of immune-related microRNAs in colostrum and milk from high and low immune responder cows on intestinal epithelial cells
Co-Investigator
Dr. B.A. Mallard

2014 $27,900
NSERC Engage Plus- Lallemand Inc.
Assessing the immunomodulatory properties of yeast using primary intestinal epithelial cells and bovine macrophages.

Principal Investigator

2014-18 $60,000
Swine Innovation Porc: Canadian Swine Research & Development Cluster 2
Innovative piglet management strategies for optimum performance up to slaughter weight and profitable pork production
Co-Investigator
Drs. C.F.M. De Lange and J. Squires

2014-17 $225,000
NSERC-CRD- Dairy Farmers of Ontario
Assessing the bioactivity of bovine colostrum and milk immune-related miRNAs from high and low immune responder cows on human IECs
Principal Investigator

2013-16 $187,082
NSERC CRD- Canadian Dairy Network
Genetic hallmark of susceptible cows through macrophage profiling of MAP infected cows
Co-Investigator
Dr. N. Bissonnette

2013-2015 $115,000
MITACS Elevate Postdoctoral Fellowship-Alltech Inc. awarded to Dr. Rebecca Fisher
The benefits of algae meal supplementation during pregnancy on piglet health
Principal Investigator

2013-2015 $43,750
Ontario Sheep Marketing Agency-OFIP Growing Forward 2
Maedi-Visna in sheep and potential interaction with *Mycobacterium avium spp. paratuberculosis*
Principal Investigator

2013-14 $42,700
Alltech Inc.
Immunomodulatory effects of Penicillium mycotoxins
Principal Investigator

2013-14 $30,000
MITACS-Accelerate Internship Program awarded to Ziwei Li
Identification and assessment of bioactive yeast strains and cell wall components
Principal Investigator

2013-16	$68,000 OMAFRA-HQP awarded to Nancy Stonos Vaccine response of acutely stressed high, medium and low cortisol response sheep Principal Investigator
2013-19	$169,000 NSERC-Discovery Genetic and epigenetic regulation of the stress response and implications for ruminant health Principal Investigator
2013	$24,000 NSERC Engage- Lallemand Inc. Assessing the immunomodulatory properties of probiotics using intestinal epithelial cells and bovine macrophages. Principal Investigator
2012	$24,500 NSERC Engage- Ontario Goat Prevalence of CAEV in Ontario goat herds Principal Investigator
2012-14	$86,000 NSERC CRD- Ontario Pork Robustness of starter pigs Co-Investigator Dr. C.F.M. De Lange
2012	$7,500 Gartshore Memorial Sheep Research Fund Impact of dietary fatty acids on fetal development Principal Investigator
2010-12	$80,000 MITACS Elevate Postdoctoral Fellowship-Alltech Inc. awarded to Dr. Bhawani Sharma Epigenetic programming and Penicillium mycotoxins Principal Investigator
2010-11	$7,950 OMAFRA Appropriate welfare considerations for sheep subject to the recto-anal mucosa associated lymphoid tissue biopsy for detection of scrapie infection Co-Investigator Dr. Paula Menzies

2010-13 $210,000
NSERC CRD- Canadian Dairy Network. Dairy Farmers of Ontario
Breed-specific gene expression profiles and DNA methylation patterns in calves infected with Mycobacterium avium subsp. paratuberculosis (MAP)
Principal Investigator

2010-11 $50,000
OMAFRA
Mycotoxins and the developing neuroendocrine-immune system
Principal Investigator

2009-12 $64,267
OMAFRA HQP awarded to Steven Oh
Effect of Penicillium mycotoxins on the development of ruminant neuroendocrine-immune system
Principal Investigator

2009-12 $232,998
NSERC CRD-Canadian Dairy Network
Applied genetic and epigenetic influences on high and low immune response phenotypes of dairy cattle
Co-Investigator
Dr. B.A. Mallard

2008-9 $103,000
NSERC CRD- Canadian Dairy Network
High and low immune response phenotypes: genes and proteins associated with health and performance
Co-Investigator
Dr. B.A. Mallard

2008-13 $185,000
NSERC-Discovery Grant
Genetics of disease resistance in ruminants: interaction between the HP-adrenal axis and the immune system
Principal Investigator

2008-09 $39,598
Ontario Ministry of Agriculture, Food, and Rural Affairs
Development of in vitro assessment technologies for detection of potential allergenicity and toxicity of novel foods
Project Leader

2007-09 $190,000
AAFC

Development of functional genomics tools to detect resistant and susceptible cows within a mastitis control program
Co-Investigator
Dr. N. Bissonnette

2008-10 $97,000
NSERC CRD- Ontario Pork
Immune system stimulation and amino acid utilization in the growing pig
Co-Investigator
Dr. C.F.M. De Lange

2007-10 $386,500
NSERC CRD- Canadian Dairy Network
The identification of genetic polymorphisms and protein biomarkers that are associated with susceptibility or resistance to bovine Johne's disease
Principal Investigator

2007-11 $410,000
Ontario Ministry of Agriculture, Food, and Rural Affairs New Directions-Ontario Sheep Marketing Agency
The impact of dietary fatty acids on inflammation during ovine pregnancy, lactation, and fetal development.
Principal Investigator

2006-11 $250,000
NSERC Network Grant
Integrative genomic and proteomic strategies to identify immunological profiles associated with enhanced host defence against mastitis pathogens
Canadian Bovine Mastitis Research Network
Co-Investigator
Dr. D. Scholl

2005 $142,254
NSERC Research Tools and Instruments Grant
Using SELDI for proteomic analysis in animal science
Principal Investigator

2004-05 $9,000
Dairy Farmers of Ontario
DFO Summer Studentship
Principal Investigator

2004 $7,000
Gartshore Memorial Sheep Research Fund
Using microarrays and real-time PCR to identify genes that regulate high and low stress responsiveness to endotoxin

Principal Investigator

2004-2006 $90,000
NSERC CRD-Canadian Dairy Network
Identification of genes involved in nutritional regulation of milk protein production by the dairy cow.
Co-Investigator
Dr. C. Robert

2004-2007 $120,000
AAFC- Canadian Dairy Network
Construction of a health trait-associated cDNA library for screening candidate genes in the mammary gland of lactating cows: developing a tool to identify major genes involved in mastitis.
Co-Investigator
Dr. N. Bissonnette

2004-06 $40,500
NSERC CRD-Canadian Dairy Network
Gene expression and protein profiling comparing the cells found in the milk of high and low SCC animals to identify markers associated with mastitis resistance.
Co-Investigator
Dr. B.A. Mallard

2004-07 $2,400,000
Ontario Research Development Challenge Fund-PYXGEN Canada Inc.
Early prediction of genetic merit for traits of economic importance in dairy cattle using gene expression profiles and dense SNP maps in young animals.
Co-Investigator
Dr. J. Cant

2004-2005 $168,178
Interpath Pty. Ltd. Australia
Evaluation of a nutraceutical suppliment (Sasha's Blend) in the treatment and prevention of cartilage inflammation
Co-Investigator
Dr. M. Lindinger

2004-2005 $43,200
Selected Bioproducts Ltd.
Evaluation of a nutraceutical suppliment (Mobility) in the treatment and prevention of cartilage inflammation
Co-Investigator
Dr. M. Lindinger

2003-4 $60,000
Food Systems Biotechnology Center
Genetics of Inflammatory Disease Resistance in Ruminants
Principal Investigator

2003-7 $30,060
Ontario Ministry of Agriculture and Food
Genetic regulation and programming of the HP-adrenal-immune axis: Implications for resistance to inflammatory diseases in sheep
Principal Investigator

2003-6 $21,000
Ontario Ministry of Agriculture and Food
Genetic regulation of inflammation: implications for disease resistance in Canadian dairy cattle
Principal Investigator

2003-6 $345,000
NSERC CRD-Canadian Dairy Network
Alternate genetic approaches to improving mastitis resistance in Canadian dairy cattle
Principal Investigator

2003-7 $136,000
NSERC Discovery Grant
Genetics of disease resistance in ruminants: interaction between the HP-adrenal axis and the immune system
Principal Investigator

2003 $25,000
Ontario Center for Agriculture Genomics
Start-up Trust Fund

2003 $303,350
Canadian Foundation for Innovation/Ontario Innovation Trust
Infrastructure for research in immunogenetics: the neuroendocrine-immune axis and the genetics of disease resistance
Principal Investigator

2002-5 $300,000
NSERC CRD-Canadian Dairy Network
Immunogenetic markers of disease resistance in Canadian dairy cattle
Co-Investigator
Dr. B.A. Mallard

2000-5 $1,558,509 (ADC)

National Institute of Health, ES0023
Potential for environmental and therapeutic agents to induce immunotoxicity
Co-Principal Investigator
Dr. K.L. White

PATENTS:

-CA2,675,242 C Bovine genetic test for susceptibility to mastitis and Johne's disease. Publication date January 15, 2019, Filed August, 11, 2009.

- US9,133,520 B2. Single nucleotide polymorphisms (SNPs) in genes associated with inflammatory diseases, Application number US 13/845,545, Publication date September 15, 2015, Filed March 18, 2013.

This is Exhibit " B " to the Affidavit of
Dr. Neil Karrow, affirmed before me on
this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

THE CONVERSATION

Academic rigour, journalistic flair

It's not yet clear whether antibodies in the blood of patients who have been infected with SARS-CoV-2 indicate immunity. Above: blood specimens for COVID-19 antibody tests. (AP Photo/Mary Altaffer)

Can antibody tests tell us who is immune to COVID-19?

Published: May 26, 2020 12.17pm EDT

Shayan Sharif
Professor of Immunology and Associate Dean, Research and Graduate Studies, University of Guelph

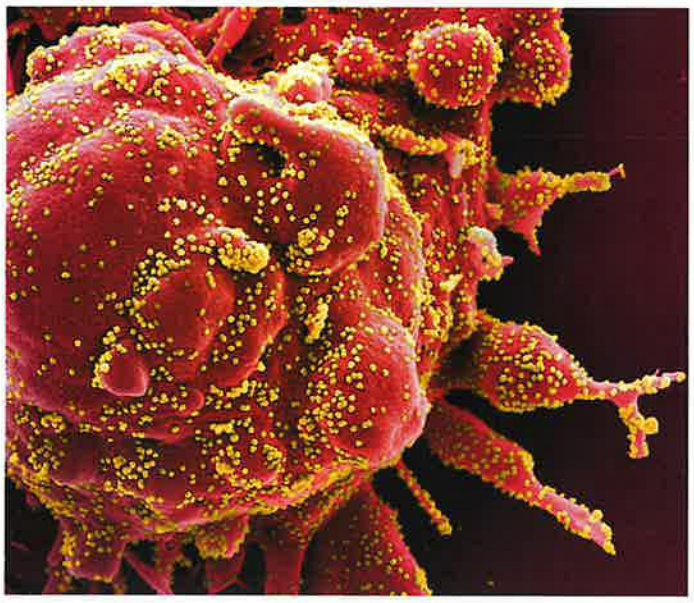
Byram W. Bridle
Associate professor, Department of Pathobiology, University of Guelph

Widespread media coverage of antibody testing for SARS-CoV-2, the virus that causes COVID-19, has generated high hopes that we will be able to readily identify individuals who are immune to this virus.

There has also been coverage about developing immunity passports, which employers can use to let people return to work. While these are all tantalizing thoughts, the idea of using antibody testing as a true measure of protection is something that requires much more research.

As immunologists, our interest is in understanding how the immune system responds to viruses, especially zoonotic viruses that can be transmitted from animals to humans, like SARS-CoV-2. Here, we share our insights into different aspects of antibody testing, including its promises as well as caveats.

Immune response to a new pathogen



Colourized scanning electron micrograph of a cell (red) from a patient sample, heavily infected with SARS-CoV-2 virus particles (yellow). (National Institute of Allergy and Infectious Diseases)

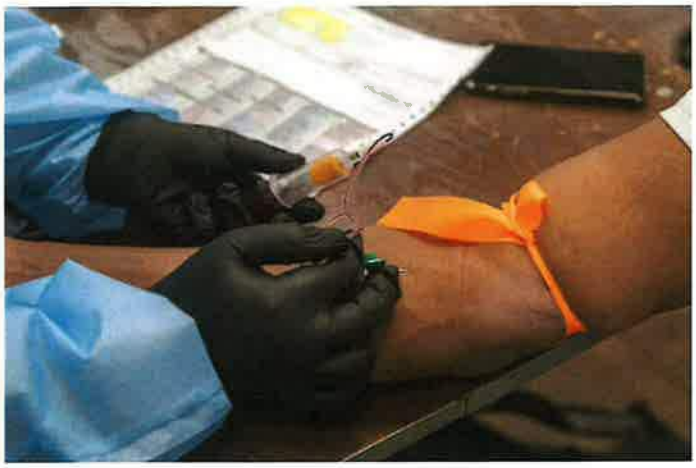
An emerging zoonotic pathogen — such as SARS-CoV-2 — is unique in the sense that humans have never been exposed to it, so our immune system has never mounted a response to this specific virus. When we are exposed to an emerging pathogen, our immune system mounts different types of responses within seven to 14 days.

Antibodies are one type of response: they are secreted into the blood and, more importantly, are present at sites of infection. In the case of SARS-CoV-2, antiviral antibodies can be found in the blood after infection, but they are also presumably present in the respiratory system, where the virus resides and propagates.

Although the presence of antibodies in an individual confirms that an infection has occurred, antibodies alone cannot differentiate between a historical versus current infection.

Antibody tests

Several companies have begun producing antibody testing kits, some of which have received regulatory approval. Currently, Health Canada has approved only one antibody test. The U.S. Food and Drug Administration has issued emergency use authorization for 12 tests, including a combination of lab-based and point-of-care tests, while 200 other devices are awaiting approval.



A registered nurse draws blood for a COVID-19 antibody test in the Harlem neighbourhood of Manhattan on May 14, 2020. Testing drives through churches in low-income communities across New York are offering COVID-19 testing to residents. (AP Photo/Mary Altaffer)

Large-scale antibody testing has already been performed in parts of the U.S. and Europe. For example, in Chelsea, Mass., 64 out of 200 people in the downtown area tested positive for COVID-19 exposure using antibody testing. Other areas have also reported high prevalence of antibody response to SARS-CoV-2, including 25 per cent in New York City, approximately 2.8 per cent in Santa Clara County, Calif., and 14 per cent in Gangelt, Germany.

While these data imply that significantly more people have been exposed to or infected with SARS-CoV-2 than have been diagnosed using nucleic acid-based tests, these antibody-positive people may not be immune to SARS-CoV-2.

Are people who have had COVID-19 immune?

Depending on the type of virus, antibodies in the blood may or may not confer protection against the virus. We can only hope that the antibodies circulating in the blood of patients infected with SARS-CoV-2 are good indicators of protection.

Read more: Know your target: Fundamental science will lead us to coronavirus vaccines

However, there is a chance that there is only a weak connection, or no connection at all, between antibody presence in the blood and protection against SARS-CoV-2. This is because antibodies in the blood will have to find their way to the respiratory system — where the virus resides — to exert their protective functions. Sometimes they do not end up in the lungs where they are most needed for protection. Also, these antibodies may not be of the right type to protect against infection or there may not be enough of them present to establish protection.

A 3D print of a spike protein of SARS-CoV-2, the virus that causes COVID-19, in front of a 3D print of a SARS-CoV-2 virus particle. The spike protein (foreground) enables the virus to enter and infect human cells. On the virus model, the virus surface (blue) is covered with spike proteins (red). (NIH)

It is speculated that protective antibodies bind to the molecular structures on the surface of SARS-CoV-2, especially its spike protein. The spike proteins are the points that cover the surface of the virus, forming the "crown" that gives coronaviruses their name. The virus uses these spikes to attach to cells of the respiratory system. The antibodies that bind to SARS-CoV-2's spike protein may prevent the virus from attaching to cells. Viruses that are not able to attach and enter a cell cannot propagate and will eventually die out.

It is safe to say that antibody testing is an excellent way to determine whether there has been exposure to the virus, but not necessarily whether protection has been established. That presents a potential danger in rushing the concept of immunity passports into use: people with positive antibody tests may behave as though they are protected against COVID-19 when, in fact, they may not be.

How can we test for immunity?

Given what we now know, can we conceivably use antibody testing as a measure of immunity? The answer is maybe! If one looks at other more familiar respiratory viruses, like influenza viruses, there is usually good correlation between antibodies in the blood and protection against influenza virus.

A sign listing COVID-19 tests available, including an antibody test, on April 28, 2020, in Houston, Texas. (AP Photo/David J. Phillip)

What needs to happen now is a series of epidemiological studies looking at people with high and low concentrations of antibodies to determine whether the presence of antibodies is associated with protection against re-infection with SARS-CoV-2 and if so, what is the minimum quantity of antibodies for conferring protection.

This process will take some time, but it is very doable. One way to speed up the process is to develop tests to assess antibodies for their potential to prevent SARS-CoV-2 infection. Using antibodies taken from the respiratory systems of individuals who have been infected, these tests would see if those antibodies could prevent the virus from infecting susceptible cells in a culture dish.

Simultaneously studying antibodies in the blood of these same individuals would then tell us how well the current "quick and easy" antibody tests correlate with the antiviral functions of the antibodies in the respiratory system.

On April 23, 2020, Prime Minister Justin Trudeau announced the formation of the COVID-19 Immunity Task Force to "... oversee the co-ordination of a series of country-wide blood test surveys that will tell us how widely the virus has spread in Canada and provide reliable estimates of potential immunity and vulnerabilities in the Canadian population."

What T cells can tell us

A scanning electron micrograph of a healthy human T-cell. (NIAID)

If it turns out that antibody tests can confirm exposure but do not indicate immunity, there are alternative approaches to immunity testing. One of the main players in immunity against viruses is a subset of cells called T-cells. These cells have an enormous capacity to recognize and respond to viruses by killing the virus-infected cells.

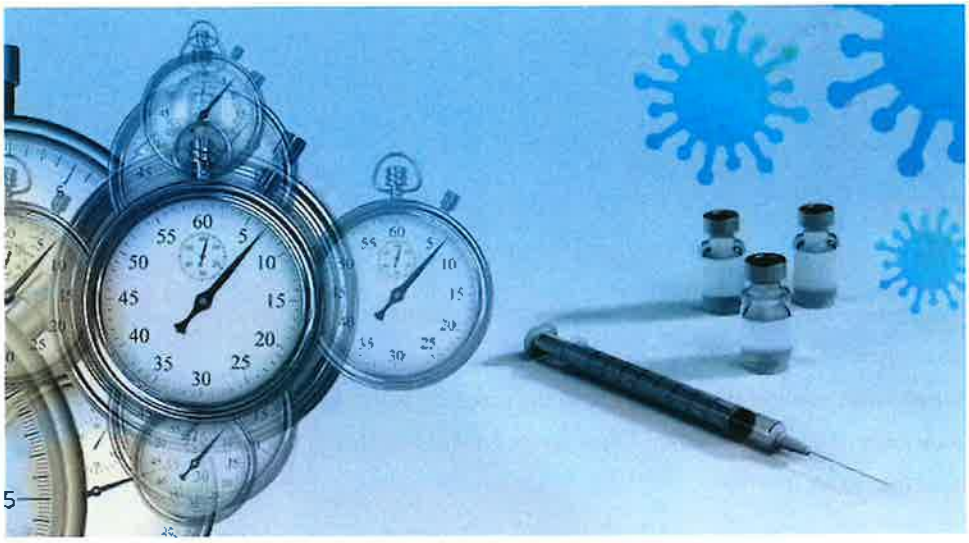
We have limited understanding of the involvement of T-cells in immunity against SARS-CoV-2, but it is possible that these cells play a pivotal role in protection. The question is whether we can use T-cell responses as indicators of immunity. The answer is both yes and no.

While it is feasible to measure T-cell responses in laboratory settings, it is time-consuming and requires a level of technical sophistication that is not available in most diagnostic labs. Also, T-cell testing will have to be done as a high-throughput procedure, meaning that a large number of samples is tested at once. Although high-throughput testing has not been fully developed for diagnostic purposes, the technology is there, so T-cell testing may play a role in assessing immunity to SARS-CoV-2.

This pandemic has been a true test for science and scientists. Studying our immune response to SARS-CoV-2 may not only be the key to identifying who is protected from the virus, but also to developing potential vaccines and treatments.

THE CONVERSATION

Academic rigour, journalistic flair



The scope and length of vaccine testing experiments usually mean decade-long timelines for development. (Pixabay)

Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk

Published: June 15, 2020 12.27pm EDT

Byram W. Bridle
Associate Professor of Viral Immunology, Department of Pathobiology, University of Guelph

Shayan Sharif
Professor of Immunology and Associate Dean, Research and Graduate Studies, University of Guelph

The average times of the fastest sprinters in the 100-metre dash are in the ballpark of 10 seconds. So, what would you think if someone promised to run the race in one second?

It typically takes a minimum of 10 years for a vaccine to complete the three consecutive phases of the clinical research pipeline. This is because of the scope and length of the experiments, the need to critically assess the results at each stage and the mountains of paperwork that are involved.

What are the chances that this can be reduced to 12 months? Indeed, it has been implied that this process can be accelerated to "warp speed."

It usually takes about 10 years to develop and test a new vaccine. (Shutterstock)

We contend that a safe and effective vaccine against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which is the causative agent of coronavirus disease COVID-19, most likely cannot be made available to the public in time to make a substantial difference to the natural outcome of this pandemic. People often cling to hope even when prospects of success are low. However, this can have negative consequences if that hope is not realized.

We are academic scientists who manage vaccine research programs. In fact, Dr. Bridle received COVID-19-focused funding to develop a novel vaccine platform. Although many of us are working hard towards developing vaccines against SARS-CoV-2, we worry that some in the scientific community have offered too much hope for this to be accomplished in a timely fashion. Sometimes these promises are used by politicians and governments to inform public policies. As a result, the integrity of the scientific community is now in the limelight and, arguably, at risk.

Herd immunity

Vaccines are an effective way for a population to achieve what is known as "herd immunity." This is the concept that the pandemic will end once approximately 60-70 per cent of people become immune to SARS-CoV-2. An alternative is to let SARS-CoV-2 run its natural course until herd immunity is achieved. With physical distancing, some epidemiologists argue this could take two years, during which time a vaccine could be developed.

Social and physical distancing signs on the floors of various business throughout Vancouver and surrounding area are pictured between May 1-12, 2020. THE CANADIAN PRESS/Jonathan Hayward

However, vaccinating at the tail end of a pandemic when disease incidence is very low and declining may be of little utility, hence the race to develop a vaccine for COVID-19. If one is not in widespread use within the first half of 2021, it will probably be too late to have a meaningful impact on control of COVID-19.

Lessons from SARS and MERS

Educators often rely on past performance to predict the future performance of students. In this respect, how was the performance of the scientific community in the wake of the original SARS-CoV, or Middle East respiratory syndrome (MERS)-CoV? The fact is, no vaccine against a coronavirus has successfully navigated the rigours of clinical testing, despite having up to 17 years to do so.

The same applies to other dangerous respiratory pathogens, such as respiratory syncytial virus. Whether enough has been learned from these past experiences to get the design of COVID-19 vaccines right remains to be seen, and still does not negate the need for a rigorous testing process that will take time.

3D print of a spike protein of SARS-CoV-2 in front of a 3D print of a SARS-CoV-2 virus particle. The spike protein (foreground) enables the virus to enter and infect human cells. On the virus model, the virus surface (blue) is covered with spike proteins (red) that enable the virus to enter and infect human cells. (U.S. National Institutes of Health)

One concern is that some vaccines can protect against disease (that is, the outcome of an infection) but not against infection (the ability of the virus to get into the body). In this scenario, vaccinated individuals could potentially become asymptomatic carriers of SARS-CoV-2, thereby spreading COVID-19. For this and many other reasons, a cautious approach must be taken to developing COVID-19 vaccines.

Vaccines already in clinical trials

What about the fact that there are front-runner vaccines already in human clinical trials? First, many of the vaccine technologies that can most readily make it to the front of the line are not necessarily the best quality. The easiest way to make a vaccine is to inactivate the pathogen or use pieces of it, and mix them with an adjuvant, which tells the immune system that the pathogen is dangerous and worth responding to.

Illustration of coronavirus structure. (Pixabay)

However, an inactivated virus or its components do not behave like the live virus, so the immune system sometimes responds to these vaccines in a way that is ineffective or sometimes even dangerous. For example, no vaccine based on the genetic material, known as ribonucleic acid or RNA, from a virus like SARS-CoV-2 has ever been approved. Further, some vaccines developed against the original SARS-CoV, after the epidemic was over, exacerbated the disease in mice.

A vaccine for COVID-19 does not have to be the best one, but it does need to be good enough to accelerate a population's progression to herd immunity. As experienced peer reviewers, we have some concerns about the rigour of some of the science surrounding COVID-19 vaccines.

Some vaccines are fast-tracking through the regulatory system before studies are completed and with minimal details of experimental results being released. Executives of a big pharmaceutical company whose vaccine is among those closest to the finish line recently sold their stocks after releasing "positive results" that were superficial, partial and that included three of eight healthy young volunteers experiencing severe adverse events.

Events like this are causing the public to become skeptical. A promising vaccine should have solid data to back it up. Those touting vaccines against COVID-19 that are in clinical trials should be asked to provide comprehensive details and results of their study. This enables objective and rigorous evaluations by the broader scientific community. A lack of complete transparency would be cause for concern.

Getting from trials to clinics

Assuming a vaccine succeeds in human trials, it then needs to be manufactured in massive quantities at an affordable price, undergo quality control testing and be distributed worldwide. Even if by some miracle this spectrum could be bridged at warp speed, one then needs to wonder if up to 70 per cent of individuals can be effectively vaccinated.

Once a vaccine is developed and approved, it would have to be mass manufactured and distributed before people could get the shot. (Pixabay)

Uptake of a vaccine could be compromised by anti-vaxxers, as well as by perceptions that warp-speed manoeuvring might be the result of cutting too many corners and compromising safety. Then there are those who simply do not respond as well to vaccines, which includes the elderly who are in the greatest need of protection.

Considering what we now know about SARS-CoV-2 vaccines, we need to take a more cautious approach and one could question if any of the vaccines that are now in pre-clinical testing can possibly help with the current pandemic. We sincerely hope that our pessimism about vaccines currently in clinical trials being ready in time is soundly proven wrong.

Even if a vaccine doesn't get developed in time, not all is lost. The array of vaccines being engineered will help with outbreaks beyond COVID-19. They can be vetted by scientists and the best technologies and associated research teams could be shortlisted to be called upon for future outbreaks. Although clinical research likely cannot be shortened to 12 months while maintaining integrity of the science, the current attempt to do so will build new and reasonable efficiencies into health regulatory policies. This will facilitate getting a wide variety of future health solutions to patients faster, but not at warp speed.

THE CONVERSATION

Academic rigour, journalistic flair

Vaccinologists have not focused their research on tailoring vaccines to induce robust immune responses in the elderly. (Shutterstock)

Why vaccines are less effective in the elderly, and what it means for COVID-19

Published: July 20, 2020 3.43pm EDT

Byram W. Bridle
Associate Professor of Viral Immunology, Department of Pathobiology, University of Guelph

Shayan Sharif
Professor of Immunology and Associate Dean, Research and Graduate Studies, University of Guelph

As the global spread of severe acute respiratory syndrome coronavirus (SARS-CoV-2) — the cause of COVID-19 — continues, we learn more about the effects of this new virus.

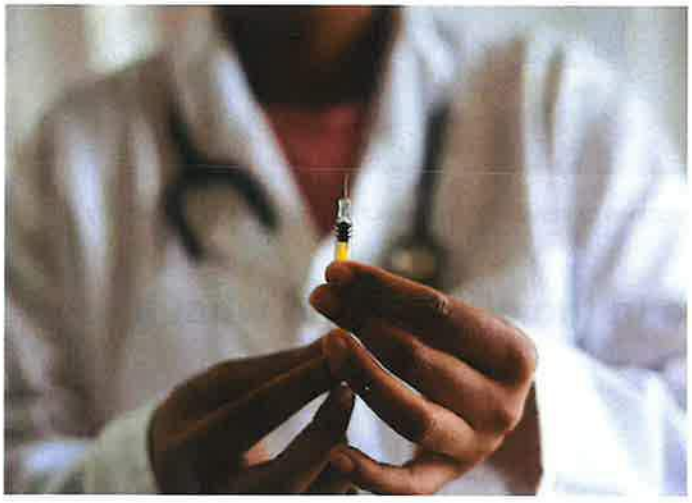
For many respiratory pathogens, including influenza viruses and respiratory syncytial viruses, the elderly experience the most severe forms of disease and the highest death rates. For example, for every 10,000 Americans between 18 and 49 years old, only 0.4 people die from the annual flu. That number increases to 5.9 people per 10,000 for those aged 65-74 years, and 47.5 people for those over 74 years old. However, most of these diseases can also have a predilection for causing severe disease in the very young.

In this respect, COVID-19 is very different. Data from relatively early in the COVID-19 pandemic showed a dramatic difference in the rates of age-associated deaths, with a case fatality rate of 4.5 per cent for patients ages 60 and older versus only 1.4 per cent for those under 60 years old, with those under 30 years ranging from zero to 0.19 per cent.

Immunosenescence

We are immunologists with research programs devoted to developing vaccines. With COVID-19 placing a spotlight on the elderly as the age demographic most in need of a vaccine, we have felt compelled to evaluate how well scientists are doing at tailoring immunization strategies for this population. Our conclusion is that vaccinologists, ourselves included, have largely failed to focus their research on tailoring vaccine technologies to induce robust immune responses in the elderly.

A critical factor that makes the elderly more susceptible to infectious diseases is what immunologists call "immunosenescence": the decline in the immune system's functionality as people age. This is also associated with an increase in the incidence of inflammatory diseases, because an elderly body tends to be in a state of chronic low-grade inflammation. This "inflamm-aging" is one reason why older people have tendencies to develop more severe forms of respiratory diseases.



Older people have a diminished responses to vaccinations because of immunosenescence. (Pexels/Retha Ferguson)

The key problem with SARS-CoV-2 infection is inflammation in the respiratory tract, which can be exacerbated in individuals predisposed towards potent inflammatory responses.

Immunosenescence also results in diminished responses to vaccination. Indeed, annual flu vaccines are notoriously less effective in the elderly. This phenomenon is very important in the context of the massive efforts and funds being invested worldwide into the ultra-rapid development of vaccines for COVID-19.

The fact that elderly people do not respond well to immunizations has largely been ignored in most discussions of COVID-19 vaccines, despite this being the group in greatest need. Most of the scientific community's experience with vaccine development for any disease has been focused on vaccinating the relatively young.

Young mice and elderly humans

Here is an interesting exercise for people reading this article: find as many original research articles as you can on the topic of vaccine development that have used animal models (it could be for any disease). Then look in the subsection of the "materials and methods" section and check the age of the animals. We were shocked by what we found.

Mice are the most common animals used in preclinical vaccine research and the overwhelming majority of these are 12 weeks old or younger. This is equivalent to people 20 years old and younger. It is comparatively much rarer for studies to use immunosenescent mice that are at least 18 months old and equivalent to an elderly human.

Translational studies that take promising preclinical discoveries and move them towards clinical trials often use non-human primates such as Rhesus macaques. In the majority of cases these are around three to six years old, which is equivalent to an adolescent or young-adult human. The same trend applies to all other animals used in vaccine research.

Early-phase clinical trials focus on safety, not efficacy of vaccines. Therefore, far too many vaccines never get tested in the context of aged immune systems until Phase 2 and 3 clinical trials. The time to find out that a vaccine does not work well in the context of immunosenescence is not at this extremely late stage, when it is too late to fix the problem. This testing should begin in the preclinical phase where an iterative process can be followed to tailor a vaccine for a senescent immune system.


The gloved hand of a lab worker holding a C57BL/6 mouse, a type commonly used in research.
A C57BL/6 mouse. (Shutterstock)

Interestingly, many commercial suppliers of animals that are purpose-bred for research do not have adequate inventories of old animals. Of concern, most old mice that are readily available are of the C57BL/6 strain. This is the most common strain used in research, and is known to have an immune system with a strong bias towards effective responses against viruses.

Intriguingly, aged mice experience a more severe form of SARS after infection, akin to elderly humans. The excessive use of young mice with immune systems that are optimal for antiviral responses, and that experience less severe disease, could bias results in a way that overestimates the potential of vaccines to perform well in the elderly.

Developing vaccines for a key demographic

People age 65 and over suffer the most severe cases of COVID-19 and have the highest associated mortality rate. If the goal is to have COVID-19 vaccines ready for public use by early 2021, the only ones that have a chance are those that are currently in clinical trials. It is likely that most of these did not undergo preclinical optimization for an elderly population, meaning these first-generation COVID-19 vaccines may perform poorly in the people that need them most.

For the COVID-19 pandemic, it is too late to go back and build these considerations into preclinical testing. However, it is imperative that researchers still in the preclinical phase incorporate head-to-head testing of their vaccine candidates in young versus aged animals and develop strategies to optimize them in the latter. This will help the world prepare for the next outbreak of a dangerous coronavirus.

For that matter, a focus on the elderly should be incorporated into other vaccine development programs, including those to treat cancers, which have the highest incidence in older people.

There are viable strategies to improve the effectiveness of vaccines in older people, including changes in formulations, doses and routes of administration. However, it takes substantial time and appropriate animal models to conduct this research. It is possible that the elderly may need fundamentally different vaccination regimens than younger people.

Although a few researchers do conduct vaccine studies in old animals, considerations for the elderly need to be adopted by far more vaccinologists. This is of growing importance for countries with aging populations. This will mean changing the current philosophy of the field of vaccine development and incorporating age as a critical variable.

THE CONVERSATION
Academic rigour, journalistic flair

Un employé inspecte des fioles d'un vaccin contre la Covid-19 produit par SinoVac dans son usine de Pékin le 24 septembre 2020. (AP Photo/Ng Han Guan)

Le futur vaccin contre la Covid-19 doit déclencher une mémoire immunitaire… en vue d'une prochaine pandémie

Published: October 14, 2020 11.32am EDT

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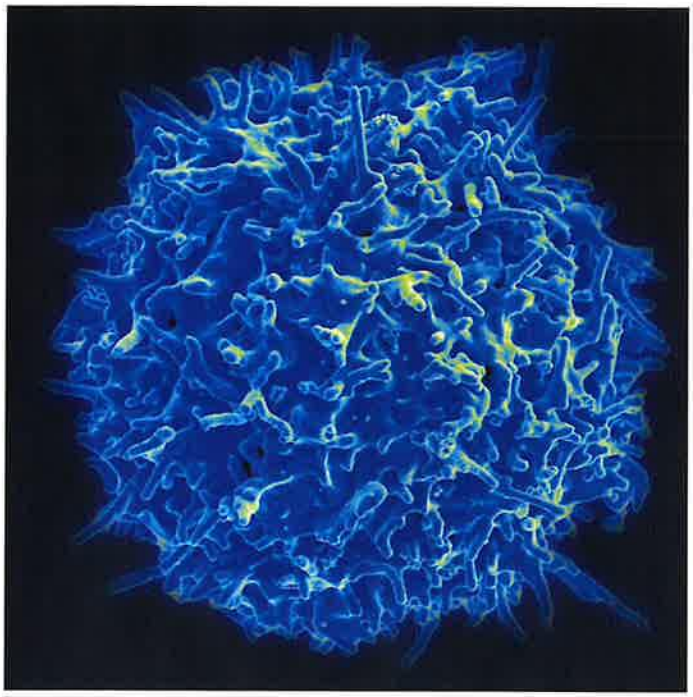
Languages

Français
English

Les athlètes savent qu'il existe deux approches différentes pour entraîner leur corps. En soulevant des poids lourds, ils peuvent arriver à atteindre une force maximale. En revanche, la musculation avec de faibles charges, mais un nombre élevé de répétitions est idéale pour développer la résistance nécessaire aux sports d'endurance.



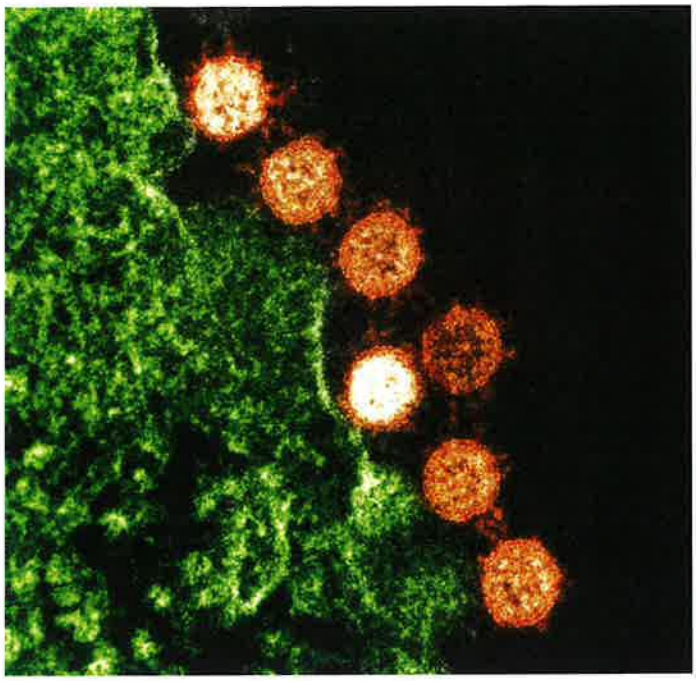
Microscopie électronique à balayage d'un lymphocyte T humain (aussi appelé cellule T) provenant du système immunitaire d'un donneur sain. NIAID, CC BY

Il existe également deux façons d'entraîner notre système immunitaire. Ce dernier peut répondre à des pathogènes dangereux de deux manières, chacune générant une attaque de l'agent infectieux par les anticorps et les globules blancs appelés lymphocytes T. Toutefois, le type de cellules T et d'anticorps diffère selon que l'agent pathogène se trouve à l'extérieur de nos cellules, comme c'est le cas pour de nombreuses bactéries, ou à l'intérieur de nos cellules, comme pour les virus.

La production d'une réaction antibactérienne n'est pas forcément le moyen idéal pour venir à bout d'une infection virale. En fait, une mauvaise réponse immunitaire peut même exacerber la maladie, comme cela a été observé chez des souris vaccinées atteintes du coronavirus du syndrome respiratoire aigu sévère (SARS-CoV), identifié en 2003.

Notre première exposition à un agent pathogène, qu'elle se fasse naturellement ou par la vaccination, peut entraîner notre système immunitaire à adopter l'un de ces deux mécanismes lorsque nous entrerons en contact avec le même agent pathogène ou un agent similaire pour le reste de notre vie. Les immunologistes appellent cela « la mémoire immunitaire entraînée ».

Première exposition



Microscopie électronique en transmission colorisée du coronavirus qui a causé l'épidémie de syndrome respiratoire aigu sévère (SARS) de 2003. Particules virales oranges en bordure d'une cellule infectée verte. (NIAID), CC BY

Nos programmes de recherche couvrent les domaines de la transmission virale, des réponses immunitaires aux virus, des agents pathogènes respiratoires tels que les virus de la grippe et de la conception de vaccins, notamment contre le SARS-CoV-2, qui est responsable de la Covid-19.

Nous aimerions souligner l'importance de l'immunité entraînée en lien avec les vaccins contre la Covid-19, car elle peut avoir des implications sur la capacité de notre système immunitaire à réagir de manière appropriée aux coronavirus hautement pathogènes futurs.

Microscopie électronique à transmission colorisée montrant le coronavirus du syndrome respiratoire du Moyen-Orient (SRMO) qui est apparu en 2012. NIAID, CC BY

Au cours des 17 dernières années, on a vu éclore trois grandes épidémies de coronavirus hautement pathogènes : d'abord le SARS-CoV en 2003, ensuite, le coronavirus du syndrome respiratoire du Moyen-Orient en 2012 et maintenant, le SARS-CoV-2. Si on se base sur le fait qu'un nouveau coronavirus hautement pathogène survient environ tous les dix ans, nous devrions nous attendre à voir apparaître d'autres virus de ce type à l'avenir. Cela signifie que la campagne actuelle de développement de vaccins contre la Covid-19 devrait tenir compte de futures épidémies.

La façon dont nous montrons aujourd'hui à notre système immunitaire à réagir au SARS-CoV-2 pourrait influencer la réponse de notre corps à de futurs coronavirus. Les vaccins, s'ils sont bien conçus, offrent la possibilité d'induire un type d'immunité entraînée optimale pour déclencher des réponses immunitaires protectrices, non seulement contre le SARS-CoV-2, mais aussi contre de futures infections par des coronavirus.

Protection contre la tuberculose

Certains scientifiques ont proposé d'exploiter le concept d'immunité entraînée dans un contexte similaire. Plus précisément, des éléments indiquent que les personnes ayant reçu un vaccin contre la tuberculose pourraient être partiellement protégées contre le SARS-CoV-2.

Microscopie électronique à balayage de la bactérie Mycobacterium tuberculosis. NIAID, CC BY

La tuberculose est une maladie respiratoire causée par une bactérie. Contrairement à de nombreuses bactéries, celle-ci vit à l'intérieur des cellules tout comme les virus. La formule du vaccin utilise une bactérie vivante, mais atténuée (affaiblie), et très semblable à celle qui provoque la maladie. Comme il s'agit d'une bactérie vivante, elle peut infecter les cellules de la même manière que la bactérie de la tuberculose.

Il en résulte une réponse immunitaire appropriée, du même type que celle qui est optimale contre les virus. Les scientifiques en ont conclu que le vaccin contre la tuberculose pourrait entraîner le système immunitaire de manière à ce qu'il puisse réagir de façon idéale à d'autres agents pathogènes qui vivent à l'intérieur des cellules, comme le SARS-CoV-2.

Évaluation des réponses

Microscopie électronique à transmission colorisée du SARS-CoV-2, le virus qui cause la Covid-19.. NIAID, CC BY

Les chercheurs mettent l'accent sur les aspects quantitatifs des vaccins candidats contre la Covid-19, notamment en calculant le nombre d'anticorps générés. Un peu partout, des organismes de réglementation en santé s'apprêtent à approuver des vaccins contre la Covid-19 qui réduisent la charge de morbidité, mais n'engendrent pas une immunité qui préviendrait complètement l'infection et la transmission. Mais ils doivent être prudents et veiller à ce que ces vaccins n'entraînent pas notre système immunitaire à avoir une réaction non optimale.

En évaluant de manière approfondie la nature et la durée de la réponse immunitaire induite par un futur vaccin contre la Covid-19, nous pouvons obtenir des réponses ciblées, efficaces et durables. Concrètement, les développeurs de vaccins devraient tenir compte de ces questions :

1. Le vaccin a-t-il induit une réponse immunitaire optimale contre les virus ? Une réponse antivirale équilibrée devrait comprendre des anticorps pour empêcher le virus d'infecter les cellules hôtes et de se répliquer à l'intérieur de celles-ci ainsi que des lymphocytes T pour tuer les virus qui passent la barrière des anticorps. Il est important que les anticorps soient du type antiviral.

2. Y a-t-il eu des réponses d'anticorps dans les voies respiratoires, et ces anticorps neutralisent-ils efficacement le virus ? On s'attache beaucoup à mesurer les anticorps dans le sang, mais le SARS-CoV-2 infecte la surface des muqueuses, dont celle des voies respiratoires, et il est essentiel de s'assurer que le vaccin induit des anticorps à ces endroits précis. De plus, il faut noter que les réponses des anticorps appropriées contre les virus sont généralement d'une ampleur bien moindre que celles dirigées contre les bactéries extracellulaires. Une grande quantité d'anticorps peut sembler un résultat prometteur, mais c'est loin d'être aussi important que le type et l'emplacement de ceux-ci.

Le message à retenir est que nous devrions insister sur le maintien d'exigences très élevées pour un vaccin contre la Covid-19 — il devra induire une réponse immunitaire appropriée sur le plan qualitatif et qui nous protégera contre l'infection par le SARS-CoV-2.

Comme un athlète, nous devons éviter de former notre système immunitaire d'une manière qui va à l'encontre de l'objectif final. Pour une vision à long terme de notre santé, il faut que notre système immunitaire soit entraîné de manière à déclencher une réponse des plus efficaces possible contre de futurs coronavirus hautement pathogènes, dont certains pourraient s'avérer plus dangereux que le virus actuel.

This article was originally published in English

THE CONVERSATION

Academic rigour, journalistic flair

A worker inspects vials of a SARS CoV-2 vaccine for COVID-19 produced by SinoVac at its factory in Beijing on Sept. 24, 2020. (AP Photo/Ng Han Guan)

Training our immune systems: Why we should insist on a high-quality COVID-19 vaccine

Published: October 7, 2020 4.11pm EDT

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Languages

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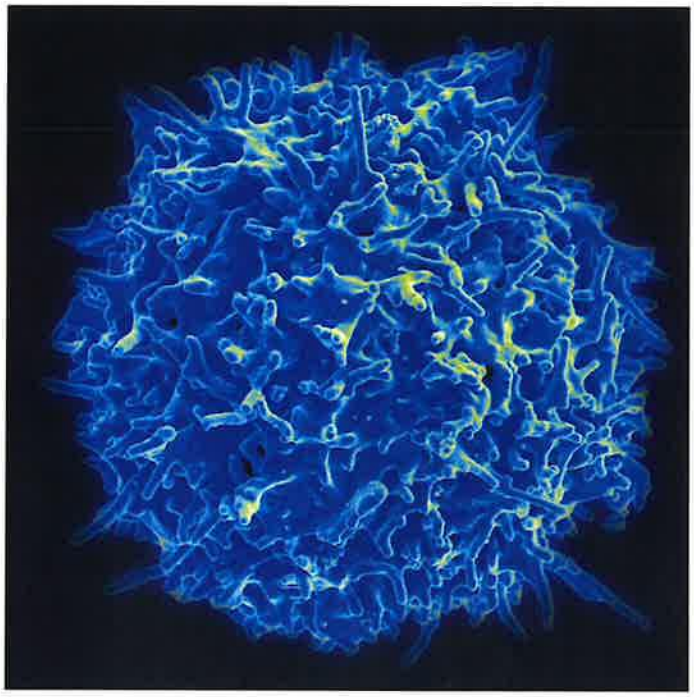
Athletes understand that there are two very different approaches that can be taken when training their bodies. For example, lifting heavy weights is a great way to achieve maximum strength. In contrast, low-load high-repetition training is ideal for developing the stamina required for endurance sports.



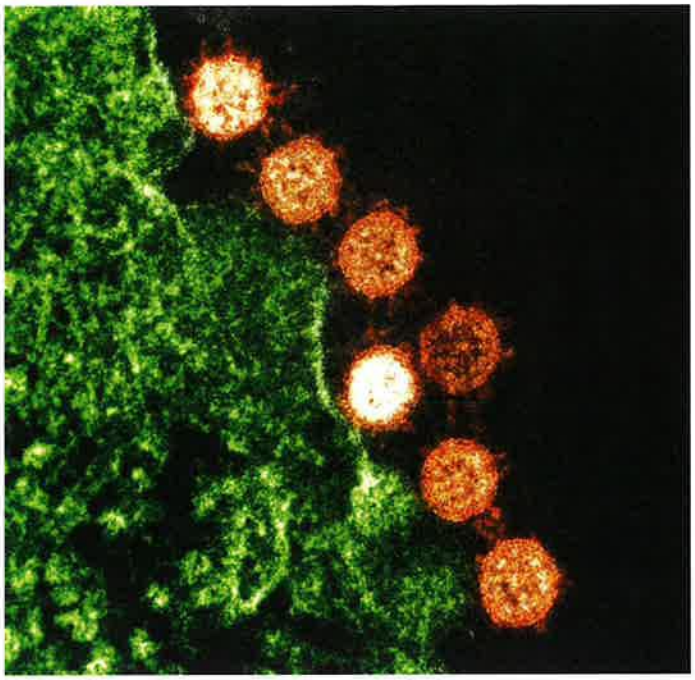
Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. (NIAID), CC BY

Remarkably, our immune system can be trained in a somewhat similar fashion. It must choose between two different responses to dangerous pathogens, both of which lead to white blood cells called T cells and antibodies targeting the infecting microbe. However, the types of these T cells and antibodies is different depending on whether the pathogen lives outside of our cells, as many bacteria do, or inside our cells, as viruses do.

Mounting an anti-bacterial response against a virus may not be an ideal way to clear a viral infection. In fact, the wrong kind of immune response can actually exacerbate disease, as was observed in vaccinated mice challenged with the severe acute respiratory syndrome coronavirus (SARS-CoV) identified in 2003.

Importantly, our first exposure to a pathogen, either naturally or via vaccination, can train our immune system to adopt one of these two biases when we respond in the future to the same or a similar pathogen for the rest of our lives. Immunologists call this "trained immunity."

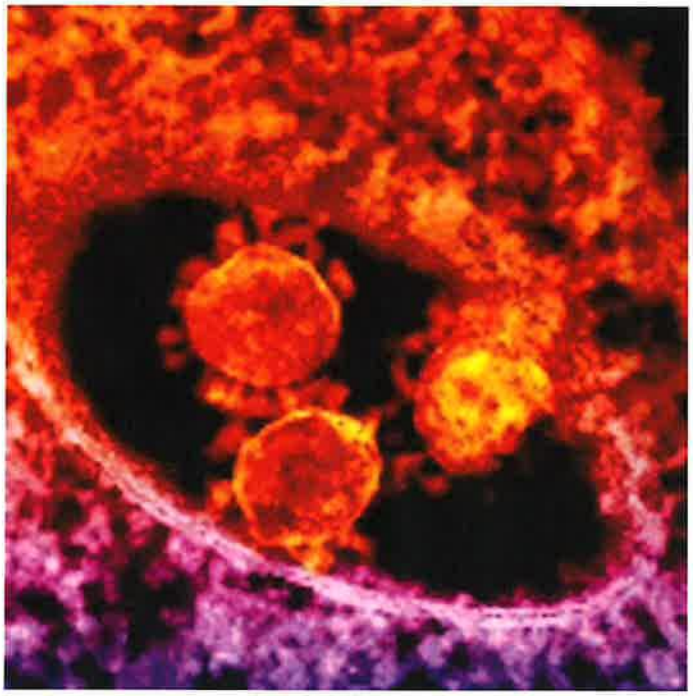
First exposure



Colourized transmission electron micrograph of the coronavirus that caused the 2003 severe acute respiratory syndrome (SARS) outbreak. Orange virus particles at the edge of a green infected cell. (NIAID), CC BY

Our research programs span the fields of viral transmission, immune responses to viruses, respiratory pathogens such as influenza viruses and vaccine development, including vaccines against SARS-CoV-2, which is the causative agent of the coronavirus disease that emerged in 2019, COVID-19.

We would like to convey the importance of trained immunity in the context of COVID-19 vaccines since this can have implications for the ability of our immune systems to respond appropriately to highly pathogenic coronaviruses in the future.



Colourized transmission electron micrograph showing Middle East respiratory syndrome (MERS) coronavirus that emerged in 2012. (NIAID), CC BY

Over the past 17 years, there have been three major outbreaks of highly pathogenic coronaviruses: the original SARS-CoV in 2003, Middle East Respiratory Syndrome coronavirus in 2012 and now SARS-CoV-2. Based on this history of having a new highly pathogenic coronavirus emerge approximately every decade, we should expect to have to deal with more of these viruses in the future. That means that the current drive to develop vaccines for COVID-19 should consider future coronavirus outbreaks.

The way we train our immune systems now to respond to SARS-CoV-2 could impact how well our bodies can respond to future coronaviruses. Vaccines, if developed properly, provide an opportunity to induce the type of trained immunity that is optimal for mounting protective immune responses, not only against SARS-CoV-2, but also against future infections with coronaviruses and/or their associated vaccines.

Tuberculosis response

Interestingly, some scientists have proposed to harness the concept of trained immunity in a related context. Specifically, there is evidence to suggest that individuals who received a vaccine against tuberculosis may be partially protected against SARS-CoV-2.

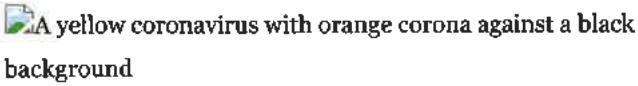
A cluster of pink rod-shaped bacteria on a black background

Scanning electron micrograph of Mycobacterium tuberculosis bacteria. (NIAID), CC BY

Tuberculosis is a respiratory disease caused by a bacterium. In contrast to many bacteria, this one, like viruses, lives inside cells. The vaccine formulation uses a live, but attenuated (modified or weakened) bacterium that is very similar to the one that causes the disease. Since it is a live bacterium, it can infect cells in the same way that the disease-causing bacteria do.

The result is an appropriate immune response that happens to be of the same type that is optimal against viruses. Scientists have concluded, therefore, that the tuberculosis vaccine might be training the immune system in such a way that it can respond ideally to other pathogens that live inside cells, including viruses like SARS-CoV-2.

Evaluating responses


A yellow coronavirus with orange corona against a black background

Colourized transmission electron micrograph of SARS-CoV-2, the virus that causes COVID-19. (NIAID), CC BY

A heavy emphasis is being placed on quantitative aspects of candidate COVID-19 vaccines, such as whether they generate high levels of antibodies. Many health regulatory agencies are poised to approve COVID-19 vaccines that reduce the burden of disease but do not induce immunity to completely prevent infection and transmission. But they should be cautious and ensure that these vaccines do not train our immune system for a response that is not optimal.

By thoroughly evaluating the nature and duration of the immune response induced by a prospective COVID-19 vaccine, we can ensure specific, effective and sustained responses against SARS-CoV-2. Specifically, vaccine developers should be able to answer these questions:

1. Did the vaccine induce an immune response that is optimal against viruses? A balanced antiviral response should include antibodies to prevent the virus from infecting host cells and replicating inside them, and T cells to kill viruses that get past the antibody barrier. Importantly, the antibodies should be of antiviral types.

2. Were there antibody responses in the respiratory tract, and do these antibodies efficiently neutralize the virus? There is significant focus placed on measuring antibody responses in the blood, but SARS-CoV-2 infects mucosal surfaces including the respiratory tract, and it is important to ensure that the vaccine induces antibodies at these relevant locations. Also, it must be noted that appropriate antibody responses against viruses are usually of much lower magnitude than those directed against extracellular bacteria. A large quantity of antibodies may seem promising, but the amount is not nearly as important as the types and locations of these antibodies.

The take-home message is that we should insist on maintaining a very high standard for a COVID-19 vaccine; one that will induce a qualitatively appropriate immune response that will protect us from infection with SARS-CoV-2.

Like an athlete, we need to avoid training our immune system in a way that contradicts the end goal. For long-term health, we must ensure that our immune systems are trained in a way that will allow us to respond most effectively against future highly pathogenic coronaviruses, some of which may prove to be more dangerous than the current one.

THE CONVERSATION

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Mink can be readily infected with SARS-CoV-2 and then pass the virus to humans. (Shutterstock)

The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness

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The importance of commercially raised animals in the COVID-19 pandemic has received much attention in the past few weeks, when a new variant of SARS-CoV-2 was detected in farmed mink. Unfortunately, mink tend to be relatively susceptible to respiratory infections, and these can readily spread through mink farms due to high-density housing.

Data from the Netherlands earlier in the pandemic have revealed that mink can be readily infected with SARS-CoV-2 and then pass the virus to humans. In Denmark, 214 people people have been infected by a variant of SARS-CoV-2 that is presumed to have mutated in Danish mink. Over 200 mink farms had tested positive for SARS-CoV-2, and at least five different mink variants of the virus have been detected so far.

These events initiated a mass culling of farmed mink in that country (although this was limited due to legal issues), and cast a spotlight on the disturbing scenario of human-to-mink-to-human transmission of SARS-CoV-2, with potential for the virus to change in mink prior to re-infecting people.

Mink are semi-aquatic mammals that are relatively susceptible to respiratory infections, which can spread through mink farms, like this one in Belarus, due to high-density housing. (AP Photo/Sergei Grits, File)

Specifically, this latest occurrence unveils the possibility that mink can serve as an alternate host to promote mutations of SARS-CoV-2, which can be passed back to humans and other animals, both domestic and wild and potentially placing the wild mustelid (minks, ferrets and related species) population at risk.

Bridging human and animal health

We are researchers in the fields of virology, immunology and pathology. Our research programs bridge human and animal health and study the transmission of viruses, immune responses to viruses, how viruses cause diseases, and developing strategies such as vaccines to prevent infectious diseases. The recent news linking mink to the current pandemic highlights the importance of research at the interface of animal and human health.

Since the start of the COVID-19 pandemic, the world has learned much about virology, as well as the concept of One Health. At the core of One Health is the idea that human and animal health are intertwined in a shared environment, and that we need to broaden our perspectives beyond human health alone.

Indeed, animals have been at the centre of this pandemic from the beginning. Overwhelming evidence suggests that this coronavirus (SARS-CoV-2), which causes COVID-19, originated from bats. There is debate about whether an intermediate animal host might have harboured additional changes to SARS-CoV-2 to produce the current virus that spreads efficiently person to person. The leading candidate for this is a scaly anteater known as a pangolin.


A pangolin emerging from a grassy area.

The pangolin, a scaly anteater, may have been an intermediate host for the SARS-CoV-2 virus. (AP Photo/Themba Hadebe)

What is known for sure is that changes to coronaviruses can occur over time due to inherent and purposeful errors in these viruses' ability to copy their genetic codes. This allows a virus to make small changes over time and is an efficient way for them to adapt to new environments.

Changes in the spike protein

One of the recently identified Danish mink strains is particularly concerning because changes in the genome occurred in what is called the virus's spike protein, which it uses to enter human cells. These changes have been detected in 12 human cases related to this particular mink variant. Fortunately, this change does not seem to correlate with worse clinical outcomes, based on a small number of cases.

The spike protein is also the primary target of natural and vaccine-induced immune responses to the virus. In theory, if SARS-CoV-2 mutates too much, the immunity derived from the parental virus, acquired either by natural infection or vaccination, could become less effective against the new strain.


A model of a spike protein in the foreground with the model of the virus in the background

3D print of a spike protein of SARS-CoV-2, the virus that causes COVID-19, in front of a 3D print of a SARS-CoV-2 virus particle. Spike proteins cover the surface of the virus and enable it to enter and infect human cells. NIH, CC BY

The good news is that, so far, there's no evidence that the mink-derived SARS-CoV-2 mutant can bypass natural or vaccine-induced immunity. Fortunately, our immune systems are designed to generate antibodies against multiple parts of the spike protein. This means that if only a small part of the spike protein is mutated, antibodies against other parts of the protein should still confer at least some protection.

'Plug-and-play' vaccine technology

The fact that SARS-CoV-2 can change highlights the need for vaccines that not only induce protective antibodies but that can also elicit robust T cell responses, which is the other major mechanism by which our immune systems can kill viruses. Like antibodies, T cells will target multiple parts of viral proteins, thereby increasing the chance of maintaining immunity against non-mutated regions of the proteins.

It might also be important to consider making vaccines that target more than one of the proteins from SARS-CoV-2. It's very difficult for a virus to make major changes to multiple proteins without compromising its fitness.

Read more: Training our immune systems: Why we should insist on a high-quality COVID-19 vaccine

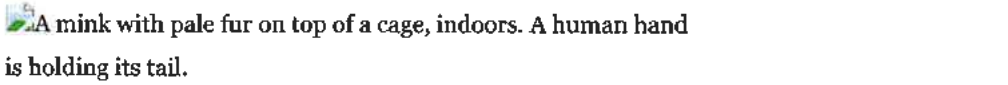
The other issue that the mink SARS-CoV-2 brings to the forefront of the vaccine development effort is the need for vaccines that are "plug-and-play." These are vaccine technologies where the viral protein the vaccine is designed to target can be readily swapped with a different version of the viral protein.

Once approved by health regulators as being safe and efficacious against a highly pathogenic coronavirus, such technologies could, in theory, be rapidly modified to target emerging mutant viruses; akin to the annual flu vaccine that gets modified every year to target emerging influenza virus variants.

Addressing threats and managing health

With mink being confirmed only recently as a possible reservoir for SARS-CoV-2, more research is urgently needed to inform rationally based decisions to cull millions of these animals. Even if mass cullings continue, it is unlikely that mink farms will be completely phased out at the global level in the near future. So the question becomes how do we manage the potential threat to human health of SARS-CoV-2 in mink over the long term?

First, enhanced biosecurity measures should be implemented on mink farms.


A mink with pale fur on top of a cage, indoors. A human hand is holding its tail.

Farmed mink, like this one from an Ontario fur farm, should be screened for coronaviruses. THE CANADIAN PRESS/ Geoff Robins

Second, screening of farmed mink for coronaviruses should be added to the surveillance programs of animal health regulatory agencies, with this information made available to human health regulators.

Third, consideration could be given to tailoring COVID-19 vaccines for animal reservoirs, which would now include farmed mink. These recommendations would not only reduce the potential spread of coronaviruses from mink to humans, it would simultaneously address SARS-CoV-2-related health issues for mink. Indeed, mink can develop COVID-19 after becoming infected with SARS-CoV-2 and it can sometimes be severe and lethal, with no effective current treatment.

This is Exhibit " C " to the Affidavit of
Dr. Neil Karrow, affirmed before me on
this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

Citations for the six peer-reviewed papers that Dr. Bridle and Dr. Sharif published together:

i. Alqazlan N, Emam M, Nagy É, **Bridle B**, Sargolzaei M, **Sharif S**. Transcriptomics of chicken cecal tonsils and intestine after infection with low pathogenic avian influenza virus H9N2. *Sci Rep*. 2021 Oct 14;11(1):20462. doi: 10.1038/s41598-021-99182-3. PMID: 34650121; PMCID: PMC8517014.

ii. Darzianiazizi M, Allison KE, Kulkarni RR, **Sharif S**, Karimi K, **Bridle BW**. Disruption of type I interferon signaling causes sexually dimorphic dysregulation of anti-viral cytokines. *Cytokine X*. 2021 Jun 6;3(2):100053. doi: 10.1016/j.cytox.2021.100053. PMID: 34189454; PMCID: PMC8215187.

iii. Stegelmeier AA, Darzianiazizi M, Hanada K, **Sharif S**, Wootton SK, **Bridle BW**, Karimi K. Type I Interferon-Mediated Regulation of Antiviral Capabilities of Neutrophils. *Int J Mol Sci*. 2021 Apr 29;22(9):4726. doi: 10.3390/ijms22094726. PMID: 33946935; PMCID: PMC8125486.

iv. Darzianiazizi M, Mehrani Y, Chan L, Mould RC, Kulkarni RR, **Sharif S**, **Bridle BW**, Karimi K. Type I Interferon α/β Receptor-Mediated Signaling Negatively Regulates Antiviral Cytokine Responses in Murine Bone-Marrow-Derived Mast Cells and Protects the Cells from Virus-Induced Cell Death. *Int J Mol Sci*. 2020 Nov 27;21(23):9041. doi: 10.3390/ijms21239041. PMID: 33261178; PMCID: PMC7729593.

v. Alqazlan N, Astill J, Taha-Abdelaziz K, Nagy É, **Bridle B**, **Sharif S**. Probiotic Lactobacilli Enhance Immunogenicity of an Inactivated H9N2 Influenza Virus Vaccine in Chickens. *Viral Immunol*. 2021 Mar;34(2):86-95. doi: 10.1089/vim.2020.0209. Epub 2020 Nov 25. PMID: 33236974.

vi. Alqazlan N, Alizadeh M, Boodhoo N, Taha-Abdelaziz K, Nagy E, **Bridle B**, **Sharif S**. Probiotic Lactobacilli Limit Avian Influenza Virus Subtype H9N2 Replication in Chicken Cecal Tonsil Mononuclear Cells. *Vaccines (Basel)*. 2020 Oct 13;8(4):605. doi: 10.3390/vaccines8040605. PMID: 33066282; PMCID: PMC7712974.

This is Exhibit " D " to the Affidavit of

Dr. Neil Karrow, affirmed before me on

this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

Exhibit D – Publications co-authored with Dr. Bridle on COVID-19

S. Tieu, A. Charchoglyan, L. Paulsen, L.C. Wagter-Lesperance, U.K. Shandilya, B.W. Bridle, B.A. Mallard, N.A. Karrow 2023. N-Acetylcysteine and Its Immunomodulatory Properties in Humans and Domesticated Animals. Antioxidants (Basel) 12(10):1867.

N.A. Karrow, U.K. Shandilya, S. Pelech, L. Wagter-Lesperance, D. McLeod, B. Bridle, B.A. Mallard BA. 2022. Correction: Maternal COVID-19 vaccination and its potential impact on fetal and neonatal development. Vaccines (Basel). 2022 Nov 14;10(11):1925

S. Tieu, A. Charch, L. Wagter-Lesperance, K. Karimi, B. Bridle, N.A. Karrow, B.A. Mallard 2022. Immunoceuticals: Harnessing their Immunomodulatory Potential to Promote Health and Wellness. Nutrients 14(19):4075.

N.A. Karrow, U.K. Shandilya, S. Pelech, L. Wagter-Lesperance, D. McLeod, B. Bridle, B.A. Mallard 2021. Maternal COVID-19 Vaccination and Its Potential Impact on Fetal and Neonatal Development. Vaccines (Basel) 9(11):1351.

This is Exhibit " E " to the Affidavit of
Dr. Neil Karrow, affirmed before me on
this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

Court File No./N° du dossier du greffe : CV-22-00691880-0000

Re: smear campaign

Byram Bridle <bbridle@uoguelph.ca>
Sun 5/30/2021 12:15 PM

To: Glen Pyle <gpyle@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>; Karen Mantel <kmantel@uoguelph.ca>; Jane Dawkins <jdawkins@uoguelph.ca>
Bcc: Bonnie Mallard <bmallard@ovc.uoguelph.ca>; Niel Karrow <nkarrow@uoguelph.ca>

Glen,

I do not use social media. So, yes, it has been happening without my knowledge.If I ever have a problem with someone's science on campus, I take it up with them. This would have been the respectful thing to do. The major problem here was the fact that you did not condemn an egregious act against a colleague when you had the opportunity.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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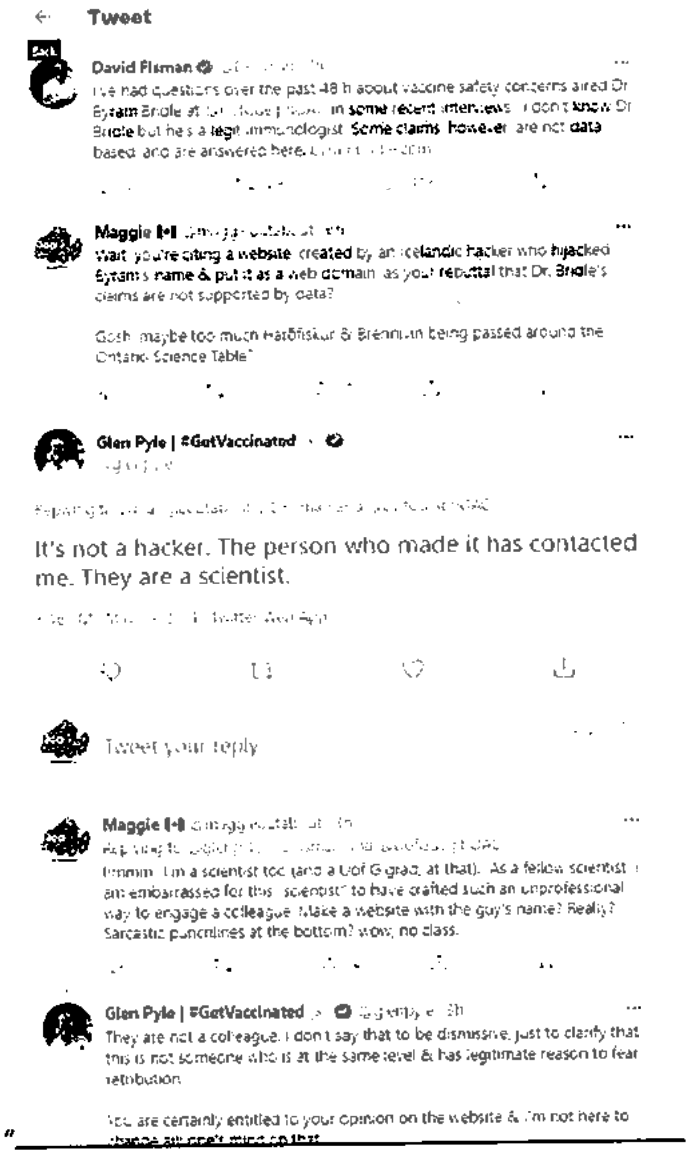
Toronto Superior Court of Justice / Cour supérieure de justice

This is Exhibit " F " to the Affidavit of
Dr. Neil Karrow, affirmed before me on
this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No./N° du dossier du greffe : CV-22-00691880-0000



Tweet

David Fisman
I've had questions over the past 48 h about vaccine safety concerns aired Dr Byram Bridle at [illegible] in some recent interviews. I don't know Dr Bridle but he's a legit immunologist. Some claims, however, are not data based, and are answered here. [illegible]

Maggie
Wait, you're citing a website created by an Icelandic hacker who hijacked Byram's name & put it as a web domain as your rebuttal that Dr. Bridle's claims are not supported by data?

Gosh, maybe too much Hatóflaur & Brennivín being passed around the Ontario Science Table"

Glen Pyle | #GotVaccinated
[illegible]

It's not a hacker. The person who made it has contacted me. They are a scientist.

[illegible]

Tweet your reply

Maggie
[illegible]
Hmmm. I'm a scientist too (and a U of G grad, at that). As a fellow scientist I am embarrassed for this "scientist" to have crafted such an unprofessional way to engage a colleague. Make a website with the guy's name? Really? Sarcastic punchlines at the bottom? Wow, no class.

Glen Pyle | #GotVaccinated
[illegible]
They are not a colleague. I don't say that to be dismissive. Just to clarify that this is not someone who is at the same level & has legitimate reason to fear retribution.

You are certainly entitled to your opinion on the website & I'm not here to change all one's mind on that.

"

From: Liam McKinnon <liam@pureart.ca>
Sent: May 30, 2021 12:29 AM
To: Jennifer Hibberd <jenniferhibberd@rogers.com>
Cc: Bonnie Mallard <bmallard@ovc.uoguelph.ca>; Byram Bridle <bbridle@uoguelph.ca>; Rocco Galati <rocco@idirect.com>; David Ross <davidarossfca@gmail.com>; Ira Bernstein <irabernstein@bell.net>; Steven Pelech <spelech@shaw.ca>; Karen Levins <Klevins@rogers.com>; nakatsuk@queensu.ca; Niel Karrow <nkarrow@uoguelph.ca>; Sonya Anderson <sonya@sizzleandsim.com>; Ashley Allen <ashleykatherineallen@gmail.com>; Steve Kirsch <stk@m10.io>; Susan Natsheh <knittingnatcho@yahoo.com>; Julie E. Ponesse

This is Exhibit " G " to the Affidavit of
Dr. Neil Karrow, affirmed before me on
this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

Court File No./N° du dossier du greffe : CV-22-00691880-0000

Re: misinformation

Byram Bridle <bbridle@uoguelph.ca>

Mon 5/31/2021 6:05 AM

To: J. Scott Weese <jsweese@uoguelph.ca>
Cc: Shayan Sharif <shayan@uoguelph.ca>; Jeffrey Wichtel <jwichtel@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>
Bcc: Bonnie Mallard <bmallard@ovc.uoguelph.ca>; Niel Karrow <nkarrow@uoguelph.ca>

Scott,

This was just sent to me...

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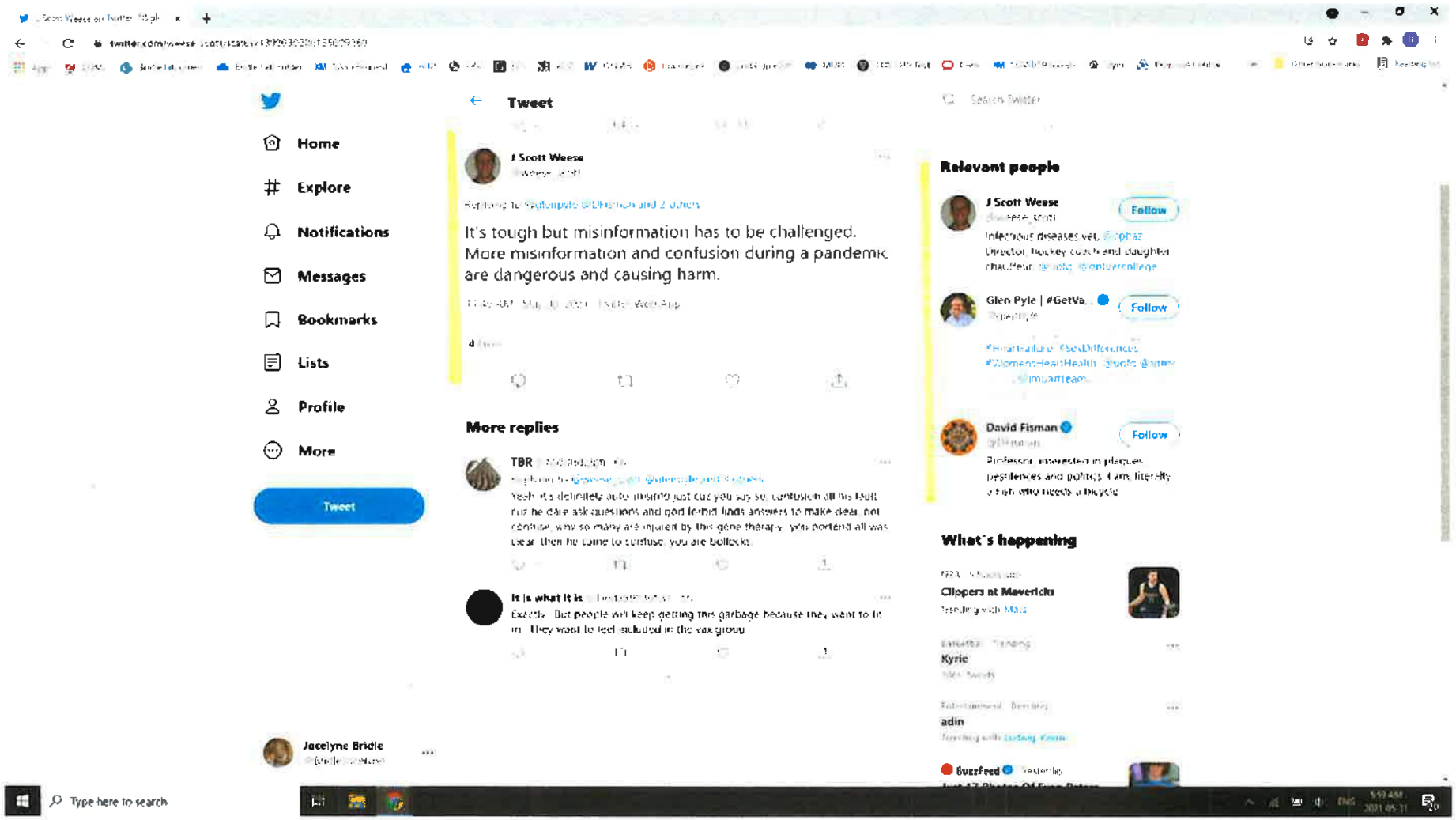

I'm glad to see that others thought it equally silly for you to discredit someone with zero evidence to back it up! Come on, you are not 10 years old anymore. Please act your age. Like it or not, I'm not going to conform to your way of thinking about the pandemic and I have scientifically valid reasons for it. I am allowed to be an independent critical thinker.

Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology

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Toronto Superior Court of Justice / Cour supérieure de justice

https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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From: Byram Bridle
Sent: Monday, May 31, 2021 5:51 AM
To: J. Scott Weese <jsweese@uoguelph.ca>
Cc: Shayan Sharif <shayan@uoguelph.ca>; Jeffrey Wichtel <jwichtel@uoguelph.ca>; Brandon Lillie <blillie@uoguelph.ca>
Subject: misinformation

Scott,

I see you have entered the foray...

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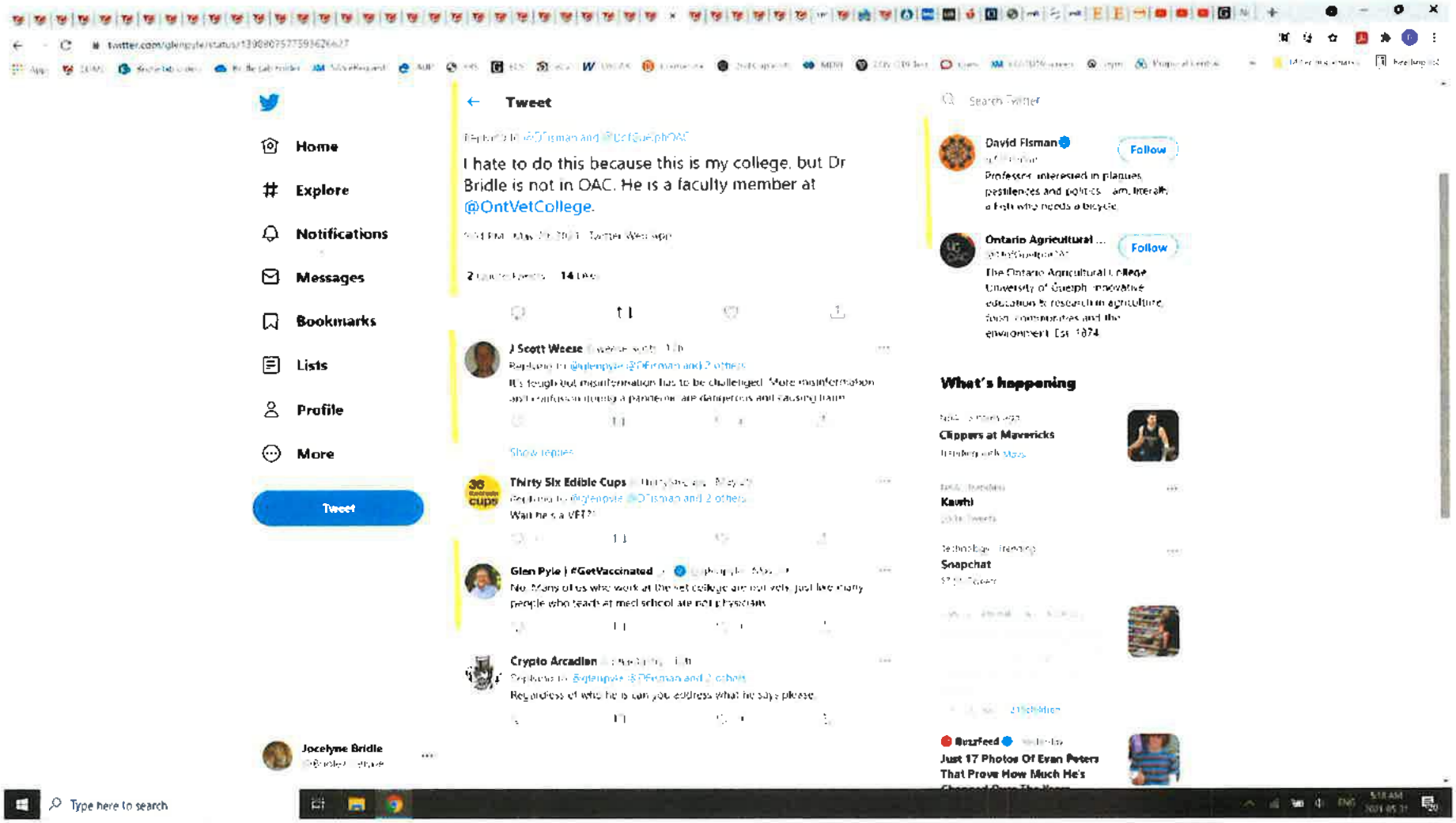

...what information are you referring to Scott? And what misinformation did I give? Interestingly, since your communication was in text, you had ample opportunity to describe: (a) what exactly you were rebutting in terms of the science I was interviewed about; and (b) citations to back-up your claim of misinformation. This is akin to saying "my colleague is giving misinformation and I can prove it with my lack of information to back up my claim". I gave a five-minute interview over the radio. You do realize that I can't show papers via the air waves, right? So what information are you criticizing? Did you have any idea what papers I was referring to? FYI, I have attached a brief report to back-up my very legitimate concerns for the health and safety of all Canadian children. I would be happy to debate with you anytime about COVID-19 vaccines if you like to do so. In the report that I have attached, please go to the link to Pfizer's own biodistribution data showing that their vaccine platform travels far and wide throughout the body and accumulates in many tissues. Also, see their report to the European Medicines Agency in which they admit that they have no pharmacokinetic/biodistribution data with the actual vaccine that is going into our children. These are basic studies that should always be done prior to any vaccine being used. Using this vaccine in children without proper biodistribution and additional

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safety data that looks at the effect of depositing the vaccine into a plethora of tissues is scientific blasphemy. Do you really think, on this basis, that there are no legitimate safety issues that should be addressed? ...because I can tell you from years of experience that is not how one goes about developing a novel treatment with integrity.

Next time, before you go ahead and fuel a fire that is roasting a colleague, please consider talking to me to determine what my rationale is. What you did here was immature and disrespectful. Do you realize the harm this smear campaign is doing to me?

I must say, it's great to have colleagues like you and Glen around. It is creating a great collegial work environment.

Jeff and Shayan: is this behaviour from Glen and Scott going to be condoned? Jeff, you will recall that Scott already implied that I didn't have the right to hold an opposing view in a recent department meeting. In the current situation, it is ridiculous that I have to present a report to show my colleagues that I actually know what I'm talking about just so I can get them to leave me alone in the world of social media. I think that this harassment in the workplace needs to stop.

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph, Ontario, Canada
N1G 2W1
Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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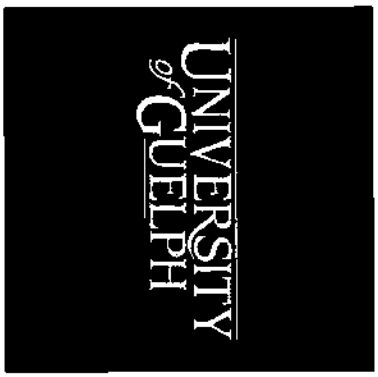
Toronto Superior Court of Justice / Cour supérieure de justice


UNIVERSITY of GUELPH

This is Exhibit " H " to the Affidavit of

Dr. Neil Karrow, affirmed before me on

this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

N0B 1B0

bmallard@uoguelph.ca

From: Niel <nkarrow2@gmail.com>
Sent: 06 July 2021 14:26
To: Paul Sibley <psibley@uoguelph.ca>; Andrew Peregrine <aperegri@uoguelph.ca>; Cathy Bauman <cbauman@uoguelph.ca>; Bonnie Mallard <bmallard@ovc.uoguelph.ca>; Lucy M Mutharia <lmuthari@uoguelph.ca>; David Kelton <dkelton@ovc.uoguelph.ca>
Subject: letter with your name on it

CAUTION: This email originated from outside of the University of Guelph. Do not click links or open attachments unless you recognize the sender and know the content is safe. If in doubt, forward suspicious emails to IThelp@uoguelph.ca

Hi Paul, Andrew, Cathy, Lucy and David, I hope you are keeping well this summer and enjoying the outdoors. I received this letter against Dr Bridle regarding his views about vaccine safety today, and I was surprised to see your names on the list of faculty in support. I have great respect for you all and thought you would advocate open discussion about such an important generational issue.

Byram is an expert in his field, and I share many of his concerns regarding vaccinating children, and also pregnant women.

The spike protein, regardless of whether or not it is from SARS-CoV2 or a vaccine, is bioactive. The mRNA vaccines use lipid nanoparticles that accumulate in numerous tissues throughout the body, which means spike protein can potentially be synthesized throughout the body. In mice, the S1 protein has also been shown to cross the BBB. As you well know, the spike protein can bind to ACE2 receptors; however, it also appears to bind to endothelial cell integrins, alpha7 nicotinic acetylcholine receptors, and Toll-like receptor 4 that results in activation of nuclear factor- kappa B leading to inflammation. There is also evidence that the spike protein can act as a superantigen eliciting polyclonal T cell activation. Also, the spike protein shares similarities to numerous host proteins setting the stage for a potential autoimmune response in at-risk people.

As this pandemic has unfolded, we have come to see that AVRs do occur as a result of COVID19 vaccination, which now include anaphylaxis, blood clots, myo and pericarditis, Guillian Barre-like Syndrome and other neurological outcomes. We were told, "the vaccines are safe and that the best vaccine is the first vaccine offered to you"; you must agree by now that this statement is not true.

It is surprising to me that someone like Byram, who is expressing concerns about vaccine safety, is shut down after providing evidence of their potential risk, when it is supposed to be the vaccine makers who should be providing the evidence of their safety!

The Canadian government is clearly making up its own vaccine plan by mixing vaccines, extending their shelf-life, wanting to vaccinate people who have already had COVID19, and vaccinating children 12+ years of age. They are also looking at vaccinating children 6-12 years of age with the same concentration of vaccine!

I, for one, advocate that everyone who wishes to receive a vaccine, be antibody tested before they get poked. There is no scientific evidence or immunological rationale for vaccinating people who have already had COVID. These vaccines could be better used on "naive" people, and this would potentially alleviate risk to people with previous immunity, which appears to be long-lasting. The safety of these vaccines has not been thoroughly tested in pregnant women and no one is talking about risk of exposure in utero, especially in the 3rd trimester when miscarriages are less likely to occur. As for children, they should also be antibody tested. I am willing to bet that many of them already have protective natural or cross-reactive immunity. For those that do not, then vaccination could be considered, but not with this generation of vaccines unless their safety is confirmed.

By the way, I have had my serum antibody assessed, and I exhibit a profile of someone who has already had COVID19! I don't recall feeling sick this past year. Perhaps, I was inoculated while volunteering on campus for the rapid antigen test. Perhaps, the face masks don't work to stop an airborne virus!

I am not writing to influence your view, I am only asking that you let others advocate for those who can not speak. This is our academic responsibility! I suspect that public confidence in vaccines will be greatly affected by all the government blunders that have occurred during the past 15 months; which is a shame because We all know how important vaccines are for preventing endemic and emerging diseases.

Best regards, N

Dr. Niel Karrow (凯尼大)
Professor of Immunology,
Department of Animal Biosciences,
University of Guelph
Guelph, Ont. Canada N1G 2W1
Tel. (519) 824-4120 ext. 53646
http://www.aps.uoguelph.ca/users/nkarrow

This is Exhibit " T " to the Affidavit of

Dr. Neil Karrow, affirmed before me on

this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

March 3, 2021

Dear Professor Charlotte Yates, President and Vice-Chancellor, and **Professor Gwen Chapman**, Interim Provost and Vice-President (Academic):

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought (*i.e.* acquisition of immunity). In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have been commissioned by the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area. Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses. Among the many reasons for this is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to allow SARS-CoV-2 to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada. It has become clear that we can't continue to rely on continual lockdowns. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. **It is from this perspective that we would like to recommend the following core strategies to support re-opening the University of Guelph campus to in-person learning in the Fall 2021 semester:**

1. **Offer comprehensive and sensitive testing for evidence of seroconversion (antibodies) against SARS-CoV-2.** Ever-accumulating data demonstrate that both naturally acquired, and vaccine-induced immunity can provide at least some level of protection from reinfection from the parental and current variant forms of SARS-CoV-2. Evidence of protective immunity either prior to and/or after vaccination would provide valuable information to guide decisions. This testing should be offered to members of the university that are both on- and off-campus. Several options for antibody testing are currently available in Canada. For example, LifeLabs currently has a test available. Even better, we have a colleague at the University of British Columbia who has developed the most comprehensive and sensitive test for seroconversion that we are currently aware of. Through collaboration with this colleague, we would be happy to assist with getting a local lab (possibly our own Animal Health Laboratory, which has an excellent quality control program and experience getting novel tests up and running) set-up to run this cutting-edge test.
2. **Offer strategically prioritized vaccinations.** Vaccination against SARS-CoV-2 should be offered to individuals wanting to return to campus. Prioritization should be based on risk of an infection progressing to disease (*i.e.* COVID-19). If doses are limited, vaccines would best be used in individuals with no evidence of immunity (based on testing in highlighted in point #1). Importantly,

vaccines should be administered precisely according the protocol that was used to have them approved for emergency use until further data is available on alternative protocols. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented evidence of it being relatively ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf). Vaccinations should be offered to university community members that are both on- and off-campus.

3. **Offer rapid antigen screening tests to detect the presence of SARS-CoV-2.** This is currently being tested on campus, and if successful, it would be logical to implement this approach more widely. It is very convenient for the workplace and should be offered to university community members that are both on- and off-campus.
4. **Offer off-campus learning/working accommodations for high-risk individuals.**
5. **Consider implementing supplemental testing.** Additional tests could help manage COVID-19 on-campus. For example, testing wastewater from buildings on campus, with an emphasis on residences could help identify 'hot spots'.
6. **Consider incorporating comprehensive data collection in consultation with our Research Ethics Board.** A lack of concerted efforts to collect comprehensive data sets has slowed the progress of research in many jurisdictions in Canada. The University of Guelph could provide a detailed analysis to support a return to campus at other institutions. Our Department of Population Medicine would be well-equipped to oversee this type of data collection. However, the rollout of vaccines and tests should not be delayed for establishing such a data collection infrastructure; rather, the infrastructure for research-quality data collection could interface with the rollout when it is ready.

Note: Implementation of suggestions 1-5 could have an impact on public health directives. Specifically, it would facilitate discussions around reduced physical distancing. Reducing physical distancing from two meters to one meter in classrooms could have a major positive impact on returning to in-person learning.

We would be happy to offer advice as our campus community moves forward. Specifically, Dr. Bridle is willing to serve on any relevant advisory committees and/or he can be a point of contact for our group, with whom he consults regularly. We also have many colleagues in the fields of virology, immunology, and public health at a variety of institutions that we consult with. We look forward to hearing your thoughts about the University of Guelph showing leadership among the academic community in getting students back to in-class learning.

Sincerely,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

March 5, 2021

Dear Dr. Nicola Mercer, Medical Officer of Health and CEO of Wellington-Dufferin-Guelph Public Health:

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought (*i.e.* acquisition of immunity). In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have been commissioned by the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive and in-depth expertise in this area. Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses. Among the many reasons for this is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to allow SARS-CoV-2 to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada. It has become clear that we can't continue to rely on continual lockdowns. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. **It is from this perspective that we would like to recommend the following core strategies to support re-opening the City of Guelph and the surrounding regions by this Fall:**

1. **Offer comprehensive and sensitive testing for evidence of seroconversion (antibodies) against SARS-CoV-2.** Ever-accumulating data demonstrate that both naturally acquired, and vaccine-induced immunity can provide at least some level of protection from reinfection from the parental and current variant forms of SARS-CoV-2. Evidence of protective immunity either prior to and/or after vaccination would provide valuable information to guide decisions. Several options for antibody testing are currently available in Canada. For example, LifeLabs currently has a test available. Even better, we have a colleague at the University of British Columbia who has developed the most comprehensive and sensitive test for seroconversion that we are currently aware of. Through collaboration with this colleague, we would be happy to assist with getting a local lab (possibly our own Animal Health Laboratory, which has an excellent quality control program and experience getting novel tests up and running) set-up to run this cutting-edge test.
2. **Offer strategically prioritized vaccinations.** Prioritization should be based on risk of an infection progressing to disease (*i.e.* COVID-19). If doses are limited, vaccines would best be used in individuals with no evidence of immunity (based on testing highlighted in point #1). Importantly, vaccines should be administered precisely according to the protocol that was used to have them approved for emergency use until further data is available on alternative protocols. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented

evidence of it being relatively ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf).

3. **Offer rapid antigen screening tests to detect the presence of SARS-CoV-2.** This is currently being tested on the University of Guelph campus, and if successful, it would be logical to implement this approach more widely. It is very convenient for the workplace.
4. **Offer accommodations for remote working/learning for high-risk individuals.**
5. **Consider implementing supplemental testing.** Additional tests could help manage COVID-19. For example, testing wastewater from buildings, with an emphasis on high-density housing and workplaces could help identify 'hot spots'.
6. **Consider incorporating comprehensive data collection in consultation.** A lack of concerted efforts to collect comprehensive data sets has slowed the progress of research in many jurisdictions in Canada. The Wellington-Dufferin-Guelph Public Health in conjunction with the University of Guelph could provide a detailed analysis to support return-to-work and return-to-school policies at other institutions. Our Department of Population Medicine would be well-equipped to oversee this type of data collection. However, the rollout of vaccines and tests should not be delayed for establishing such a data collection infrastructure; rather, the infrastructure for research-quality data collection could interface with the rollout when it is ready.

Note: Implementation of suggestions 1-5 could have an impact on public health directives. Specifically, it would facilitate discussions around reduced physical distancing. Reducing physical distancing from two meters to one meter in workplaces and classrooms could have a major positive impact on returning to in-person work and learning.

We would be happy to offer advice as our regional community moves forward. Specifically, Dr. Bridle is willing to serve on any relevant advisory committees and/or he can be a point of contact for our group, with whom he consults regularly. We also have many colleagues in the fields of virology, immunology, and public health at a variety of institutions that we consult with. We look forward to hearing your thoughts about the Wellington-Dufferin-Guelph Public Health Unite showing leadership within Canada in getting local citizens back to in-person work and in-class learning.

Sincerely,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

Dear Fellow Canadians:

We are four faculty members at the University of Guelph. Dr. Byram Bridle is a viral immunologist, Dr. Sarah Wootton is a virologist, and Drs. Mallard and Karrow are immunologists. Generally, policies for COVID-19 have been generated after consultations focusing mainly on the opinions of physicians, epidemiologists, and other public health experts. However, at its core, COVID-19 is a problem at the interface of immunology and virology, both in terms of its pathogenesis and the primary solution being sought, which is acquisition of immunity against the virus SARS-CoV-2. In addition to our group having in-depth knowledge of these fields, Drs. Bridle and Wootton have received funding from the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area.

Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks; this was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed. Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses.

Among the many reasons for this virus becoming endemic is the propensity of SARS-CoV-2 to mutate over time, which will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly-focused immunity that targets a single protein known as the spike. These two major issues will combine to potentiate SARS-CoV-2 being able to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada.

It has become clear that we can't continue to rely on continual lockdowns due to the impact on mental health, delays to other medical treatments, a sinking economy, and so on. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities. It is also important to remember that the majority of cases of COVID-19 in Canada are mild-to-moderate, and the death rate has been quite low (22,514 deaths out of 914,697 cases or 592/million as of March 16 2021 - Coronavirus Dashboard [ncov2019.live]). Sadly, at least 70% of those deaths have been in people over 80 years of age, in long-term care (Dr. R. Bibby, Sociologist, University of Lethbridge; http://www.reginaldbibby.com/specialcovid19analyses.html). On the upside, there is now also good evidence that the majority of those recovered from COVID-19 have protective immunity (reviewed by Sette and Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell (2021), DOI: https://doi.org/10.1016/j.cell.2021.01.007).

It is from this perspective that we have been advocating for several core strategies to support re-opening our country to in-person work and learning. An important aspect of this is offering strategically prioritized vaccinations. Specifically, we have been advocating for the **administration of safe and effective COVID-19 vaccines according the protocol that was used to have them approved** for emergency use, until further data is available and reviewed and approved by Health Canada to support alternative protocols. In support of this goal, we have two recommendations:

1. Consideration should be given to avoiding the use of the AstraZeneca vaccine, for which there is documented evidence of it being ineffective against the South African variant of SARS-CoV-2, which we reiterate is now in Canada. Specifically, it was shown to be only 10% effective against the South African variant, with the cut-off for approval being 50%. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf). Additionally, its use has been suspended in at least ten European countries until undesirable potential side-effects can be further investigated. For Ontarians, the Chief Medical Officer definitively stated in a letter to pubic health units in the province that individuals may opt out of receiving the AstraZeneca vaccine on the basis that it is admittedly of lower efficacy than the others (see the highlighted text on page 2 of the attached letter).

2. The intervals for the two-dose COVID-19 vaccines should adhere to what was officially approved by Health Canada and the manufacturers, which is 21- and 28-days for the Pfizer and Moderna vaccines, respectively. The rationale for this is presented below...

The history of Canada's move to extend COVID-19 intervals to an unprecedented four months.

Last week, the CBC launched a story to highlight the path that has led many jurisdictions in Canada to begin implementing an interval of up to four months for both the Pfizer and Moderna COVID-19 vaccines (https://www.cbc.ca/news/health/canada-covid-19-vaccine-delay-risk-1.5939134). It apparently began with a letter from an epidemiologist at the British Columbian Centre for Disease Control to the editor of *The New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMc2036242). In this letter it was claimed that Pfizer failed to realize the efficacy of its own vaccine and that its effectiveness as a single-dose regimen is actually a remarkable 92%. It is important to note that this is based on an extrapolation of a statistically underpowered, biased, limited data set from a trial that was never designed to test single-dose efficacy. Further, the extrapolation required several assumptions to be made that may or may not be true; there simply is no empirical data to know either way.

What many do not realize is that the researchers for Pfizer published a rebuttal to this letter in which they stated: "**In response to Skowronski and De Serres: we would like to emphasize that alternative dosing regimens of BNT162b2 have not been evaluated.**" Pfizer's own data has suggested that single-dose effectiveness might be just over 50%, with their admission of the caveat that their study was never designed to test this properly. Nonetheless, the idea that extended intervals will work well is being propagated, despite a lack of empirical evidence. Indeed, Dr. Bridle has confirmed via interviews with people coming out of local vaccine clinics that some of them are being told that a single dose has been shown to be 92% effective based on 'published data'. This is simply untrue and not the way science is supposed to work. The validity of alternative protocols is up for debate in the scientific community.

Any intervals that deviate from what Health Canada and the vaccine manufacturers have agreed to, represents experimentation, especially in the absence of any new validated data from a phase 3 clinical trial. However, in Ontario and many other jurisdictions in Canada, the change in the vaccine interval has been proposed. See the attached letter from Ontario's Chief Medical Officer as an example of this. In short, the intervals have been lengthened without sufficient empirical data to justify it. In contrast, the intervals provided by Health Canada are based on empirical data. The effectiveness of the two-dose regimens with 3- or 4-week intervals is known. The effectiveness of the two-dose regimens with any other interval is a 'best guess'. This background leads into a potentially more serious issue regarding informed consent...

Is informed consent being practiced properly in COVID-19 vaccine clinics?

In Ontario, the attached consent form should be hard-signed by everybody prior to receiving one of the experimental vaccines. Please note that this form requires a person to have read or to have read to them the vaccine information sheet (see the highlighted text on page 3 of the consent form). Please note the highlighted text on pages 4 and 6 of the vaccine information sheet that is appended to this letter. Consent is being given to receiving the dose at Health Canada's recommended interval of 3- (Pfizer) or 4-weeks (Moderna). No alternative intervals are described. Remarkably, however, many (if not most) attendees at the COVID-19 vaccine clinics are being told after receiving their first dose (*i.e.* once they are committed to the treatment) that they will likely have to wait up to four months to receive the second dose. **People are consenting to the 3-4-week interval** (3 weeks for Pfizer's vaccine; four weeks for the Moderna vaccine) **but are then being told that they cannot receive the second dose for another four months.** For those who would like to insist on receiving their vaccine as per Health Canada's recommended interval, we suggest you take a hard-copy of the vaccine information sheet to the clinic and have

dose.

Why might the interval for two-dose vaccines matter?

Some proponents of lengthening the interval argue there can be no harm. However, there is some scientific basis for suggesting that lengthening intervals could cause harm: 1. The companies themselves suggest a single dose is significantly less efficacious than two doses. This could put individuals at prolonged risk of getting infected while waiting for the second dose. This could be a particular problem for those who are at high risk. 2. It is unknown if the duration of immunity (i.e. how long a person is protected) conferred by a single dose extends to four months; it is possible that there may be no protection at this point. 3. It is unknown if immunological memory conferred by the first vaccine will last long enough for a second dose, given four months later, to serve as a proper 'booster vaccine'. If a proper boost is not conferred, the two-dose effectiveness could be reduced below the 95% effectiveness shown with the approved interval. 4. Induction of long-term, relatively weak immunity could potentially promote the emergence of immune-evasive mutants. This would be similar to what has been observed over and over again with the emergence of dangerous antibiotic-resistant bacteria; it is potentiated by the misuse of the therapeutic agents designed to effectively treat the pathogens. Promotion of immune-evasive SARS-CoV-2 would put everyone at greater risk. Although these are cautionary possibilities, **they are no less valid than the speculations that led to adopting untested long intervals**. Given these are novel nucleic acid vaccine platforms, approved for emergency use only, it might be wise to err on the side of caution. The take-home message is: Longer intervals might be OK, but they also might create problems. We simply don't know yet. On this basis, **those who want to receive the vaccines according to how they were approved for emergency use should be entitled to this.** However, **public health officials seem to be over-riding this right, even though it contradicts their own informed consent procedure, Health Canada, and the vaccine manufacturers.**

With sincere concern for our fellow Canadians,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Sarah K. Wootton
Associate Professor of Virology

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

March 23, 2021

Dear Fellow Canadians:

Scientists Express Urgent Concerns Over Current COVID-19 Vaccine Policies

University Of Guelph Faculty Speak Up:

The following urgent concerns are being expressed by the following faculty members at the University of Guelph:

- Dr. Byram Bridle is a viral immunologist
- Dr. Bonnie Mallard is an immunologist
- Dr. Neil Karrow is an immunologist

Generally, policies for COVID-19 have been generated with relatively little consultation with immunologists, including viral immunologists. However, at its core, COVID-19 is a problem at the interface of immunology and virology.

This interface is both in terms of its pathogenesis and the primary solution being sought, which is acquisition of immunity against the virus SARS-CoV-2. In addition to our group having in-depth knowledge of these fields, Dr. Bridle received funding from the federal government and the government of Ontario to develop vaccines for COVID-19. As such, our group has extensive expertise in this area. Please note that information about COVID-19 vaccines is rapidly changing. The information presented below is accurate as of March 23, 2021.

Has The Goal To Flatten The Curve Been Forgotten?

Early in the pandemic, the goal was to 'flatten the curve' of documented cases of COVID-19 by implementing a lockdown for a few weeks. The purpose was to facilitate hospitals being able to support us in learning how to live with SARS-CoV-2 without medical resources becoming overwhelmed.

Although never clearly stated, the goal seems to have morphed into a 'zero tolerance policy' in which life will not return to normal until daily cases have been eliminated. The large amount of available scientific data suggests this will not be a feasible goal. Indeed, COVID-19 will almost certainly become endemic, akin to the annual outbreaks of influenza viruses.

Will SARS-CoV-2 Become Endemic?

Among the many reasons for this virus becoming endemic is the propensity of SARS-CoV-2 to mutate over time. This will result in the ongoing emergence of novel variants, and this problem is exacerbated by the fact that current vaccines against SARS-CoV-2 confer overly focused immunity that targets a single protein known as the spike.

These two major issues will combine to potentiate SARS-CoV-2 being able to escape vaccine-induced immunity. Indeed, this has already happened as demonstrated by the AstraZeneca vaccine failing in a clinical trial in South Africa against the South African variant, which is already circulating in Canada.

How Can We Live With This Virus While Still Maximizing Health And Safety?

It has become clear that we can't continue to rely on continual lockdowns due to impact on mental health, delays to other medical treatments, a sinking economy and so on. Instead, we must return to the original goal of learning to live with this virus while maximizing the health and safety of our communities.

It is also important to remember that the majority of cases of COVID-19 in Canada are mild-moderate, and the death rate has been quite low (22,676 deaths out of 933,798 cases or 596/million people as of March 22, 2021 - Coronavirus Dashboard (ncov2019.live).

Sadly, at least 70% of those deaths have been in people over 80 years of age, in long-term care (Dr. R. Bibby, Sociologist, at the University of Lethbridge – Research of Reginald W. Bibby (reginaldbibby.com)).

On the upside, there is now also good evidence that the majority of those recovered from COVID-19 have protective immunity (reviewed by Sette and Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell (2021), https://doi.org/10.1016/ j.cell.2021.01.007).

Therefore, we need to identify those with immunity from natural exposure using available antibody testing, and strategically prioritize those at highest risk, who need and want to be vaccinated, according to the manufacturers currently approved vaccination protocols.

How Can Vaccines Be Prioritized According To Manufacturers Approved Protocols?

It is from this perspective that we have been advocating for several core strategies to support re-opening our country to in-person work and learning. An important aspect of this is offering strategically prioritized vaccinations.

Specifically, we have been advocating for the administration of safe and effective COVID-19 vaccines according the protocol that was used to have them approved for emergency use, until further data is available and reviewed and approved by Health Canada to support alternative protocols.

In support of this goal, we have two recommendations:

1. Consideration should be given to avoiding the AstraZeneca vaccine, for which there is documented evidence of it being ineffective against the South African variant of SARS-CoV-2, which is now in Canada. It was only 10% effective against the South African variant, with the cut-off for approval being 50% (https://www.nejm.org/doi/full/10.1056/NEJMoa2102214?query=featured_home).

2. It has also proven to be less effective in a head-to-head comparison with Pfizer's vaccine (https://www.cell.com/cell/pdf/S0092-8674(21)00226-9.pdf).

   For Ontarians, the Chief Medical Officer definitively stated in a letter to pubic health units in the province that individuals may opt out of receiving the AstraZeneca vaccine on the basis that it is admittedly of lower efficacy than the others (see the highlighted text on page 2 of the attached letter).

3. The intervals for the two-dose COVID-19 mRNA vaccines should adhere to what was officially approved by Health Canada and the manufacturers, which is 21- and 28-days for the Pfizer and Moderna vaccines, respectively. The rationale for this is presented below...

Why The Concern Over Changing The Manufacturers Approved Protocols?

The history of Canada's move to extend COVID-19 intervals to four months is unprecedented. Recently, the CBC launched a story to highlight the path that has led many jurisdictions in Canada to begin implementing an interval of up to four months for both the Pfizer and Moderna COVID-19 vaccines (https://www.cbc.ca/news/health/canada-covid-19-vaccine-delay-risk-1.5939134).

It apparently began with a letter from an epidemiologist at the British Columbian Centre for Disease Control to the editor of *The New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMc2036242).

In this letter it was claimed that Pfizer failed to realize the efficacy of its own vaccine and that its effectiveness as a single-dose regimen is a remarkable 92%. It is important to note that this is based on an extrapolation of a statistically underpowered, biased, limited data set from a trial that was never designed to test single-dose efficacy. Further, the extrapolation required several assumptions to be made that may or may not be true; there simply is no empirical data to know either way.

What many do not realize is that the researchers for Pfizer published a rebuttal to this letter in which they stated: "In response to Skowronski and De Serres: **we would like to emphasize that alternative dosing regimens of BNT162b2 have not been evaluated.**" Pfizer's own data has suggested that single-dose effectiveness might be just over 50%, with their admission of the caveat that their study was never designed to test this properly.

Nonetheless, the idea that extended intervals will work well is being propagated, despite a lack of empirical evidence. Indeed, Dr. Bridle has confirmed via interviews with people coming out of local vaccine clinics that some of them are being told that a single dose has been shown to be 92% effective based on 'published data'. This is simply untrue and not the way science is supposed to work. The validity of alternative protocols is up for debate in the scientific community.

Notably, on March 22nd, Canada's chief science adviser, Dr. Mona Nemer, spoke out against lengthening dosing intervals for Canadian seniors, citing not only a lack of scientific evidence to support it, but even emerging evidence to contraindicate it (https://www.ctvnews.ca/health/coronavirus/research-doesn-t-back-vaccine-dose-delay-for-seniors-canada-s-chief-science-adviser-says-1.5358075).

Any intervals that deviate from what Health Canada and the vaccine manufacturers have agreed to, represents experimentation, especially in the absence of any new validated data from a phase 3 clinical trial. However, in Ontario and many other jurisdictions in Canada, the change in the vaccine interval has been implemented.

See the attached letter from Ontario's Chief Medical Officer as an example of this. In short, the intervals have been lengthened without sufficient empirical data to justify it. In contrast, the intervals provided by Health Canada are based on empirical data. The effectiveness of the two-dose regimens with three-

or four-week intervals is known. The effectiveness of the two-dose regimens with any other interval is a 'best guess'. This background leads into another potentially serious issue regarding informed consent...

Is Informed Consent Being Practiced Properly In Canadian COVID-19 Clinics?

According to Ontario's Ministry of Health website, the attached consent form should be hand-signed by everybody prior to receiving one of the experimental vaccines. Please note that this form requires a person to have read or to have read to them the vaccine information sheet (see the highlighted text on page 3 of the consent form). Please note the highlighted text on pages 4 and 6 of the vaccine information sheet that is appended to this letter.

The Ontario Ministry of Health website appears to be requiring consent to be given to receiving the second dose of the mRNA vaccines at Health Canada's recommended interval of three- (Pfizer) or four-weeks (Moderna). No alternative intervals are described. Remarkably, however, most attendees at the COVID-19 vaccination clinics are being told that they cannot receive the second dose for another four months.

For those who would like to insist on receiving their vaccine as per Health Canada's recommended interval, we suggest you take a hard-copy of the vaccine information sheet to the clinic and have them confirm that they will adhere to the protocol you are consenting to prior to letting them administer the first dose.

WHY MIGHT THE INTERVAL FOR TWO-DOSE VACCINES MATTER?

Some proponents of lengthening the interval argue there can be no harm. However, there is some scientific basis for suggesting that lengthening intervals could cause harm:

1. The companies themselves suggest a single dose is significantly less efficacious than two doses. This could put individuals at prolonged risk of getting infected while waiting for the second dose. This could be a particular problem for those who are at high risk.

2. It is unknown if the duration of immunity (*i.e.* how long a person is protected) conferred by a single dose extends to four months; it is possible that there may be no protection at, or even before this point.

3. It is unknown if immunological memory conferred by the first vaccine will last long enough for a second dose, given four months later, to serve as a proper 'booster vaccine'. If a proper boost is not conferred, the two-dose effectiveness could be reduced below the 95% effectiveness shown with the approved interval.

4. Induction of long-term, relatively weak immunity could potentially promote the emergence of immune-evasive mutants. This would be similar to what has been observed over and over again with the emergence of dangerous antibiotic-resistant bacteria; it is potentiated by the misuse of the therapeutic agents designed to effectively treat the pathogens.

Promotion of immune-evasive SARS-CoV-2 would put everyone at greater risk. Although these are cautionary possibilities, they are no less valid than the speculations that led to adopting untested long

intervals. Given these are novel nucleic acid vaccine platforms, approved for emergency use only, it might be wise to err on the side of caution.

5. A pre-print of a relevant scientific article was posted on-line (https://www.medrxiv.org/content/10.1101/2021.03.03.21251066v1). It has not yet undergone peer review. However, we routinely review these kinds of articles and have concluded that the core data set appears to be valid. This article describes results of a study with the Pfizer vaccine. Importantly, the authors have concluded "since the majority of vaccinees did not obtain neutralizing antibody titers after the first vaccination, we suggest that **postponing a second vaccination with this vaccine is neither advisable for younger nor elderly populations**." In short, a single dose of Pfizer's vaccine would be expected to leave most people unprotected against SARS-CoV-2. Therefore, extending the interval to four months would not meet the goal of getting twice as many people partially protected, as our public health officials are claiming. Instead, it could cause large numbers of people to be left unprotected for a prolonged period.

What's the Take-Home Message?

A longer interval might be okay for the Moderna vaccine, but it also might create problems. We simply don't know yet. Cutting-edge data from a properly conducted scientific study suggested that a prolonged interval for the Pfizer vaccine is dangerous. On this basis, those who want to receive the vaccines according to how they were approved for emergency use should be entitled to this.

However, public health officials seem to be over-riding this right, even though it appears to contradict Health Canada, the vaccine manufacturers, Canada's chief science advisor, and the informed consent procedure posted on the Ontario Ministry of Health website.

With sincere concern for our fellow Canadians,

Dr. Byram W. Bridle
Associate Professor of Viral Immunology
E-mail: bbridle@uoguelph.ca
Tel.: 519-824-4120 x54657

Dr. Bonnie Mallard
Professor of Immunology

Dr. Niel Karrow
Professor of Immunology

This is Exhibit " J " to the Affidavit of

Dr. Neil Karrow, affirmed before me on

this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

From: Byram Bridle <bbridle@uoguelph.ca>
Date: Thursday, June 24, 2021 at 6:39 AM
To: "J. Scott Weese" <jsweese@uoguelph.ca>, Glen Pyle <gpyle@uoguelph.ca>
Cc: "OVC-PATHOBIO-FACULTY (ovc-pathobio-faculty@listserv.uoguelph.ca)" <ovc-pathobio-faculty@listserv.uoguelph.ca>, Tarek Saleh <tsaleh@uoguelph.ca>, JJW <jwichtel@uoguelph.ca>, Laurie Arnott <l.arnott@exec.uoguelph.ca>
Subject: Invitation to publicly discuss COVID-19 vaccines for children

Hi Scott and Glen,

I am sick and tired of your immature behaviours in social media. The continual fanning of the flames of the smear campaign against me is hurtful, harmful, and childish. Graduate students of other faculty members have taken notice and are appalled by the ongoing behaviour. Glen, you were caught in an outright lie (see below). You know who set-up the libelous website and lied to our college administration about knowing this. Will you reveal the name of the person who set-up the site to facilitate its removal or do you continue to feel it is appropriate to cause major ongoing harm to the career of a colleague? It is notable that neither one of you has been willing to engage me in any discussions about the science. Talking to someone who can respond in real-time is very different than slamming them in one-sided Tweets. I do not have a social media presence and you provide great examples of why this was a wise decision. It is time to start acting your age. I invite you to discuss the science underpinning the use of COVID-19 vaccines in children in an on-line public forum. You are the local experts on COVID-19 vaccines and now have an opportunity to demonstrate to our colleagues, and the public at large that I do not know what I am talking about in a respectful discussion. We can find a moderator and we can either do this one-on-one, the two of you and then I will choose one colleague to attend with me, or you can even select one additional colleague and we will have teams of three. You have one week to respond to this invitation. The public discussion will take place within a week of me receiving a response. A negative response or non-response will be taken as a public acknowledgement that you have been wrong and will be implied as a public apology. To help you prepare, please see the attached open letter that was written by the inventor of the mRNA vaccine technology, read my guide for parents (the full version, not the two-pager), which can be found at this website: https://www.canadiancovidcarealliance.org/, and view this video in which I rebut every argument made against me that I was aware of... https://rumble.com/vilrsj-doctor-talks-10-dr-byram-bridle-returns-fire-to-critics.html

The time starts now.

A few examples of the many Tweets sent to me by horrified graduate students and some colleagues from around the world can be found below (Scott and Glen, do you really want the public and our trainees to believe that this is how we conduct our business at the U of G?; Are you willing to work towards re-building a respectful work environment at OVC?)...

Sincerely,
Byram

Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Office Room #4834
Lab Room #3808
Building #89 (NW corner Gordon/McGilvray)
Department of Pathobiology
University of Guelph
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Office Telephone #519-824-4120 x54657
Lab Telephone #519-824-4120 x53616
E-mail: bbridle@uoguelph.ca
https://ovc.uoguelph.ca/pathobiology/people/faculty/Byram-W-Bridle

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Original Tweet from Glen Pyle.

This was later deleted!

The next page shows his e-mail where he lied about knowing the scientist who made the website...

RE: smear campaign

Glen Pyle <gpyle@uoguelph.ca>
Sun 3/30/2021 1:00 PM
To: Byram Bridle <bbridle@uoguelph.ca>
Cc: Jeffrey Wichtel <jwichtel@uoguelph.ca>; Shayan Sharif <shayan@uoguelph.ca>; Brandon Lilke <blilke@uoguelph.ca>

Hi Byram.

I'm removing some of the cc on this in the hope that a more focused discussion will help. Jeff conveyed to me the suggestion that we try a more focused approach and I understand he did the same for you. Hopefully this helps.

Here is the lie!

First, I appreciate the clarification about the article. Stress or not, I can see how a small language error (inadvertent) can cause a misunderstanding. Happy to move past that.

Second, I don't know who made the website. You've mentioned you are not on social media so you may not be aware that some people chose to remain anonymous. The website was flagged to me and that was the info I was given. Others tried to tag it to Dr Fisman and someone mentioned a hacker. I simply clarified that my understanding was this was not the case. I think you can appreciate that had someone been mistakenly linked to material they didn't create, that could create stress for them.

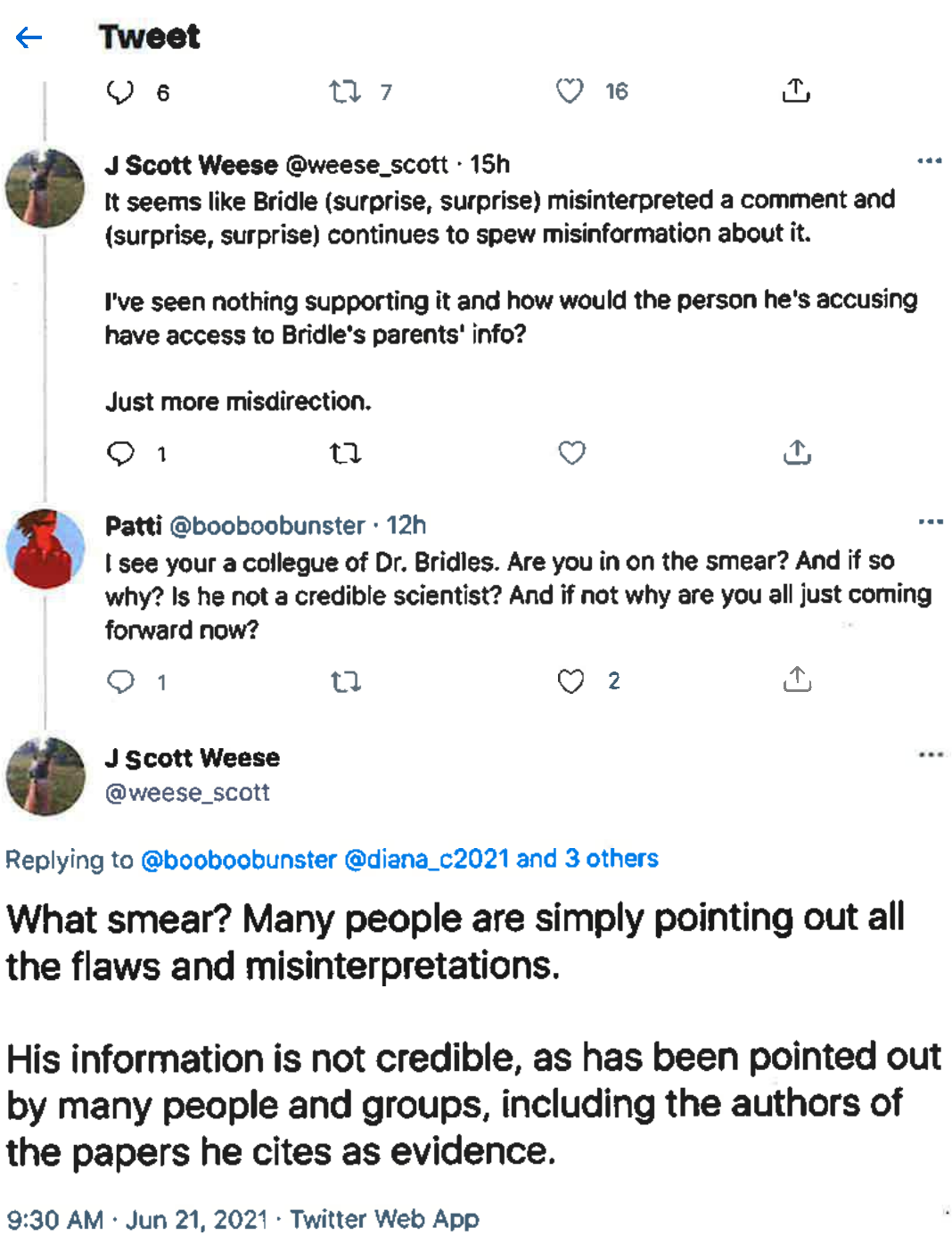
Finally, I would like to point out that anything I posted was based on publically available information and that I have stuck to the evidence. I have not attacked you as a person and have no intention of doing so. I think we can have profound disagreements about the science and stay away from character attacks. If others have made it personal I don't condone that. In all honesty, I have not seen personal attacks like that, but these things do happen on social media and I don't think they help any side of the debate. I myself have been on the receiving end, including threats of violence, so I can speak from experience.

We have deep disagreements over the science. I have no issue with you presenting your arguments based on studies and data, and have never called for your academic freedom to be curtailed. You don't need my permission, so hopefully that last statement doesn't come across like that. I hope that you will afford me the same opportunity to discuss the scientific literature, and we can disagree (or perhaps be swayed by each other's arguments).

I am sorry you feel you have been personally attacked and that this has created stress. If I have inadvertently posted something that appears to be personal, I apologize without reservation. I can't be responsible for the words of others, but let me clearly state that anyone who attacks you as a person is not supported by me.

Glen.

Here is Scott defending the release of my parents' private medical information by a practicing physician (Dr. David Fisman, who seves on Ontario's COVID-19 Science Advisory Table)...



Tweet

6 7 16

J Scott Weese @weese_scott · 15h

It seems like Bridle (surprise, surprise) misinterpreted a comment and (surprise, surprise) continues to spew misinformation about it.

I've seen nothing supporting it and how would the person he's accusing have access to Bridle's parents' info?

Just more misdirection.

1

Patti @booboobunster · 12h

I see your a collegue of Dr. Bridles. Are you in on the smear? And if so why? Is he not a credible scientist? And if not why are you all just coming forward now?

1 2

J Scott Weese
@weese_scott

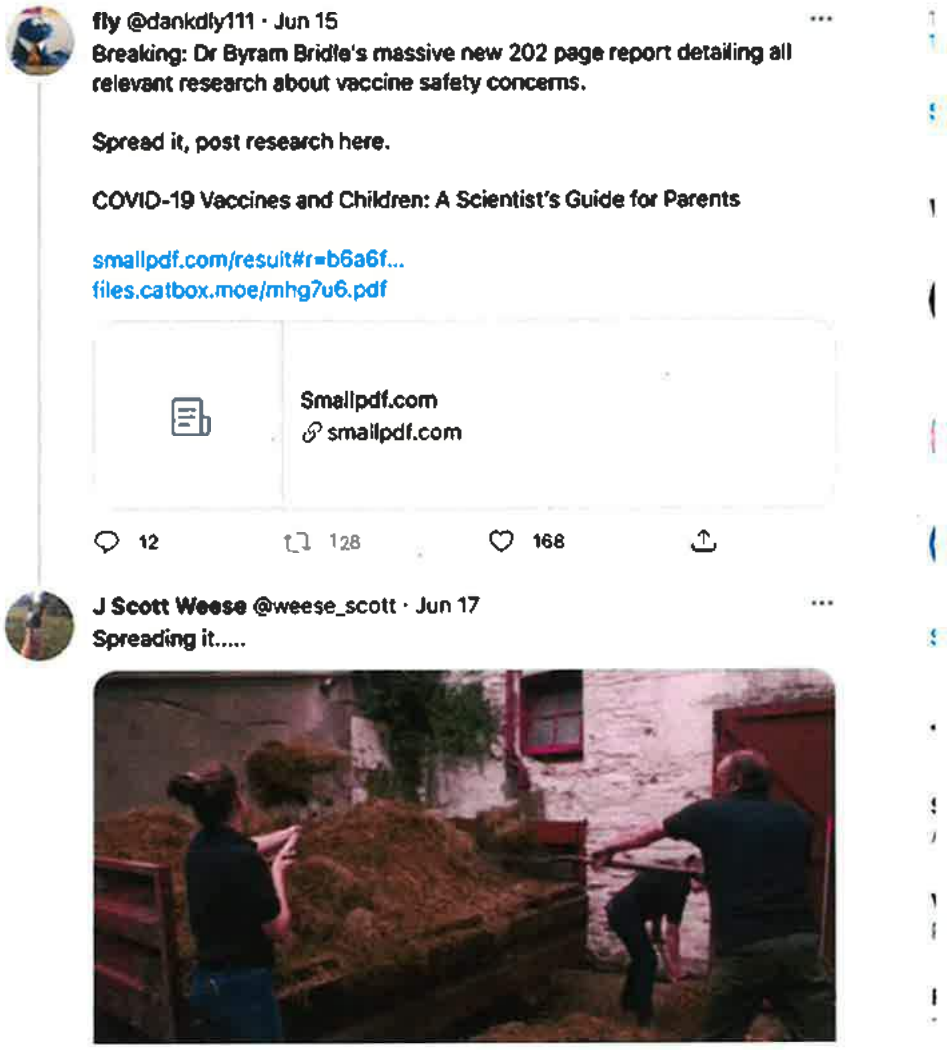
Replying to @booboobunster @diana_c2021 and 3 others

What smear? Many people are simply pointing out all the flaws and misinterpretations.

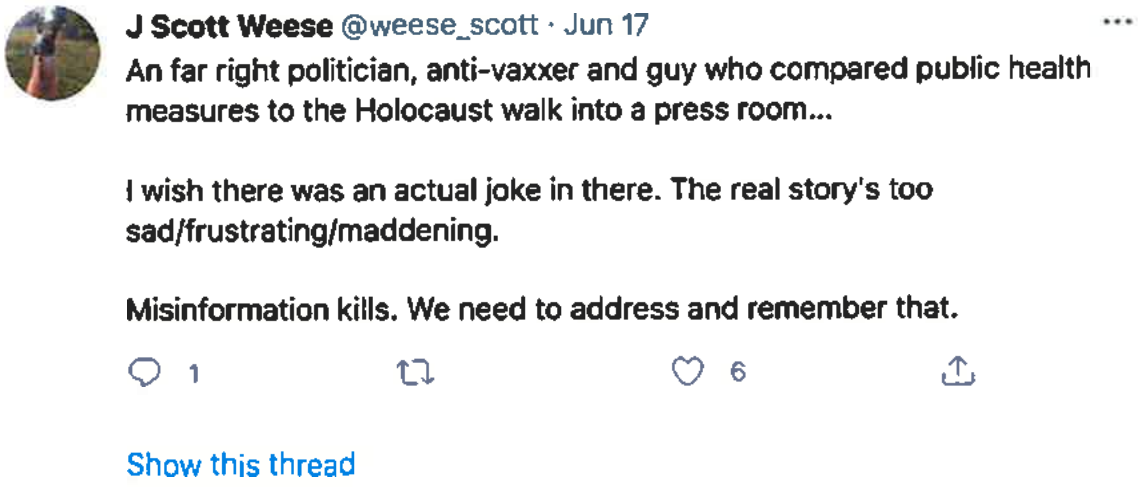
His information is not credible, as has been pointed out by many people and groups, including the authors of the papers he cites as evidence.

9:30 AM · Jun 21, 2021 · Twitter Web App

An example of Scott's mature approach to scientific discourse...



Another sign of Scott's maturity (this was in response to a press conference that I was invited to participate in at Parliament Hill about censoring open scientific and medical discussions)...



...publicly referring to a vaccinologist whose research program and publication record focuses on vaccines is libel.

This is Exhibit " K " to the Affidavit of

Dr. Neil Karrow, affirmed before me on

this 15th day of December 2023

A Commissioner for Taking Oaths
Amina Sherazee Barrister and Solicitor

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

To: Brandon Lillie <blillie@uoguelph.ca>, Shayan Sharif <shayan@uoguelph.ca>, Jeff L Caswell <jcaswell@uoguelph.ca>, John Lumsden <jsl@ovc.uoguelph.ca>, Bonnie Mallard <bmallard@ovc.uoguelph.ca>
Subject: Department of Pathobiology

CAUTION: This email originated from outside of the University of Guelph. Do not click links or open attachments unless you recognize the sender and know the content is safe. If in doubt, forward suspicious emails to IThelp@uoguelph.ca

Hi Brandon, I understand that you are now the Chair of Pathobiology. Congratulations, I'm sure you will do an excellent job. I have greatly enjoyed working with members of your department and have much respect for most of your faculty. I have collaborated with You, Caswell, Plattner, Sharif, Mallard, Sargolzaei, Peregrine, and Wootton, and have been blessed with the opportunity to exchange communications with Bienzle, Boerlin, Gyles, Bridle, Hayes, MacInnes, Lumsden, Nagy, Prescott, Hodgins and others while sitting on various university committees.

As I see it, something is seriously wrong over there!

I came across a Tweet that I find very disturbing (attached). I don't know Weese, nor do I care to, but his tweets are very immature and unprofessional. I believe as colleagues, we should be able to listen to and respect each other, and hopefully learn together. We are stronger as a group than we are individually. I am embarrassed by Weese's childish behaviour and I am ashamed to be affiliated with the same university that he attends. Since when did we learn to steep so low? Is it a cry for attention because we have been in isolation for the last 18 months? If he disagrees with Bridle, then why doesn't he just sit down with him and discuss his concerns? Why the public slandering? This kind of caddy behaviour makes us all look bad and it says so much more about Weese's character than what Bridle stands for. Moving forward, I think a mediator should be considered. In the short-term please somehow curtail these Tweets. Thanks N

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Hey @uofg

Here's your favourite anti-vaxxer faculty spouting more lies ON UNIVERSITY LETTERHEAD.

At what point will you actually try to "Improve life"

still waiting....

not holding my breath though.

Vero Likes Freedom @Veronikalzabela · 8h
Dr. Byram Bridle wrote a letter that says NO to vaccine mandates.

"....disbursement of any medical guidance that results in injury could carry legal liability. "

It's addressed to the Thames Valley District School Board. ••

Dr. Niel Karrow (凱尼大)
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Court File No./N° du dossier du greffe : CV-22-00691880-0000

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

J Scott Weese Retweeted

David Fisman @DFisman · Nov 10

A good read from [illegible] on close linkages between antivaxxers, antimaskers and neo-Nazis in Canada. Media need to start calling this for what it is. H/t [illegible]

readpassage.com

Media Has Ignored The Anti-Vax Movement's White Supremacist Roots

Anti-vaccine, anti-mask and anti-lockdown movements are, at their core, new mobilizations of white supremacy.

110 678 1.2K

J Scott Weese @weese_scott · Nov 10

Vaccines induce cancer recurrence (no evidence).
Vaccines are minimally effective (they're very good)
Ivermectin works (clear evidence it doesn't)
Various conspiracies.
...and more...

Good material for any fact checkers.

Veroos19 @Veroos19 · Nov 10

WHY ARE HIGHLY VACCINATED COUNTRIES EXPERIENCING COVID OUTBREAKS? - VACCINOLOGIST
bitchute.com/video/di4O1pXV_

13

Veroos19
@Veroos19

WHY ARE HIGHLY VACCINATED COUNTRIES EXPERIENCING COVID OUTBREAKS? - VACCINOLOGIST

bitchute.com

Why are highly vaccinated countries experiencing COVID outbreaks? - Dr Byra...
Dr Byram Bridle, Viral Immunologist & Associate Professor at the University of Guelph, speaks publicly about the concerns of the Vaccine, risks with Cancer ...

2:31 PM · Nov 10, 2021 · Twitter for Android

J Scott Weese @weese_scott · Nov 12

Yes, there are some lawyers spending most of their time crowd sourcing funds and threatening (or initiating) lawsuits to silence criticism.

Personal experience here.

Health Nerd @GidMK · Nov 11

Lawsuits are a very common method, for example. Powerful people talk nonsense about how important free speech is to them then sue for defamation at the drop of a hat

Show this thread

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Court File No.: **CV-22-0069-1880-0000**

Dr. BYRAM BRIDLE	Glen PYLE et al
-and-	
Plaintiffs	Defendants

ONTARIO
SUPERIOR COURT OF JUSTICE
PROCEEDING COMMENCED AT TORONTO

AFFIDAVIT OF DR. NEIL KARROW

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Lawyer for the Plaintiff

Electronically filed / Déposé par voie électronique : 18-Dec-2023
Toronto Superior Court of Justice / Cour supérieure de justice

Court File No.: **CV-22-0069-1880-0000**

Dr. BYRAM BRIDLE
Plaintiffs

-and-

Glen PYLE et al
Defendants

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ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDING COMMENCED AT TORONTO

RESPONDING (Plaintiffs') MOTION RECORD
(s.137.1 Anti-SLAPP Motion)

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