April 13, 2021

Dear Mr. Michael Swinwood, B.A., LL.B, Elders Without Borders,

As requested, here is my report about multiple issues related to severe acute respiratory syndrome-coronavirus-2, which can be transmitted human-to-human, causing atypical pneumonia (COVID-19) in a subset of infected individuals.

Sincerely,

Dr. Byram W. Bridle, PhD

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List of Abbreviations	
COVID-19	coronavirus disease that emerged in 2019
Ct	cycle threshold
DNA	deoxyribonucleic acid
IFR	infection fatality rate
NAAT	nucleic acid amplification test
NAT	nucleic acid test
PCR	polymerase chain reaction
RNA	ribonucleic acid
RT-PCR	reverse transcription - polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
VOCs	variants of concern

1. The Problem

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can cause atypical pneumonia, known as 'coronavirus disease that was identified in 2019' (COVID-19) in a subset of individuals. For most people, COVID-19 causes, at most, mild or moderate illness. For some, SARS-CoV-2 is not even a pathogen since it does not cause disease in them. However, for two well-defined demographics, COVID-19 can be potentially severe and even lethal. This includes individuals who are immunocompromised and the elderly, especially if co-morbidities exist. Shortly after the COVID-19 pandemic was declared in Canada, caution was exercised through the declaration of emergency orders and implementation of a what was supposed to be a short-term lockdown to allow time to: (a) assess the severity of the situation, and (b) slow the first wave of cases of COVID-19 so hospitals would not get overwhelmed. This was to be a temporary measure to 'flatten the curve', which referred to a stabilization in the daily reported cases of COVID-19 when plotted on a graph. Then, we would learn to live with the virus, like we have with the man other respiratory pathogens to which we were exposed. However, more than one year later, we have experienced cyclic emergency lockdown orders on a background of constant isolation, physical distancing, and masking measures. Ontario's response to the declared pandemic has not altered despite overwhelming scientific data that show the risk of severe and lethal disease is almost entirely limited to two well-defined demographics. Rather than taking a balanced approach, in which economic, physical and human resources could be focused on protecting the most vulnerable, Ontario has opted for a very long-term 'one-size-fits-all' approach that has had dramatic consequences for the minority of high-risk individuals as well as low-risk people, who are in the majority. What follows is a discussion some of the data that highlight where COVID-19 policies have been flawed and/or have caused harm, which, in some cases, has been irreparable.

2. Dr. Byram W. Bridle's Credentials and Role in the COVID-19 Pandemic

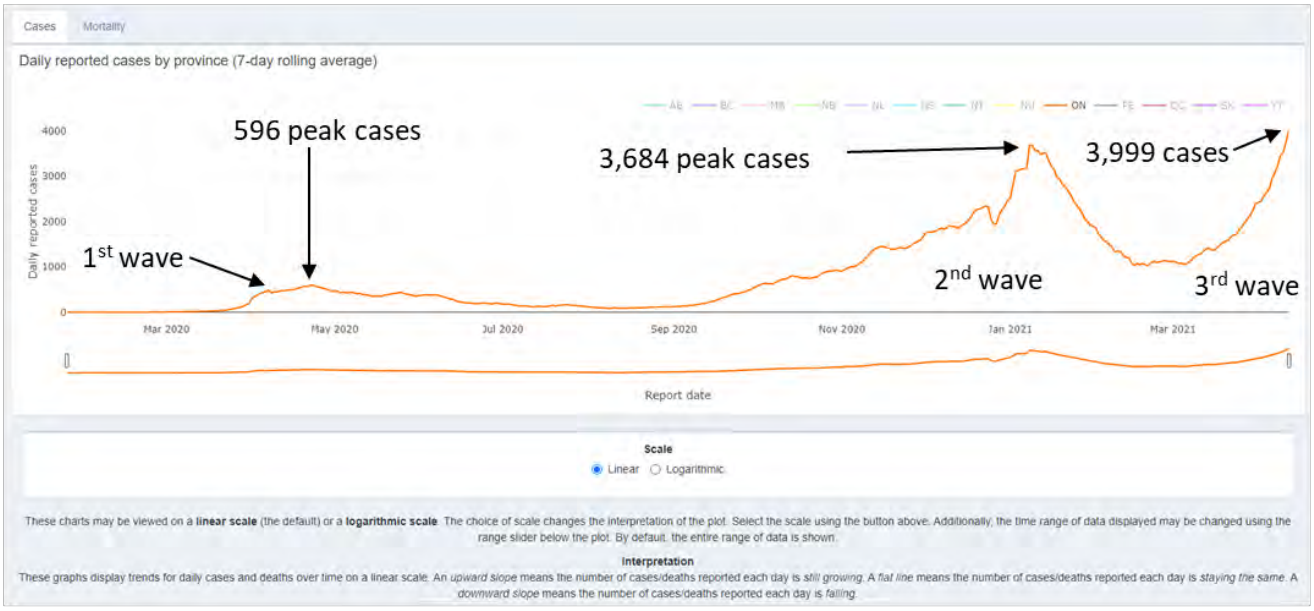
Dr. Bridle is an Associate Professor of Viral Immunology in the Department of Pathobiology at the University of Guelph. His academic appointment as an independent researcher and faculty member began in January 2012. He received a MSc and PhD in immunology and completed a post-doctoral fellowship in viral immunology. His research program focuses on the development of vaccines to prevent infectious diseases and treat cancers, as well as studying host immune responses to viruses. He teaches in several courses at the undergraduate and graduate level on the topics of immunology, virology, and cancer biology. He is also involved in training Canada's next generation of multidisciplinary researchers. With respect to COVID-19, Dr. Bridle received funding from the Ontario government (COVID-19 Rapid Research Fund, Ministry of Colleges and Universities) and federal government (Pandemic Response Challenge Program, National Research Council of Canada) to develop vaccines against COVID-19. He also holds numerous grants in support of his cancer research and basic viral immunology research programs. Since the beginning of the COVID-9 pandemic he has been actively involved in disseminating fact-based, balanced scientific information to the public and policy makers to assist people with making fully informed decisions. Additional qualifications can be found in his curriculum vitae.

3. SARS-CoV-2: A Virus that Follows Typical Population Dynamics

As of April 1, 2020, the population of Ontario was 14,745,040[1]. As seen in figure 1, there have been two complete waves of reported cases of COVID-19 and as of writing, we are in a third wave. Unfortunately, Ontario has refused to document the severity of 'cases', which can potentially range from asymptomatic (in which case they would not be a case of COVID-19 because there is no apparent disease) to mild to moderate to severe but non-lethal to severe and lethal. As such, one is unable to appreciate that the cases have progressed towards lower average severity over time. Where this is evident, however, is in figure 1b which shows ever-declining fatality associated with cases, despite dramatic increases in the peak number of daily cases with each successive wave. A reasonable and probable explanation for this is that those who were most susceptible to COVID-19 died in the first wave, which is to be expected for any potentially lethal infectious pathogen. Remarkably, only two Ontarians under the age of 20 have had their deaths attributed to COVID-19 over the past year plus ~3.5 months (figure 2b). Clearly, COVID-19 is not a serious issue for young Canadians. This is in stark contrast to most other infectious respiratory pathogens that often cause substantial cases of severe and lethal disease in the very young (*i.e.* <10 years of age). Among all Ontarians under the age of 60, a total of 367 have died in the past ~15.5 months (figure 2b); and among these, many would have had pre-existing and pre-disposing medical conditions.

Conclusion: The dynamics of spreading of SARS-CoV-2 and its decreasing harm to the population of Ontario over time is typical of infectious diseases. SARS-CoV-2 has not demonstrated novel or unprecedented population dynamics. From an immunological perspective, the data in figures 1 and 2 are indicative of an infectious agent that has been running a typical course in the population. Its harm is decreasing over time. Mortality data for Ontarians under the age of 60 demands that a proper risk-benefit analysis be performed to place the high cost of pandemic-associated public health policies into a proper context. For example, 2009 was a year in which deaths due to motor vehicle accidents were relatively low; 569 Ontarians died. These types of annual deaths would also be preventable with the implementation of stay-at-home orders. Further, many chronic fatal diseases (*e.g.* cancers, heart disease, etc.) have been relatively neglected in favour of diverting resources to COVID-19 lockdown measures. This will result in irreparable future harm in the form of increased death rates that have yet to be determined. And this does not account for other deaths indirectly caused by COVID-19 policies, including suicides due to increased mental health issues, etc. Indeed, the Ontario government needs to determine if their current policies have placed a premium on lives lost due to COVID-19 over those lost to other causes. Revising or revoking these policies could result in a net saving of lives in Ontario.

(A)



(B)

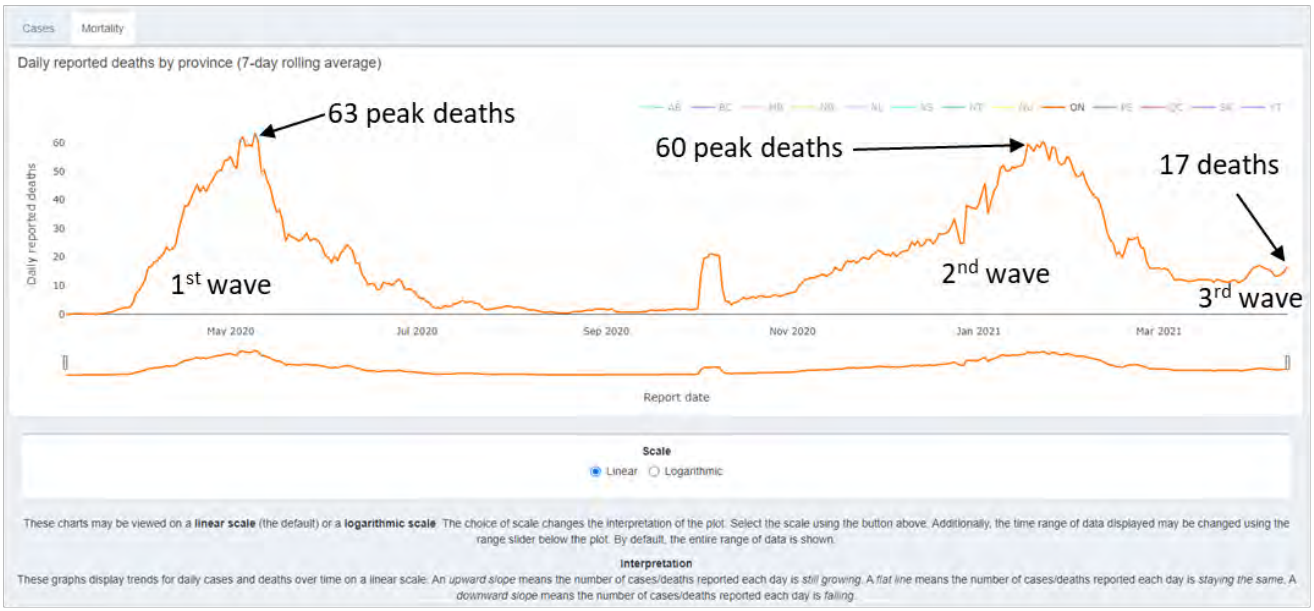


Figure 1: COVID-19 case and mortality data for Ontario.
(A) This graph shows the number of daily 'cases' of COVID-19 in Ontario. Note that the definition of a case is controversial due to issues related to how these are defined. (B) The number of daily deaths attributed to COVID-19 in Ontario. These data were downloaded on April 13, 2021 from the COVID-19 dashboard, for which data are curated by the COVID-19 Canada Open Data Working Group, Dalla Lana School of Public Health, University of Toronto (https://art-bd.shinyapps.io/covid19canada/).

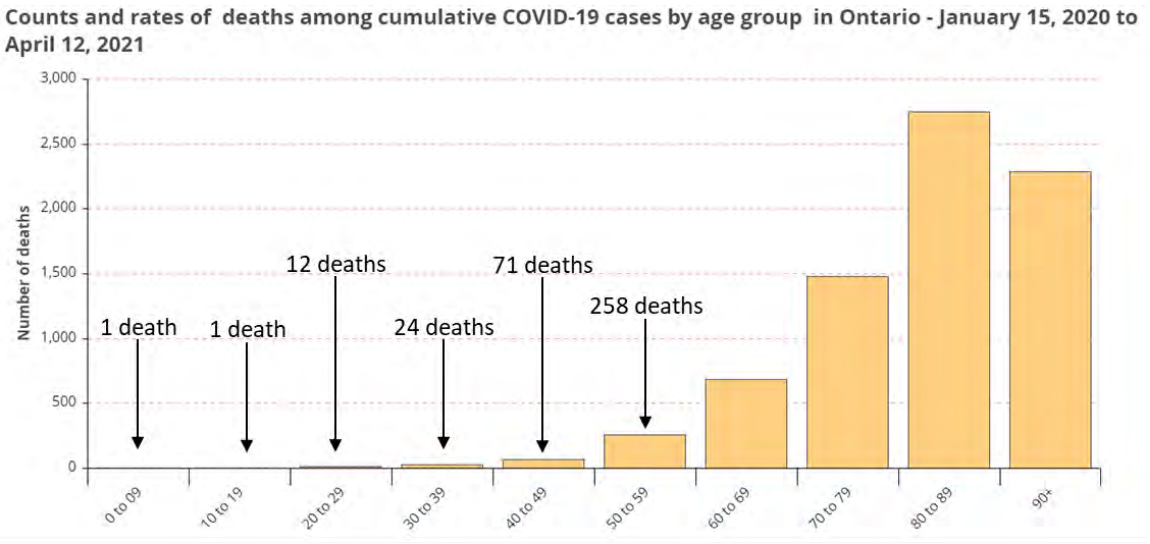


Figure 2: Cumulative deaths in Ontario that were attributed to COVID-19.
This graph shows cumulative deaths by age group. These data were downloaded on April 13, 2021 from the website for Public Health Ontario (https://www.publichealthontario.ca/en/data-and-analysis/infectious-disease/covid-19-data-surveillance/covid-19-data-tool?tab=ageSex)

4. SARS-CoV-2 is Not a Problem of Pandemic Proportions

Infection fatality rate (IFR) is a way to assess how dangerous a pathogen is. It is calculated based on the number of people that die from among the total number that were 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%. Indeed the IFR for a bad 'flu' season can be as high as ~0.1%[2].

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 be a lack of testing for evidence of seroconversion (*i.e.* when pathogen-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 globally, the total number of infections that have occurred keeps getting re-adjusted to higher numbers. As a result, the IFR for SARS-CoV-2 has been steadily declining. Remarkably, as the data regarding total infections has become more accurate, the IFR for SARS-CoV-2 has dropped to only ~0.15%[3]. It is also possible that this IFR will drop even further as the extent of unnoticed infections is further elucidated. Indeed, a recent study found that proportion of people in British Columbia that had been exposed to SARS-CoV-2 is likely substantially higher than previously appreciated[4].

Conclusion: The IFR for SARS-CoV-2 was vastly overestimated at the beginning of the declared pandemic. It is now approaching the range of a serious influenza outbreak, but with severity of disease limited to a more restricted demographic (*i.e.* unlike influenza viruses, SARS-CoV-2 is not particularly dangerous to the very young).

5. Results of PCR Tests to Detect SARS-CoV-2 Must be Interpreted with Great Caution

A common way to detect the presence of a virus in a clinical sample is to use what is called a nucleic acid test (NAT). These kinds of tests work by detecting the presence of the genetic material (*i.e.* genome) of the virus. Indeed, viral genomes are composed of building blocks known as nucleic acids. Commonly used NATs fall under the umbrella term 'nucleic acid amplification tests' (NAATs). These tests incorporate a step that amplifies or increases the amount of the virus-derived genetic material, thereby making it easier to detect. There are different kinds of NAATs, including but not limited to 'reverse transcription - polymerase chain reaction' (RT-PCR), 'transcription-mediated amplification' (TMA), and 'loop-mediated isothermal amplification' (LAMP). However, since RT-PCR is the most common method being used in laboratory-based testing during the pandemic, that will be the focus of this discussion.

A specific form of PCR is most prevalent for detecting SARS-CoV-2. It is known as 'real-time RT-PCR'. A real-time PCR is also known as a quantitative PCR and it monitors the amplification of a targeted piece of genetic material. Importantly, it can, in theory, provide information about the relative amount of virus-derived genetic material that was present in a sample (*i.e.* few versus many viral particles).

A PCR test is designed to detect genetic material made of deoxyribonucleic acid (DNA). However, the genome of SARS-CoV-2 is made of ribonucleic acid (RNA). As such, the PCR test cannot be performed until a reverse transcription step is performed, which copies the genetic code of the viral RNA into DNA, which is much more stable than RNA. The PCR can then be performed, which involves using what are called 'primers' that are designed to bind to unique sequences that are present in a viral genome. The primers are short pieces of DNA that are designed to bind at either end of a segment of the viral genome. If the primers bind, a molecule known as a 'polymerase' will use the viral genome as a template to extend the primers until the target gene segment has been completely copied. This works by varying the temperature of the sample. A high temperature is used to get double-stranded DNA to separate into single strands. Next, an 'annealing' temperature is used to allow the primers to bind to the single strands of DNA. Finally, a third temperature is used to promote 'extension' of the primers until the targeted gene sequence has been copied. This constitutes a single cycle of the test. Multiple cycles are employed to increase the copies of the targeted gene segment exponentially. A fluorescent dye is usually added to the sample that incorporates into the targeted gene segment. If enough gene segments get amplified, a special machine can detect the amount of the fluorescent dye. The amount of dye usually correlates with the number of viral genomes in the clinical specimen. An important piece of information derived from the RT-PCR test is the 'cycle threshold' (Ct) value. The Ct value is the number of cycles that the test had to be run for the fluorescent signal to exceed background levels.

There are many steps involved in the optimization of RT-PCR tests before they can be used. If properly designed, a good-quality PCR test can be sensitive enough to detect very small quantities of viral genetic material. However, when it comes to RT-PCR testing for SARS-CoV-2, caution must be exercised when interpreting results. Importantly, poorly optimized RT-PCR tests can have high background signals. Further, the greater the number of cycles used in a RT-PCR assay, the greater the chance of erroneous

non-specific amplification of non-targeted genetic material. The National Collaborating Centre for Infectious Diseases in Canada published the general guide for interpreting results of RT-PCR tests for SARS-CoV-2 shown in table 1[5].

Ct Value	Indication	Interpretation
<25	High levels of SARS-CoV-2 genomic load	Patients with higher SARS-CoV-2 genomic loads are more likely to develop severe outcomes and require intubation and severe outcomes. Patient needs to be monitored.
25-30	Moderate levels of SARS-CoV-2 genomic load	
>30	Low levels of SARS-CoV-2 genomic load	Low SARS-CoV-2 genomic load can be found early in infection when viral replication has just begun. Additionally, it can indicate the later phases of infection after the virus has been cleared and has left behind remnants of its genomic content. Interpretation requires clinical context.

Table 1: Guide to interpreting results of RT-PCR test results.
The Collaborating Centre for Infectious Diseases in Canada published the general guide for interpreting results of RT-PCR tests shown in this table. (https://nccid.ca/publications/understanding-rt-pcr-tests-and-results/)

In addition to the potential for false signals at high Ct values, note that high values can also be indicative of detection of non-viable viral particles. It is important to note that SARS-CoV-2 particles can exist in two basic forms: 1. Replication-competent; this is the form with the potential to cause COVID-19. 2. Replication incompetent; this cannot cause COVID-19. Following clearance of SARS-CoV-2 from the body, full and/or partial genomes of SARS-CoV-2 can remain for many days. One key reason for this is that some phagocytic cells, which are a component of the innate immune system, can be long-lived. The three primary phagocytic cells in the body are neutrophils, macrophages, and dendritic cells. Neutrophils are the 'first responders' of the immune system. They rapidly infiltrate sites of SARS-CoV-2 infection and begin to phagocytose (*i.e.* consume or internalize) SARS-Cov-2 particles. The neutrophils, which are short-lived, then recruit macrophages and dendritic cells to the site of infection. Note that dendritic cells also reside at strategic sites of infection where they can immediately begin to phagocytose SRAS-CoV-2. The macrophages and dendritic cells are much larger than neutrophils and can phagocytose relatively large quantities of the virus and can be relatively long-lived. One of the reasons for this is because these two cell types are critical for activating T cells and B cells, which are the key effectors against viral infections. Phagocytosis of SARS-CoV-2 is a mechanism to kill and remove the virus from the body and to activate other immunological effector cells. As such, these can be a source of SARS-CoV-2 genomes that could be amplified by a RT-PCR test. However, these genomes would not have the potential to cause COVID-19. Persistence of whole or partial genomes that are not associated with infectious particles is well-documented for a variety of viruses, including measles[6], Middle East respiratory syndrome-coronavirus[7], and other coronaviruses[8].

A very recent scientifically peer-reviewed article argued that a reasonable cut-off for cycle numbers for good-quality RT-PCR tests for SARS-CoV-2 is **thirty-four**[9]. However, most RT-PCR tests for SARS-CoV-2 exceed 34 cycles[10]. For example, Public Health Ontario runs the test at 40 cycles. Their definition of a negative result is if there was no fluorescent signal detected at the end of the full 40 cycles. Any signal detected at the end of 38 cycles is declared to be a positive case. Remarkably, if they detect the viral genome between 38 and 40 cycles, they define the result as a 'probable case' for public health reporting.

Jonathan Gubbay, a medical microbiologist with Public Health Ontario, has been quoted on their website as saying the following: "In Ontario, we use PCR as the gold standard of testing for COVID-19 because it is able to successfully detect tiny amounts of the virus (sensitivity) with a low chance for error (accuracy) compared to other types of lab tests."[11]. The problem is that PCR tests do not represent gold standard assays for determining if potentially infectious viruses are present. Instead, the gold standard assay for this is the inoculation of cultured cell lines and then looking for evidence of infection (*e.g.* cytopathic effect, which means killing of cells[12]. An *in vitro* biological assay like this can then be used to correlate Ct values with infectivity of SARS-CoV-2. However, this type of gold standard functional test has not actually been standardized to date in Canada. Interpreting the RT-PCR test is challenging, to say the least, without a functional test to compare it to. Of particular concern in the context of the high cycle numbers being used by labs such as those at Public Health Ontario (*i.e*. 40 cycles, with 38 being defined as 'positive'), is the fact that several studies have been conducted to determine the highest Ct value at which SARS-CoV-2 could be successfully cultured in cells. The results were 25[13], 26[14], 22-27[15], 30[16]. This suggests that tests with CT values above 22-30 are almost certainly not indicative of the presence of replication-competent SARS-CoV-2. The conclusion is that it is erroneous to declare samples with high Ct values, especially those above 30, as being positive for infectious SARS-CoV-2. It was even concluded in a study by La Scola B, *et al*., concluded that patients testing 'positive' with Ct values above 33-34 could likely be discharged from hospitals[17]. This means that a very large but unknown number of positive cases reported in Ontario were likely not true positives.

RT-PCR-based testing in Ontario is not standardized. Across the province labs use different sample preparation methods, protocols, and gene targets. Variability in CT values (up to 8 cycles). This has prompted Public Health Ontario to discourage the reporting of Ct values <35 alongside test results. Indeed, Ct values <35 are only available upon special request[11].

The types of specimens and the quality of their collection can Influence the results of RT-PCR tests. Public Health Ontario recommends this for sample collection for use with the RT-PCR assay: "The gold standard for sample collection method is the nasopharyngeal swab, a swab inserted deep into a person's nose. However, other sample types exist including combinations of a nose and throat swab and also saliva samples.".[11] This is of concern because the United States Centres for Disease Control and Prevention "does not recommend NAATs that use oral specimens (*e.g.,* saliva) for confirmatory testing and instead suggests the use of specimens that are considered optimal for detection, such as nasopharyngeal, nasal mid-turbinate, and anterior nasal swabs."[18].

It is important to note that the problems associated with laboratory-based RT-PCR assays for the detection of SARS-Cov-2 are likely worse for point-of-care tests that rely on similar technology. Indeed, the United States Centres for Disease Control and Prevention acknowledge that "Sensitivity varies by test, but laboratory-based NAATs generally have higher sensitivity than point-of-care tests or tests that can be used anywhere."[18]. Further, the United States Centres for Disease Control and Prevention and the United States Food and Drug Administration note the following limitations of RT-PCR tests for SRS-CoV-2: 1. The presence of viral RNA in the sample might not indicate the presence of infectious virus, 2. The presence of viral RNA does not necessarily imply that SARS-CoV-2 is the causative agent of COVID-19, 3. The test cannot rule out diseases caused by other bacterial or viral pathogens, 4. The test is not

suitable for screening blood and blood products for the presence of SARS-CoV-2, 5. If the virus mutates in the predetermined target region, the test is invalid[19].

6. 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 disease. Indeed, we are all 'asymptomatic carriers' in the sense that we harbor vast numbers of bacteria and viruses in our bodies. However, these normal microbiomes usually do not cause us any disease, unless we become immunosuppressed or '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 that is infected with the virus but fails to develop COVID-19.

Viral culture studies suggest that pre-symptomatic individuals can potentially shed infectious SARS-CoV-2 one to two days before the onset of symptoms and continue to be infectious up to seven days thereafter[20]. However, a study of the prevalence of SARS-CoV-2 in ~10 million people in Wuhan, China found no evidence of asymptomatic transmission[21]. 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"[22]. 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"[23].

On its own, a positive result on a PCR test to detect SARS-CoV-2 is insufficient to diagnose COVID-19. 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 a successful immune response and may have remnant viral particles of partially degraded viral genetic material inside relatively long-lived phagocytic cells that have killed the virus. 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 COVID-19, the infection would also have to be associated with expected signs and/or symptoms. The latter is known as a clinical diagnosis and would be based on evaluation by a physician, in conjunction with the test results. A gold-standard test for infectivity of a virus is a cell-based functional assay that determines the potential to cause cell death. However, such an assay is not in routine use in Canada. The absence of a test of the infection-potential of a virus 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 would be taken out of the hands of physicians and placed into the hands of technicians employed by testing laboratories.

Positive PCR tests for SARS-CoV-2 in asymptomatic people are often based on high Ct values, which, in and of themselves, raise the question of whether these individual harbors infectious viral particles. The low prevalence of positive RT-PCR tests in asymptomatic people often does not differ much from the false positive rate. These issues combined with 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[24].

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[25].

Conclusion: Testing of asymptomatic people for the presence of portions of the SARS-CoV-2 genome does not make medical nor economic sense. Positive test results cannot be interpreted in a clinically meaningful way. Also, there is no substantial evidence to suggest that people who are asymptomatic represent a substantial risk of causing COVID-19-related hospitalizations or deaths in others.

7. Individuals Who Had COVID-19 Cannot Re-Transmit the Virus

When people get infected with a respiratory pathogen, their immune system detects the virus as something that is dangerous and worth responding to. Rapid innate immune responses provide early effector mechanisms to being clearing the virus from the body. The innate arm of the immune system will also induce an adaptive immune response. The primary effectors against viruses in the adaptive arm of the immune system are cytotoxic T cells that can kill virally infected cells to prevent them from serving as a 'virus-production factory', and B cells, which can produce antibodies to neutralize the virus and prevent it from entering cells. The most notable characteristic of the adaptive immune response is that it results in the generation of immunological memory. This allows a host to respond much more rapidly and to a much greater magnitude when re-exposed to the same pathogen. The result is that the virus gets cleared so rapidly that there is usually no disease.

Note that some non-immunologists have erroneously concluded that memory conferred by natural infection with SARS-CoV-2 is not long-lasting. However, this has been based on assessments that show declining concentrations of virus-specific antibodies. The antibodies are produced by B cells. The antibodies are merely proteins in circulation with limited half-lives. They will be cleared from circulation over time. The relevant measure of memory is detection of memory B and T cells. A memory B cells can rapidly initiate the production of massive quantities of antibodies upon re-exposure to the pathogen.

Several published studies have shown that the immune response against SARS-CoV-2 infections is robust, effective, broadly targets multiple components of the virus and confers memory that lasts at least as long this aspect has been able to be studied within the context of a novel pandemic[26, 27, 28, 29, 30, 31].

Conclusion: The scientific evidence demonstrates that immune responses following infection with SARS-CoV-2 are protective and long-lasting. There is no evidence that people who previously tested positive

for SARS-CoV-2 represent a substantial risk of causing COVID-19-related hospitalizations or deaths in others.

8. SARS-CoV-2 Variants of Concern

Many viruses mutate over time. This includes coronaviruses. Indeed, these viruses have an error-prone mechanism of copying their genome. This provides a strategy to adapt to novel environmental pressures. Of concern for SARS-CoV-2 is the potential for randomly generated mutants to sufficiently alter the structure of their spike protein to be able to evade the narrowly conferred spike protein-specific immunity conferred by all of the first-generation COVID-19 vaccines while maintaining the ability to infect cells. Since the beginning of the pandemic, large numbers of mutant viruses have been identified. However, three core lineages of the variants are of current concern[32]: 1. B.1.1.7, also known as the UK variant[33], 2. B.1.351, also known as the South African variant[33], 3. P.1, the Brazilian variant[34]. SARS-CoV-2 from the B1.351 lineage can largely bypass the immunity conferred by AstraZeneca's COVID-19 vaccine. However, the Pfizer and Moderna vaccines remain effective against all three lineages for the VOCs.

Some of the VOCs seem to be associated with more efficient spreading between people. This is likely due, at least in part, to the increased affinity of their spike protein for the ACE2 molecule that SARS-CoV-2 uses to enter cells. However, there is no evidence that the current VOCs are associated with a higher incidence of severe or fatal COVID-19.

Importantly, naturally acquired immunity against SARS-CoV-2 has been shown to be both long-lasting and protective. Notably, this type of immunity would be expected to be particularly protective against emerging VOCs because it is very broad, meaning that it targets multiple components of SARS-CoV-2, with both T cells and antibodies induced as effector mechanisms. Indeed, evidence of the breadth of naturally acquired immunity has recently been published[4]. In contrast, current vaccine-induced immunity targets a single protein, with a strong bias towards antibody-mediated responses. Notably, the B.1.1.7, B.1.351, and P.1 variants of SARS-CoV-2 are of concern because of their altered spike proteins, particularly in the 'receptor binding domain' (*i.e.* the portion that binds to the ACE2 molecule on host cells), which is the primary target of neutralizing antibodies. So, although there is evidence of some monoclonal antibodies failing to recognize the spike protein in some VOCs and some convalescent sera (*i.e.* sources of antibodies) being less able to neutralize the VOCs, T cells can effectively recognize conserved regions of the spike protein as well as other viral proteins.

Since SARS-CoV-2 has shown such a propensity to mutate, it is reasonable to expect this virus will become endemic. Indeed, should a variant emerge that can completely bypass the spike-specific immunity conferred by the current vaccines, additional immunizations will be required with re-designed vaccines, especially for those without naturally acquired broad-based immunity.

Conclusion: The goal in Canada should not be to get everyone vaccinated per se. Instead, the goal should be to get as many Canadians immune to SARS-CoV-2 as possible. There are two ways to achieve this: 1. Vaccination, 2. Natural acquisition of immunity. The great news is that Canada might be closer to the natural acquisition of herd immunity than what was previously appreciated[4], likely due, in large part, to the ongoing spread of the virus after the implementation of ineffective masking and misguided

physical distancing policies that failed to account for the physics behind aerosol-mediated transmission of SARS-CoV-2. Like many other viruses, including other coronaviruses and influenza viruses, SARS-CoV-2 will likely become endemic, meaning that we may encounter new versions of the virus on a regular and long-term basis. As such, it is imperative that we learn to live with SARS-CoV-2 rather than attempting to hide from it; just like we have done with the other respiratory pathogens that we have accepted as a trade-off for living our lives outside the confines of lockdowns.

9. Masking Lacks Rationale in the Context of SARS-CoV-2 Spreading via Aerosols

It is now widely recognized that SARS-CoV-2 is effectively spread via aerosols coming from the respiratory system[35, 36, 37, 38, 39]. A pulmonary (*i.e.* lung-derived) aerosol is a suspension of fine water droplets suspended in exhaled air. Many people who wear glasses will be familiar with these aerosols. Indeed, when a person exhales onto the lenses of their glasses to polish them with a cloth, the liquid being deposited is due to the condensation of the lung-derived aerosol. Also, these aerosols can be readily visualized when exhaling into cold air, which causes the fine droplets to condense (*i.e.* drop out of the gaseous phase). Indeed, this condensation effect of cold air minimizes the distance that respiratory aerosols can travel since the condensed water droplets are relatively large. However, in warm air these aerosols are invisible and can potentially travel long distances depending on the rate of ambient air flow. The masks in common use among Canadians (*e.g.* surgical and cloth masks) lack standardization, users are not required to undergo fit-testing, and even if these were done, they would still lack the ability to prevent the spread of aerosols. Low-cost masks do not seal properly around the face, with leaks commonly occurring around the nose and at the joints of the jaw. Due to simple physics in which air will follow the path of least resistance, most exhaled and inhaled air will leave and enter via these gaps in the masks. This is further exacerbated by anything that increases these gaps. An example would include a beard, which would separate the mask from the chin, thereby replacing the mask material with a coarse-haired filter with massive pore sizes relative to the size of a virus. Anyone who wears glasses and a mask can attest to the venting issue around the nose, as it often causes the lenses to fog. It seems illogical to force a person's pulmonary exhaust to flow over their eyes, since this is a known route of infection for SARS-CoV-2 and could, therefore, potentiate spreading of the infection in an individual. It was shown that ocular tissues express entry receptors for SARS-CoV-2 and conjunctivitis is common among people diagnosed with COVID-19, sometimes even preceding the onset of signs and symptoms of respiratory distress[40]. As such the eyes could potentially serve as both a portal of entry and a source of person-to-person transmission.

Air venting past the ears, which is the other common location of leakage with low-cost masks, means that aerosols are generally directed behind a person. However, public health policies usually recommend that people turn away from other individuals if they must pass within proximity. If anything, this simply increases the chance of someone being exposed to pulmonary aerosols with a higher flow rate. The principles of distributing pulmonary aerosols over the eyes and behind a person also holds true for face shields. This highlights how poorly thought out masking policies are. Even if low-cost masks were properly sealed around the neck and face, SARS-CoV-2-laden aerosols and still readily pass through the relatively large pore sizes of the filtering material. Indeed, a study published in 2019 found that the low-cost masks had pore sizes ranging from 80 to 500 µm in diameter[41]. Water droplets that come from the lungs are defined as 'large droplets', 'small droplets' or 'droplet nuclei' and range in size from >60

µm, 10-60 µm, and <10 µm in diameter, respectively[42]. Coughs and sneezes will discharge droplets of all sizes. However, regular breathing and talking primarily discharges small droplets and droplet nuclei. Notably, SARS-CoV-2 has a diameter of only ~1 µm. This means that virus-laden droplets in pulmonary aerosols will have a maximum diameter of ~62 µm, with the vast majority being much smaller (remember that the pores in low-cost masks are ≥80 µm. As such, low-cost masks fail to stop the spread of SARS-CoV-2. One of the biggest challenges in relaying the science is the 'invisibility' of the microbial world. To place this into a context that is easier to picture, this would be akin to thinking that a person is locked inside a house when the walls have huge gaping holes (*i.e.* the leakage points were there proper seals are lacking) and the front door is open (*i.e.* representing the pore size of a mask). The reality of this scenario is that the person is free to come and go as they wish.

Also, aerosols from the lungs can travel beyond two meters and the directionality will be dictated by air currents[43]. Although the viral load that a person would be exposed to from aerosols would decrease with distance, the long-range potential of aerosols highlights the arbitrariness of 2-meter physical distancing policies. Also, buildings with poor ventilation, which encompasses most buildings in Canada, facilitate the build-up of aerosols over time, which further confounds the value of two-meter distancing[44].

Demonstration of inadequate sealing of low-cost masks around the face are shown in figures 3 and 4. The relative size of SARS-CoV-2-laden water particles and pores of low-cost masks is shown inf figure 5. Figure 6 shows how readily aerosols can pass through masks, even when having to pass through five three-ply surgical masks. Figure 7 shows the personal protective equipment required to safely work with containment level-3 pathogens such as SARS-CoV-2

Figure 3: The leakiness of low-cost masks.
These are screen shots taken from a video showing cold-mediated condensation of a pulmonary aerosol when exhaling while wearing two three-layer surgical masks that had the metal bar pinched over the nose. (A) at the end of the inhalation. (B) During exhalation aerosol exiting the lungs is condensing in the cold air. (C) At the end of the exhalation, the profound amount of aerosol released from the mask after a single exhalation is evident.

(A)

(B)

Figure 4: The leakiness of low-cost masks.

These are screen shots taken from a video showing fogging of eyeglasses when wearing a three-layer surgical mask. (A) While inhaling, the metal bar over the nose is pinched to maximize the 'seal'. (B) During exhalation aerosol exiting the lungs is condensing on the lenses of the glasses, causing them to fog.

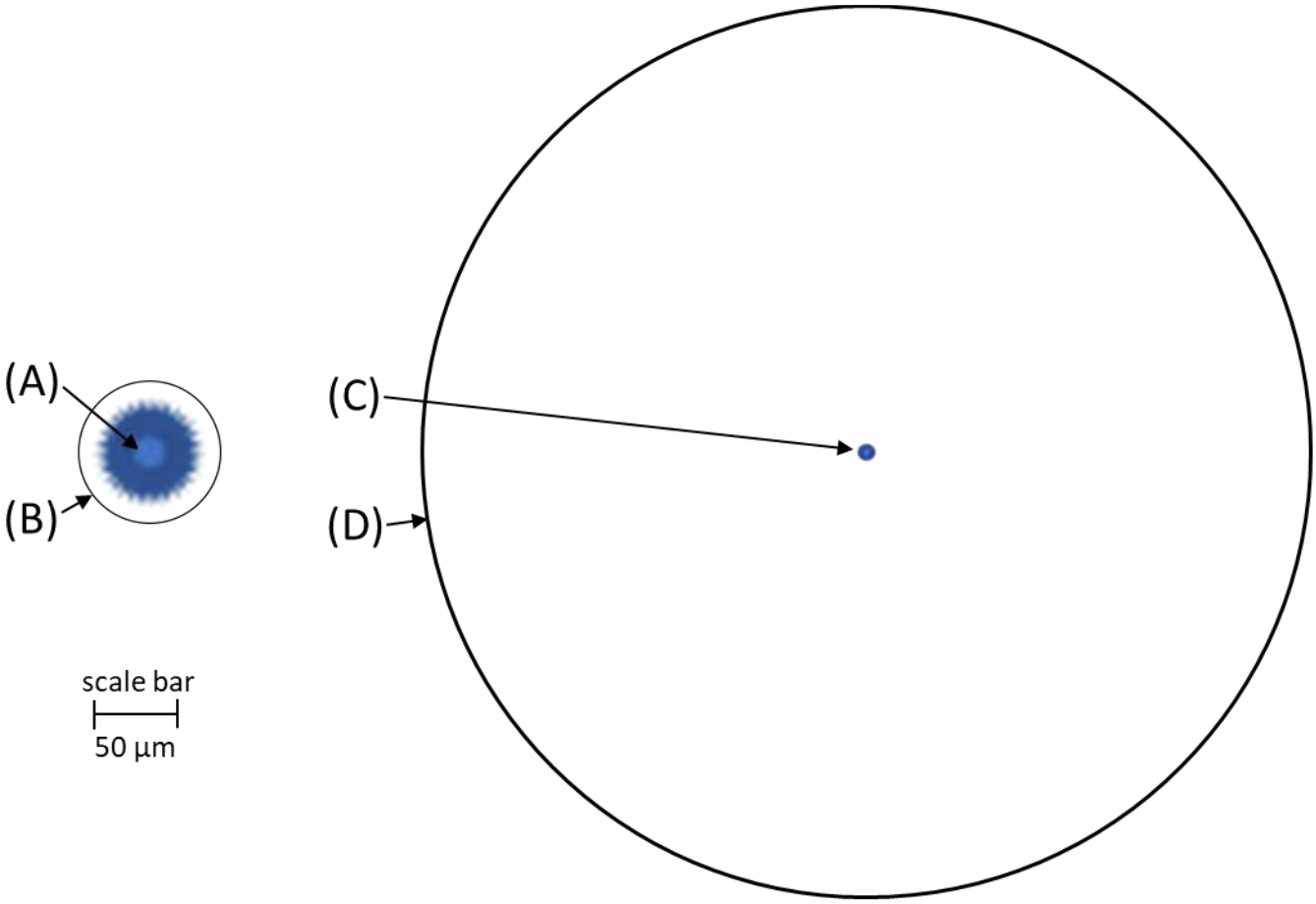


Figure 5: The relative size of SARS-CoV-2-laden water particles and pores of low-cost masks. SARS-CoV-2 particles have a diameter of ~1 µm. Water droplets in air exhaled from the lungs can be classified into three sizes. Large droplets are >60 µm, small droplets are 10-60 µm in diameter, and droplet nuclei are >10 µm in diameter. Individuals who are not coughing or sneezing will exhale an aerosol that consists almost entirely of droplet nuclei and small droplets. (A) The largest of the small droplets that are laden with SARS-CoV-2 will have a diameter of ~62 µm. (B) The smallest pore size of a low-cost mask is ~80 µm. (C) The largest of the droplet nuclei that are laden with SARS-CoV-2 will have a diameter of ~12 µm. (D) The largest pore size of a low-cost mask is ~500 µm.

= virus-laden droplet = pore in a low-cost mask

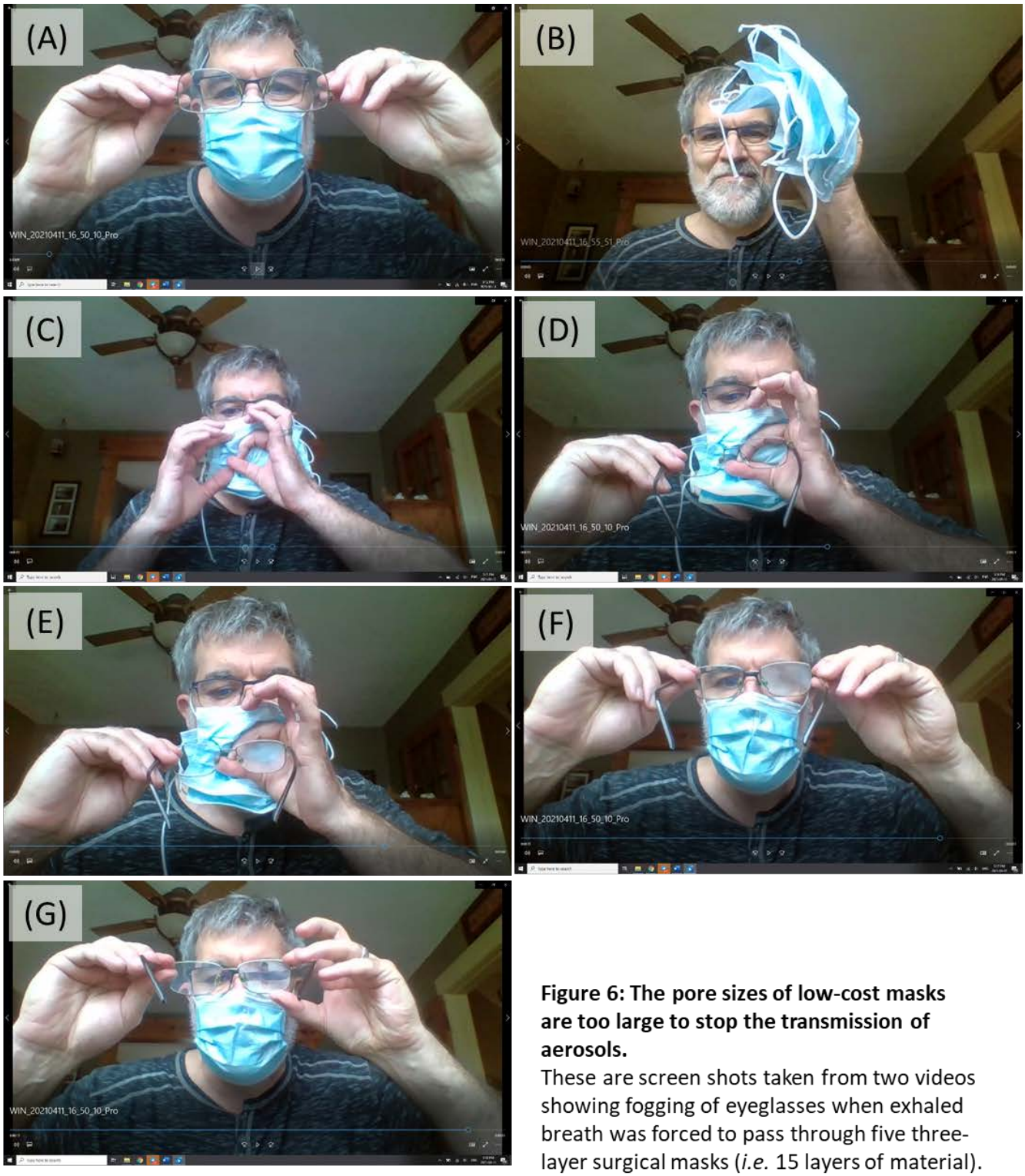


Figure 6: The pore sizes of low-cost masks are too large to stop the transmission of aerosols.

These are screen shots taken from two videos showing fogging of eyeglasses when exhaled breath was forced to pass through five three-layer surgical masks (*i.e.* 15 layers of material). (A) This image shows the clarity of the eyeglasses when no fogging is present. (B) Five surgical masks were placed sequentially over the mouth. (C) A ring was made with the finger and thumb to apply pressure around the lips and seal the mask so the only place exhaled air could exhaust was through the five three-ply surgical masks. (D) Beginning to exhale through the five masks. (E) Near the end of exhalation. (F) Post-exhalation evidence of fogging is present on the lens of the eyeglasses to the right of the image. (G) So much aerosol had condensed on the lens of the eyeglasses that a cross pattern could be drawn in the liquid.

Figure 7: Personal protective equipment required to safely work with containment level-3 pathogens such as SARS-CoV-2.

SARS-CoV-2 is defined as what is known as a 'containment level-3 pathogen' by the Public Health Agency of Canada. The personal protective equipment that they require scientists to use to ensure safe handling of SARS-CoV-2 typically includes the following: 1. Handling of SARS-CoV-2 can only be done inside a certified containment level-3 facility. 2. Anything containing SARS-CoV-2 can only be opened inside a biological safety cabinet, which is designed to provide a barrier between the virus and the scientist. 3. The scientist must wear a full body suit, including shoe covers and gloves. A head covering with a clear face shield and that seals around the neck and face must be worn. The head covering is connected by a tube that is attached to a pump that delivers filtered air into the head covering, thereby maintaining positive pressure (*i.e.* ambient air cannot flow into the head covering). Personal protective equipment that is known to prevent the wearer from being infected with a containment level-3 pathogen, such as SARS-CoV-2, is shown in figure 3.

A person wearing a low-cost mask would not be allowed to enter a containment level-3 facility due to a profound lack of protection. There is, therefore, a large discrepancy between what truly protects an individual from SARS-CoV-2 and the public health messaging surrounding cloth and surgical masks, which falsely implies a substantial amount of protection.

There are potential harms associated with long-term masking. Not only do masks fail to efficiently stop the spread of COVID-19-laden aerosols, in some cases they may cause harm. Although the pores sizes of low-cost masks are too large to prevent the passage of viruses, bacteria are much larger, as are dust and other environmental particles. Long-term prevention of exposure to the microbial world and natural environment in children has been associated with an increased incidence of allergies, asthma and autoimmune diseases based on an immunological principle known as the 'hygiene hypothesis' (see section 10 for the details). Another potential harm of wearing masks is the psychological effect it has on adherence to public health protocols. The false sense of security that a mask confers causes many people to become less aware of or less concerned with the practice physical distancing. Additional problems include things like blunting social cues by preventing reading of facial body language, muffling speech (a particular concern for individuals with pre-existing speech disorders) and preventing lip-reading.

Overall conclusion: Once one realizes that SARS-CoV-2 can pass through low-cost masks and travel >2 meters and sometimes much further on 'droplet nuclei' in pulmonary aerosols, it becomes readily apparent that the policies of mask-wearing and two-meter physical distancing are not adequately protective against the spread of SARS-CoV-2. If low-cost masking combined with only two-meter physical distancing does little to prevent the spread of SARS-CoV-2, it would be expected that a relatively high proportion of Canadians would have naturally acquired immunity to the virus over the past year. Indeed, this is precisely what was found in a recently published study that showed that the majority of apparently healthy adults in British Columbia have evidence of naturally acquired immunity[4].

10. Prolonged Isolation and Masking of Children Can Cause Irreparable Harm to Their Immune Systems

There is an immunological concept known as the 'hygiene hypothesis'[45, 46]. The core of the idea is that we live in a microbial world; an environment full of bacteria, parasites, viruses, and fungi. Further, our interactions with these microbes after birth are extremely important to educate our immune systems to function properly. When we are born, our immune systems are still maturing. Sally F. Bloomfield, *et al.*, described the concept of immunological development post-birth well in their published study: "The immune system is a learning device, and at birth it resembles a computer with hardware and software but few data. Additional data must be supplied during the first years of life, through contact with microorganisms from other humans and the natural environment."[47]. The immune system has many potent mechanisms for killing pathogens. It needs to be carefully regulated to ensure it can eliminate dangerous microbes from the body without causing excessive harm to our own tissues[48]. The interactions we have with our environment early in life are essential for our immune systems to learn to differentiate between safe versus dangerous disease-causing microbes. Our bodies are covered inside and out with micro-organisms that, under normal circumstances, happily co-habitate with us and promote a healthy immune system. If infants, toddlers, and young children are not sufficiently exposed to the microbial world around them, their ability to properly regulate their own immune systems can be compromised[49]. As per the computer analogy, the data that get uploaded into the software are incomplete. This 'lack of data' can cause the immune system to struggle to differentiate between what is truly dangerous and should be eliminated, and what is not dangerous and should not be responded to. In plain terms, this scenario can promote allergies[49], asthma[50], and autoimmune diseases[51].

Scientists are moving away from using the term 'hygiene hypothesis' because it could be misinterpreted as meaning that hygiene is not good for a developing immune system. This is not true. Moderation and targeted hygiene would be best. Specifically, we need to practice proper hygiene in the context of trying to prevent infectious diseases, but still allow our immune systems to interact with safe and essential microbes. Many middle-income countries have seen an epidemic of allergic diseases over the past several decades[52]. This is, in part, due to increased urbanization which is akin to living in 'concrete jungles' with reduced exposure to the natural environment[53]. Societies have also adopted behaviours that limit exposure to microbes[54]. Overuse of antibiotics exacerbates the problem by non-discriminately eliminating 'good' microbes along with the 'bad' ones[55].

Here are important conclusions stated in a recent article: "Evidence suggests a combination of strategies, including… increased social exposure through sport, other outdoor activities, less time spent indoors… may help… reduce risks of allergic disease. Preventive efforts must focus on early life"[47].Now think about government-led reactions to the pandemic caused by SARS-CoV-2. The policies that have been enacted contradict the recommendations to ensure proper immunological development in children. Data suggest that SARS-CoV-2 does not represent a greater danger to children than the annual flu[56, 57]. Yet social interactions of children have been severely limited, including removing them from schools. Most of their extracurricular activities have been cancelled and they have been discouraged from leaving their homes. Even the air they breathe is often filtered by masks and there is prevalent use of hand sanitizers. In short, most COVID-19 policies have maximized the potential for children to develop dysregulated immune systems. As a viral immunologist, I was not overly concerned about this in the early stages of the pandemic when 'temporary' measures were put in place to 'flatten the curve' depicting daily cases of COVID-19[57]. However, many governments now seem to have adopted a zero-tolerance policy for COVID-19, even though they have not declared this. Consequently, the youngest among us have had their immunological development compromised for one year and growing. An

unfortunate and under-appreciated long-term legacy of Canada's reaction to the 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. Interestingly, it has been noted that the new messenger RNA-based COVID-19 vaccines[58] that are packaged inside liposome nanoparticles are contraindicated for some individuals with a propensity towards severe allergic responses[59]. Ironically, we may be setting up many of our youth to develop hypersensitivities to this vaccine technology when they are older.

Notably, some of Ontario's polices take the isolation of children to an extreme. This includes orders to place young apparently healthy children into isolated quarantine for fourteen consecutive days if they have schoolmate test positive for SARS-CoV-2. As an example, see the order presented to Dr. Byram Bridle to place his eleven-year-old son with special needs (Down Syndrome) into solitary quarantine (appendix 1).

Conclusion: Raising children during the pandemic has largely occurred in isolated and highly sanitized environments that are unprecedented in extent and duration. These kids are at greater risk of developing hypersensitivities and autoimmune diseases than anyone before them. The immune systems of children are not designed to develop in isolation from the microbial world. To minimize further life-long damage to their immune systems, masking and isolation policies must be rescinded as soon as possible.

11. Early Treatment Options that Represent Reasonable Alternatives that Would Preclude the Enactment of Emergency Orders and the Emergency Use Authorization of Experimental Vaccines

As a researcher with funding to develop COVID-19 vaccines, I have been monitoring developments with respect to early treatment options very closely. These include the use of hydroxychloroquine, vitamin D3, and ivermectin. Although each of these appear to be valid, safe, and effective treatment options, due to time constraints, I have focused over the past year on careful examinations of the growing body of literature but using ivermectin as an effective early treatment for COVID-19. I was originally somewhat concerned that my vaccine research could be impacted in the absence of their emergency use authorization. Indeed, I have been very surprised that emergency use authorization of experimental vaccines has remained in place despite an avalanche of data that strongly supports the safe and effective use of ivermectin to treat COVID-19 when the drug is administered early in the disease presentation and is supervised by a physician. To demonstrate how much evidence there is in support of ivermectin for the treatment of COVID-19, I have attached an exhaustive list and summary of relevant references in appendix 2.

Executive Summary

- Whereas vaccines are effective at preventing disease in an otherwise healthy individual, alternative treatments are urgently required for patients already infected with SARS-CoV-2 virus. To date, this has consisted of keeping patients alive while they build up their own immunity to fight the disease.
- In a proof-of-concept *in vitro* study, it was shown that the drug ivermectin inhibits the replication of SARS-CoV-2.

- Subsequent clinical studies in over 22 countries had demonstrated using TaqMan RT-PCR that the replication of the virus was indeed reduced, collating with improvements in the patient's medical condition.
- Shorter hospitalization and lower mortality rates were observed in patients treated with ivermectin when compared to the placebo group.
- Ivermectin was shown in clinical studies to be effective when administered prophylactically to human subjects.
- Ivermectin has been used for treating patients for around 40 years, with a proven safety record.

Introduction

Whereas vaccines are effective at preventing disease in an otherwise healthy individual[60], nothing is better at fighting disease than utilizing a person's own immune system. However, once someone is already infected with the disease, a vaccine would be of no use. Therefore, alternative treatments are urgently required for patients already infected with SARS-CoV-2. To date, this has consisted of keeping patients alive while they build up their own immunity to the disease. Health Canada has not authorized any drugs to prevent, treat or cure COVID-19 in patients, except for Veklury (remdesivir) from Gilead Sciences Canada Inc., to treat COVID-19 in patients with pneumonia requiring supplemental oxygen[61]. However, there is still a gap that needs to be filled to effectively treat patients infected with SARS-CoV-2. It is recommended that ivermectin should be considered as a suitable candidate to fill the treatment gap for early out-patient treatment for COVID-19, and as a prophylactic, during the vaccine rollout period.

Ivermectin – Proof-of-Concept

Using TaqMan RT-PCR, Caly *et. al*. (2020) demonstrated that ivermectin effectively inhibited replication of SARS-CoV-2 *in-vitro* by blocking the ability of IMPα/β1 to bind to the coronavirus cargo protein in the cytoplasm, therefore, preventing it from going through the nuclear pore complex (NPC) and entering the nucleus (figure 8).

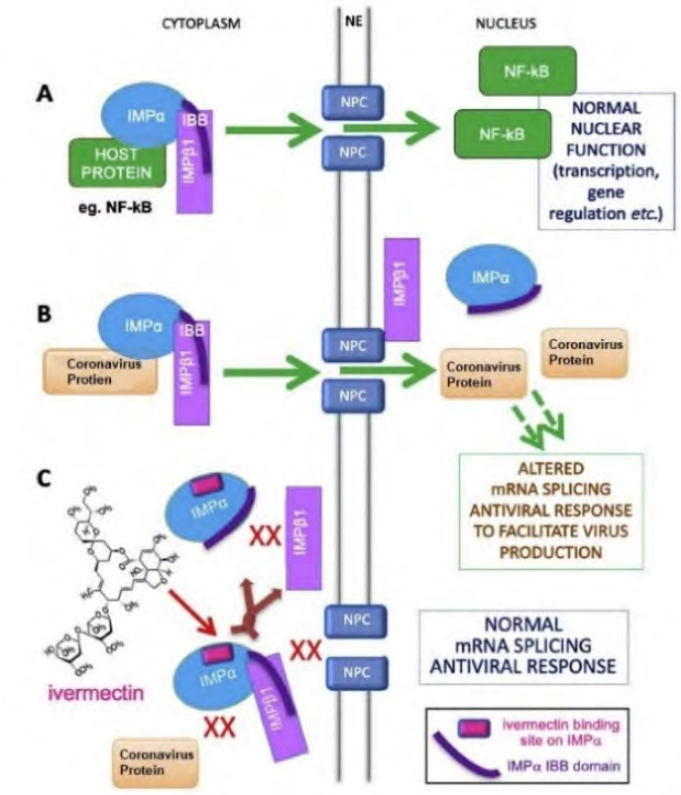


Figure 8. Schematic of ivermectin's proposed antiviral action on Covid-19

- **A. Normal cell function**
- **B. Cell infected with Covid-19**
- **C. Ivermectin initiating an antiviral response**

(Modified from: Jans DA and Wagstaff KM., The broad spectrum host-directed agent ivermectin as an antiviral forCovid-19?: https://doi.org/10.1016/j.bbrc.2020.10.042)

The authors noted a 93–99.8% decrease in viral RNA for ivermectin versus control at 24 hours both in the released and cell-associated viral RNA, respectively. Likewise, they reported that by 48 hours there was a >5000-fold decrease of viral RNA, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 hours. Consistent with this, no further reduction in viral RNA was observed at 72 hours. Under the conditions tested, the IC_{50} of ivermectin treatment was determined to be approximately 2 µM. Ivermectin has an established safety profile for human use and is approved both by the US FDA and Health Canada. It's been used for a number of treatments since the 1980s, including treatments for intestinal infections, lice, scabies, and river blindness. Now that this drug has been found to inhibit replication of SARS-CoV-2 *in vitro*, it was not surprising that clinical studies were subsequently initiated throughout the world.

Ivermectin – Clinical Trial Data

Currently, there are approximately 70 clinical trials worldwide evaluating the clinical benefit of ivermectin to treat or prevent Covid-19. However, these trials include variations on dosing regimens, combination therapies, and prophylactic protocols[62]. To illustrate these differences, the results of two clinical trials using different dosing regimens will be described, focusing specifically on the dosing regimen, prior to

summarising the results from a meta-analysis of clinical trials of ivermectin to treat infection with SARS-CoV-2.

Clinical trial in Bangladesh[63]

This randomized, double-blind, placebo-controlled trial was conducted to determine the rate of viral clearance, and safety of ivermectin in adult patients with COVID-19. The study was comprised of three groups of 24 patients each:

Group 1: Oral ivermectin alone (12 mg once daily for 5 days)

Group 2: Oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on Day-1, followed by 100 mg every 12 h for the next 4 days),

Group 3: Placebo control group.

The Inclusion/exclusion criteria, as well as demographics, etc. of the patients enrolled are outlined in their publication. In this study, although there was a significant difference in the rate of viral clearance in favour of ivermectin, there was no significant difference in the patent's clinical recovery, or the time at which the patient was in hospital. However, this study does concur with the *in-vitro* proof of concept results.

Clinical trial in Egypt[64]

This was a large multicenter double blind randomized controlled clinical trial (RCCT) study design was carried out on; 400 symptomatic patients, and 200 human subjects not infected with the Covid-19 virus. The study comprised of 6 groups of 100 patients/subjects per group:

Group 1: 100 patients with mild/moderate COVID-19 received a four-day course of Ivermectin at 0.4mg/kg body weight, maximum 4 tablets (6mg/tablet), once daily dose.

Group 2: 100 patients with mild/moderate COVID-19 as a control group received hydroxychloroquine (400 mg every 12 hours for one day followed by 200 mg every 12 hours for five days).

Group 3: 100 patients with severe COVID-19 received a four-day course of Ivermectin at 0.4mg/kg body weight, maximum 4 tablets (6mg / tablet), once daily dose.

Group 4: 100 patients with severe COVID-19 as a control group received hydroxychloroquine (400 mg every 12 hours for one day followed by 200 mg every 12 hours for nine days).

Group 5: 100 health care (pre-exposure) and/or household (post-exposure) patients' contacts received a prophylactic dose of ivermectin 0.4mg/kg single oral dose before breakfast to be repeated after one week in addition to personal protective measures (PPM).

Group 6: 100 health care and or household patients' contacts stick to the PPM only as a control group.

The Inclusion/exclusion criteria, as well as demographics etc. of the patients enrolled are outlined in their publication. This study had also demonstrated a significant difference in the rate of viral clearance in favour of ivermectin. However, unlike the previous study, the patent's prognosis and the number of days spent in hospital was also statistically significant, in favour of the ivermectin treatment (table 2).

Table 2. Summary of outcomes after 4 days treatment with ivermectin

	Ivermectin	Control	Ivermectin	Control	P value
Prognosis No. (%)	**Mild / moderate**		**Severe**		
Improved Progressed Died	99(99%) 1(1%) 0(0%)	74(74%) 22(22%) 4(4%)	94(94%) 4(4%) 2(2%)	50(50%) 30(30%) 20(20%)	< 0.001
Hospital stays (days) mean±SD	5±1	15±8	6±8	18±8	< 0.001
RT- PCR (days) mean±SD	5±1	10±4	6±1	12±4	< 0.001

Extracted from: Elgazzar, et. al., Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic: https://doi.org/10.21203/rs.3.rs-100956/v3

The study also demonstrated that ivermectin was effective at preventing the disease in normal subjects. Therefore, it can be used prophylactically (table 3).

Table 3. Comparison between Group V PPE plus ivermectin prophylaxis versus Group VI PPE only as a control group

	Group 5 Ivermectin	Group 6 Control	Test	P- value
Confirmed infected subjects by RT-PCR	2(2%)	10(10%)	X^2=5.6738	< 0.05

Extracted from: Elgazzar, et. al., Efficacy and Safety of Ivermectin for Treatment and prophylaxis of COVID-19 Pandemic: https://doi.org/10.21203/rs.3.rs-100956/v3

In both studies, the dosages of ivermectin used were well tolerated with no serious adverse side effects.

The main difference between both studies i.e. [63]and [64] was the dosage of ivermectin administered to patients infected with SARS-CoV-2, 0.2mg/kg/day versus 0.4mg/kg/day with food, respectively. When comparing both studies, the difference as to whether treatment was effective or not was dependent upon the dosage given. Although in the Ahmed *et. al*. study, the rate of viral clearance was in favour of ivermectin, it was not to the same extent as that observed in the Elgazzar *et. al*. study (Figure 8).

Figure 8. Viral clearance vs. dosage – A comparison between the Ahmed, *et. al*. and Elgazzar *et. al*. studies.

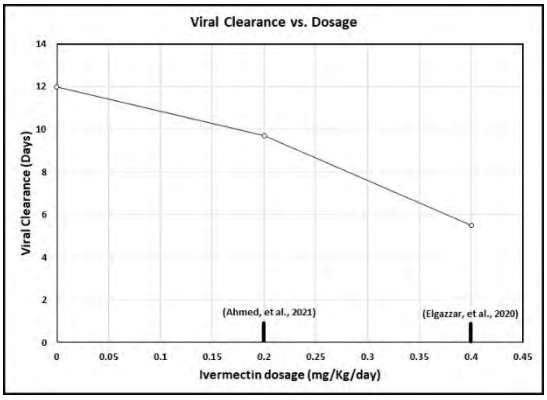


Figure 8 also shows that the rate of viral clearance is proportional to dose, further validating the *in vitro* model, that ivermectin inhibits viral replication.

Meta-analysis of clinical trials of ivermectin to treat Covid-19 infection

Ivermectin, a widely available generic drug, is currently re-purposed for the treatment of patients with the COVID-19 virus, being evaluated in clinical trials throughout the world. So, the first question one must ask is: Do we have enough clinical evidence to support the worldwide approval of ivermectin to treat

COVID-19? Although data from a single clinical trial may be considered unsuitable by Health Canada, the combined data from all of the available clinical trials to date should be large enough to reliably assess the clinical efficacy of ivermectin, and that is where the meta-analysis of the available clinical trials comes in. The second question is: What are going to be our endpoints?

For patients infected with SARS-CoV-2, it would be:

1. PCR negativity
2. Clinical recovery
3. Hospitalisation
4. Survival

For the subjects involved to assess the prophylactic properties of ivermectin, it would be the number of people subsequently infected with SARS-CoV-2 as a percentage of the total. Comparing the ivermectin treated with the control group.

Meta-analysis was performed by Front Line Covid-19 Critical Care Alliance (FLCCC) using data from multiple clinical trials to determine the effectiveness of ivermectin to treat patients infected with SARS-CoV-2.[65]

This group had performed meta-analysis on 23 studies. The report is complete and was successfully to the US National Institute of Health (NIH) for consideration. The section of their conclusions as it appears in the report is as follows:

"The FLCCC recommendation is based on the following set of conclusions derived from the existing data, which will be comprehensively reviewed below:

1) Since 2012, multiple in vitro studies have demonstrated that ivermectin inhibits the replication of many viruses, including influenza, Zika, Dengue and others (Mastrangelo *et al*., 2012; Wagstaff *et a*l., 2012; Tay *et al*., 2013; Götz *et al*., 2016; Varghese *et al*., 2016; Atkinson *et al*., 2018; Lv *et al*., 2018; King *et al*., 2020; Yang *et al*., 2020).

2) Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue via several observed and proposed mechanisms (Caly *et al*., 2020a).

3) Ivermectin has potent anti-inflammatory properties with in vitro data demonstrating profound inhibition of both cytokine production and transcription of nuclear factor-κB (NF-κB), the most potent mediator of inflammation (Zhang *et al*., 2008; Ci *et al*., 2009; Zhang *et al*., 2009).

4) Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses (Arevalo *et al*., 2020; de Melo *et al*., 2020).

5) Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients (Behera *et al*., 2020; Bernigaud *et al*., 2020; Carvallo *et al*., 2020b; Elgazzar *et al*., 2020; Hellwig and Maia, 2020; Shouman, 2020).

6) Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms (Carvallo *et al*., 2020a; Elgazzar *et al*., 2020; Gorial *et al*., 2020; Khan *et al*., 2020; Mahmud, 2020; Morgenstern *et al*., 2020; Robin *et al*., 2020).

7) Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients (Elgazzar *et al*., 2020; Hashim *et al*., 2020; Khan *et al*., 2020; Niaee *et al*., 2020; Portmann-Baracco *et al*., 2020; Rajter *et al*., 2020; Spoorthi V, 2020).

8) Ivermectin reduces mortality in critically ill patients with COVID-19 (Elgazzar *et al*., 2020; Hashim *et al*., 2020; Rajter *et al*., 2020).

9) Ivermectin leads to striking reductions in case-fatality rates in regions with widespread use (Chamie, 2020).[5]

10) The safety, availability, and cost of ivermectin is nearly unparalleled given its near nil drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered (Kircik *et al*., 2016).

11) The World Health Organization has long included ivermectin on its "List of Essential Medicines." (https://trialsitenews.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/; https://www.who.int/publications/i/item/WHOMVPEMPIAU201907)

Data from the meta-analysis report referenced in this briefing, were recently presented to the NIH as mentioned above. On January 14, 2021, the NIH Treatment Guidelines Panel upgraded their recommendation on the use of ivermectin for COVID-19. The NIH is making it an option for use in the treatment of patients with COVID-19. In addition, the meta-analysis report performed by the FLCCC has been accepted for publication by the American Journal of Therapeutics entitled: "FLCCC Meta-Analysis Evidencing Promise of Ivermectin as Treatment for COVID-19".

What is the status in Canada regarding the use of ivermectin for treating patients with COVID-19?

As stated above, the only drug that Health Canada has authorized with conditions is remdesivir for the treatment of patients with COVID-19. On November 20, 2020 the WHO issued a statement recommending against the use of remdesivir in patients with COVID-19 due to the observed lack of efficacy[66]. Despite this, Canada is continuing to use remdesivir as a treatment for those with severe late-stage COVID-19.

Conclusion: Having reviewed the scientific literature, the conclusion can be drawn that the data is such that Canada should include ivermectin for early out-patient treatment for COVID-19, and as a prophylactic, while people are being vaccinated. As far as integrity goes, multiple clinical trials from different countries saying the same thing, that the treatment works, both in the early and late stages of the disease. Principal Investigators on these studies were acting in good faith with no financial interests by the institutions carrying them out. The data from these trials are available for consideration[65], and there are clinical trials worldwide still ongoing. Ivermectin has been used to treat patients for around 40 years, has a proven safety record, off-patent, cheap, and available. Safely is not an issue since ivermectin has been approved for human use both in the USA and Canada. Ivermectin has never been withdrawn off the market for safety reasons. The dosages proposed for the treatment of COVID-19 for prophylaxes and out-patients is more than covered based upon the data from the Phase 1 ascending dose study in the NDA submission (US FDA, 2008), subsequently published in a peer reviewed publication (Guzzo, et al., 2002).

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