Court File No. CV-20-00652216-000

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Applicant/Respondent

AND

ADAMSON BARBECUE LIMITED
AND WILLIAM ADAMSON SKELLY

Respondents/Applicants

AFFIDAVIT OF EXPERT WITNESS Dr. Harvey Risch
sworn April 12, 2021

April 13, 2021

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1. My name is Doctor HARVEY RISCH, I live in New Haven, Connecticut, United States of America, and I have expertise in epidemiology.
2. My qualifications, employment and educational experiences support my expertise. I attach as Exhibit "A" to this affidavit, a copy of my *curriculum vitae.*
3. I was retained by the Respondents through an Engagement Letter dated March 26, 2021. I attach as Exhibit "B" to this affidavit, a copy of the signed Engagement Letter.
4. The Engagement Letter set out the nature of the opinion being sought and each issue in the proceeding to which the opinion related. I attach as Exhibit "C" to this affidavit, a copy of the 'Schedule "A" to the Engagement Letter setting out this information.
5. Based on the foregoing, I undertook to provide an expert opinion respecting each issue, and where there was a range of opinions given, a summary of the range and the reasons for my own

opinion within that range is provided. I attach as Exhibit "D" to this affidavit, a copy of my Expert Opinion.

6. For ease of reference, I have prepared a Compendium with excerpts from certain citations in my report to which I refer and I direct the Court's attention. I attach as Exhibit "E" to this affidavit, a Compendium.
7. Finally, I acknowledge that I owe a duty to the Court in the presentation of my expert opinion. I attach as Exhibit "F" to this affidavit, a Form 53, Acknowledgement of Expert's Duty.
8. I make this Affidavit to support the Expert Opinion being provided to the Court as requested by the Respondents and for no improper purpose.

Affirmed before me)
this 12 day of April, 2021 at)
Milford in Connecticut.)
[redacted])
Commissioner of Oaths)

[redacted]
Dr. Harvey Risch

ALBERTO BERNARDEZ
Notary Public, State of Connecticut
My Commission Expires Aug. 31, 2024

Exhibit "A"

This is the Affidavit of [redacted]

Dr. Harvey Risch

affirmed before me this 12th day of April, 2021.

[redacted]

Commissioner of Oaths

ALBERTO BERNARDEZ
Notary Public, State of Connecticut
My Commission Expires Aug. 31, 2024

Curriculum Vitae for: HARVEY A. RISCH, M.D., PH.D.

Professor of Epidemiology
Yale School of Public Health, Yale School of Medicine

Business Address: Yale School of Public Health
60 College Street, LEPH 413
P.O. Box 208034, New Haven, CT 06520-8034
Phone: [redacted]; Fax: (203) 785-4497
E-mail: [redacted]

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:

7/01-	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: 86. Publication citations: more than 35,500 research citations as of March 20, 2020.

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-)

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)
Fundamentals of Epidemiology (Yale University CDE/EMD 508) (Course developer)
Principles of Epidemiology II (Yale University CDE 516) (Course 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-)
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-)
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 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:

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)

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-)
Chair, Department of Chronic Disease Epidemiology, Epidemiology Competencies Committee (2015-)
Committee for Academic and Professional Integrity (2018-2021)
Education Committee (2019-)

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-)
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:

<u>Accepted for Publication or In-Press</u>

Shen Y, **Risch H**, Lu L, Ma X, Irwin M, Lim J, Taddei T, Pawlish K, Brown R, Wang Z, Jia W, Wong L, Mayne S, Yu H. Risk factors for hepatocellular carcinoma (HCC) in the northeast of the United States: Results of a case-control study. Accepted for publication, Cancer Causes Control. PMCID: PMC Journal in Process.

Xiao Y, He L, Chang W, Zhang S, Wang R, Chen X, Li X, Wang Z, **Risch H**. Self-harm behaviors, suicidal ideation and associated factors among rural left-behind children in west China. Accepted for publication, Annals of Epidemiology. *Not a result of NIH funding.

Lor GCY, **Risch HA**, Fung JW, Yeung SLA, Wong IOL, Zheng W, Pang H. Reporting and guidelines for Mendelian randomization analysis: a systematic review of oncological studies. Accepted for publication, Cancer Epidemiol. *Not a result of NIH funding.

Feng H, Gusev A, Pasaniuc B, Wu L, Long J, Abu-Full Z, Aittomäki K, Andrulis IL, Anton-Culver H, Antoniou AC, Arason A, Arndt V, Aronson KJ, Arun BK, Asseryanis E, Auer PL, Azzollini J, Balmaña J, Barkardottir RB, Barnes DR, Barrowdale D, Beckmann MW, Behrens S, Benitez J, Bermisheva M, Białkowska K, Blanco A, Blomqvist C, Boeckx B, Bogdanova NV, Bojesen SE, Bolla MK, Bonanni B, Borg A, Brauch H, Brenner H, Briceno I, Broeks A, Brüning T, Burwinkel B, Cai Q, Caldés T, Caligo MA, Campbell I, Canisius S, Campa D, Carter BD, Carter J, Castelao JE, Chang-Claude J, Chanock SJ, Christiansen H, Chung WK, Claes KBM, Clarke CL; GEMO Study Collaborators; EMBRACE Collaborators; GC-HBOC study Collaborators, Couch FJ, Cox A, Cross SS, Cybulski C, Czene K, Daly MB, de la Hoya M, De Leeneer K, Dennis J, Devilee P, Diez O, Domchek SM, Dörk T, Dos-Santos-Silva I, Dunning AM, Dwek M, Eccles DM, Ejlertsen B, Ellberg C, Engel C, Eriksson M, Fasching PA, Fletcher O, Flyger H, Fostira F, Friedman E, Fritschi L, Frost D, Gabrielson M, Ganz PA, Gapstur SM, Garber J, García-Closas M, García-Sáenz JA, Gaudet MM, Giles GG, Glendon G, Godwin AK, Goldberg MS, Goldgar DE, González-Neira A, Greene MH, Gronwald J, Guénel P, Haiman CA, Hall P, Hamann U, Hake C, He W, Heyworth J, Hogervorst FBL, Hollestelle A, Hooning MJ, Hoover RN, Hopper JL, Huang G, Hulick PJ, Humphreys K, Imyanitov EN; ABCTB Investigators; HEBON Investigators; BCFR Investigators; OCGN Investigators, Isaacs C, Jakimovska M, Jakubowska A, James P, Janavicius R, Jankowitz RC, John EM, Johnson N, Joseph V, Jung A, Karlan BY, Khusnutdinova E, Kiiski JI, Konstantopoulou I, Kristensen VN, Laitman Y, Lambrechts D, Lazaro C, Leroux D, Leslie G, Lester J, Lesueur F, Lindor N, Lindström S, Lo WY, Loud JT, Lubiński J, Makalic E, Mannermaa A, Manoochehri M, Manoukian S, Margolin S, Martens JWM, Martinez ME, Matricardi L, Maurer T, Mavroudis D, McGuffog L, Meindl A, Menon U, Michailidou K, Kapoor PM, Miller A, Montagna M, Moreno F, Moserle L, Mulligan AM, Muranen TA, Nathanson KL, Neuhausen SL, Nevanlinna H, Nevelsteen I, Nielsen FC, Nikitina-Zake L, Offit K, Olah E, Olopade OI, Olsson H, Osorio A, Papp J, Park-Simon TW, Parsons MT, Pedersen IS, Peixoto A, Peterlongo P, Peto J, Pharoah PDP, Phillips KA, Plaseska-Karanfilska D, Poppe B, Pradhan N, Prajzendanc K, Presneau N, Punie K, Pylkäs K, Radice P, Rantala J, Rashid MU, Rennert G, **Risch HA**, Robson M, Romero A, Saloustros E, Sandler DP, Santos C, Sawyer EJ, Schmidt MK, Schmidt DF, Schmutzler RK, Schoemaker MJ, Scott RJ, Sharma P, Shu XO, Simard J, Singer CF, Skytte AB, Soucy P, Southey MC, Spinelli JJ, Spurdle AB, Stone J, Swerdlow AJ, Tapper WJ, Taylor JA, Teixeira MR, Terry MB, Teulé A, Thomassen M, Thöne K, Thull DL, Tischkowitz M, Toland AE, Tollenaar RAEM, Torres D, Truong T, Tung N, Vachon CM, van Asperen CJ, van den Ouweland AMW, van Rensburg EJ, Vega A, Viel A, Vieiro-Balo P, Wang Q, Wappenschmidt B, Weinberg CR, Weitzel JN, Wendt C, Winqvist R, Yang XR, Yannoukakos D, Ziogas A, Milne RL, Easton DF, Chenevix-Trench G, Zheng W, Kraft P, Jiang X. Transcriptome-wide association study of breast cancer risk by estrogen-receptor status. Genet Epidemiol 2020;1-27. doi: 10.1002/gepi.22288. PMCID: PMC Journal in Process.

Zhong J, Jermusyk A, Wu L, Hoskins JW, Collins I, Zhang M, Lei S, Chung CC, Zhang T, Xiao W, Albanes D, Andreotti G, Arslan AA, Babic A, Bamlet WR, Beane-Freeman L, Berndt S, Borgida A, Bracci PM, Brais L, Brennan P, Bueno-de-Mesquita B, Buring J, Canzian F, Childs EJ, Cotterchio M, Du M, Duell EJ, Fuchs C, Gallinger S, Gaziano JMM, Giles GG, Giovannucci E, Goggins M, Goodman GE, Goodman PJ, Haiman C, Hartge P, Hasan M, Helzlsouer KJ, Holly EA, Klein EA, Kogevinas M, Kulke MH, Kurtz RJ, LeMarchand L,

Malats N, Mannisto S, Milne R, Mocci E, Neale RE, Obazee O, Oberg AL, Olson SH, Orlow I, Patel AV, Peters U, Porta M, Real FX, Rothman N, Scelo G, Sesso HD, Severi G, Silverman D, Sund M, Thornquist MD, Tobias GS, Van Den Eeden SK, Visvanathan K, Wactawski-Wende J, Wentzensen N, White E, Yu H, Zeleniuch-Jacquotte A, Hoover R, Brown K, Kooperberg C, **Risch HA**, Jacobs EJ, Li D, Yu K, Shu X-O, Chanock SJ, Wolpin BM, Stolzenberg-Solomon R, Olson S, Chatterjee N, Klein AP, Smith JP, Kraft P, Shi J, Petersen GM, Zheng W, Amundadottir LT. A transcriptome-wide association study (TWAS) identifies novel candidate susceptibility genes for pancreatic cancer. Accepted for publication, J Natl Cancer Inst. PMCID: PMC Journal in Process.

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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:

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.

Exhibit "B"

This is the Affidavit of [redacted]

Dr. Harvey Risch

affirmed before me this 12th day of April, 2021.

[redacted]

Commissioner of Oaths

ALBERTO BERNARDEZ
Notary Public, State of Connecticut
My Commission Expires Aug. 31, 2024

Elders Without Borders
237 Argyle Avenue, Ottawa, ON, K2P 1B8 - 613-852-8384

March 26, 2021

ENGAGEMENT LETTER

BY EMAIL [redacted]

Dr. Harvey Risch
Chronic Disease Epidemiology
PO Box 208034, 60 College Street
New Haven, CT, 06520-8034
United States

Dear Dr. Harvey Risch,

This "Engagement Letter" confirms that you have been retained by Elders without Borders and Nirmala Armstrong Law Office to complete an expert report and testimony in connection with the following legal matter:

Her Majesty the Queen in Right of Ontario v. Adamson Barbecue Limited & William Adamson Skelly, Court File No. CV-20-00652216-0000, presently pending before the Superior Court of Justice, located on 330 University Avenue, at the City of Toronto, in the Province of Ontario.

We have received your Curriculum Vitae ("CV") on your credentials, experience, and publications. You agree that you are qualified to perform the services and tasks as described and directed onto you in the Expert Report Guidelines by the deadline of **April 5, 2021**. Please see attached as Schedule "A" of this Engagement Letter, a copy of the Expert Report Guidelines.

This agreement shall be interpreted under the laws of the Province of Ontario.

Your signature below represents your agreement with the terms set forth herein. Please return a signed copy of this letter to my office.

[redacted]

Michael Swinwood B.A. LL.B
ELDERS WITHOUT BORDERS

[redacted]

Dr. Harvey Risch

ELDERS WITHOUT BORDERS
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Nirmala Armstrong (LSO #37487F)
Email: narmstronglaw@gmail.com

Exhibit "C"

This is the Affidavit of [redacted]

Dr. Harvey Risch

affirmed before me this 12th day of April, 2021.

[redacted]

Commissioner of Oaths

ALBERTO BERNARDEZ
Notary Public, State of Connecticut
My Commission Expires Aug. 31, 2024

Schedule "A" - EXPERT REPORT GUIDELINES

On March 17th, 2020, the Ontario Government declared an emergency under the *Emergency Management Civil Protection Act*, R.S.O. 1990, c. E.9 ("EMCPA") invoking regulations by the Lieutenant-Governor pursuant to the emergency on the basis that, "… the outbreak of a communicable disease namely COVID-19 coronavirus disease constitutes a danger of major proportions that could result in serious harm to persons."

As such, the provincial government of Ontario has been placing the Province of Ontario into COVID-19 emergency lockdown/restriction measures (also referred to as non-pharmaceutical interventions) as outlined in the Reopening Ontario Act, 2020 in response to the novel COVID-19 coronavirus disease. Likewise, the municipal governments, such as the municipal government of Toronto in this legal matter, have been mirroring the Province's Reopening Ontario Act and placing cities into lockdowns/restrictions, impacting the Respondent, William Adamson Skelly, and the general public's Canadian Charter of Rights and Freedoms.

In your Expert Report, please opine on the following issues:

1. Outpatient usage of hydroxychloroquine with zinc, and ivermectin.
2. Case series studies on good treatment benefit vs mortality.
3. Studies of safety and adverse end points with outpatient HCQ.

Exhibit "D"

This is the Affidavit of [redacted]

Dr. Harvey Risch

affirmed before me this 12th day of April, 2021.

[redacted]

Commissioner of Oaths

ALBERTO BERNARDEZ
Notary Public, State of Connecticut
My Commission Expires Aug. 31, 2024

Hydroxychloroquine in Early Treatment of High-Risk COVID-19 Outpatients: Efficacy and Safety Evidence

Harvey A. Risch, MD, PhD
Professor of Epidemiology, Yale School of Public Health
April 8, 2021

- Every one of the now 9 studies of high-risk outpatient hydroxychloroquine (HCQ) use has shown significant 2-fold or better risk reduction for hospitalization or mortality.
- The numerous systematic case-series studies have shown exceedingly good treatment benefit vs mortality. They have already saved many tens of thousands of lives.
- The "natural experiment" studies of population medication responses provide compelling evidence of temporal relations between medication use and mortality reduction.
- The RCT studies proclaimed supposedly as definitively showing no benefit of HCQ use in outpatients have all involved almost entirely low-risk subjects with virtually no hospitalization or mortality events and are uninformative and irrelevant for bearing upon these risks according to HCQ use in high-risk outpatients.
- HCQ has been safely used for 65 years by hundreds of millions of people worldwide, in tens of billions of doses, in people with autoimmune and other chronic diseases, in children, in pregnant women etc. It is one of the safest medications known.
- The FDA has no systematic evidence of fatal adverse events from hydroxychloroquine prophylaxis or outpatient treatment use and has invalidly used evidence in hospitalized inpatients to create a false public warning by extrapolating to outpatient use.
- The totality of any or fatal cardiac arrhythmia events among more than 13,000 patients treated with hydroxychloroquine or hydroxychloroquine+azithromycin is zero.
- The large database study of more than 900,000 older patients taking hydroxychloroquine shows no excess all-cause mortality and no excess occurrence of fatal cardiac arrhythmia. The same study, of 320,000 older patients taking hydroxychloroquine + azithromycin, shows no excess all-cause mortality and minuscule excess fatal arrhythmia frequency, estimated 9/100,000 patients, compared to the large number of patients whose lives will be saved by outpatient use of these medications.
- A small percentage of high-risk COVID-19 patients, likely less than 5%, may have contraindications to use of hydroxychloroquine alone or combined with azithromycin. Clinical decisions about such use are part of standard physician workup and apply to most FDA-approved medications and do not detract from use.
- The need for outpatient use of hydroxychloroquine is crucial for saving the lives of tens of thousands of high-risk COVID-19 patients until the pandemic subsides. Even with widespread vaccination, cases of the disease will still occur, and many of those patients will need immediate treatment.

Introduction

Numerous studies by now have examined use of hydroxychloroquine (HCQ) with respect to a range of outcomes in COVID-19 disease, to the point that indiscriminate or "cherry-picked" selection from among the studies can support almost any assertion about these associations. However, given the pressing need to reduce disease mortality dramatically, that outcome, or its main predecessor, hospital admission, are the logical foci of research bearing upon therapeutic utility of HCQ. Further, the proposed mechanism of action of HCQ lies in its antiviral properties, either in parallel with or in support of zinc ions, which may be naturally sufficient in healthy younger people but may require supplementation in older people or those with chronic morbidities. In addition, current evidence suggests that low-risk people, i.e., people under age 60 years and not obese (BMI<30) and without chronic comorbidities such as diabetes mellitus, hypertension, cardiovascular disease, COPD, asthma, kidney disease, immunocompromise etc., need only symptomatic management for COVID-19 and do not need to be treated, except in the infrequent circumstance of progression to dyspnea under light activity, typically PO_2<94%, at which point they become high-risk and active treatment is warranted. Thus, the intended application of HCQ is for use of HCQ and its companion medications (zinc, antibiotics azithromycin or doxycycline, anticlotting agents, vitamin D, and possibly prednisone or budesonide starting on symptoms day-6 or at dyspnea; these combinations denoted by "HCQ+" use) in high-risk patients as early as possible after clinical diagnosis of COVID-19 or true-positive SARS-CoV-2 test result (McCullough et al., 2020). For this reason, only studies of HCQ in this specific application contribute relevant evidence: early outpatient use, high-risk patients, hospitalization or mortality as endpoints.

Second, a long debate exists about types of studies upon which reliance can be placed for evidential reasoning and decisions about clinical utility. This debate may have originated with the recognition in the 1950s or 1960s that observational studies (case-control studies, cohort studies, large case-series studies etc.) are associational in nature and potentially subject to biased or confounded information and false-positive (or false-negative) results. Alternatively, well-conducted, large-enough, representative double-blinded randomized controlled trials (RCTs) can provide quasi-experimental evidence. In reductio ad absurdum, some licensing and approval bodies have made policies to include only evidence from RCTs. However, it is well known that RCTs are generally designed according to statistical power for detecting magnitude of association of the primary endpoint, not for limiting imbalanced proportions in the treatment arms residual to randomization, and that they are subject to many other potential flaws and are easily distorted or subverted in practice (Frieden, 2017; Deaton and Cartwright, 2018). Additionally, a massive amount of work has been carried out in empirically comparing the results of RCTs to their nonrandomized counterpart studies. The definitive Cochrane Library meta-analysis of what includes tens of thousands of individual studies demonstrates that standard adjusted modern nonrandomized trials show virtually identical results to their randomized counterparts (Anglemyer et al., 2014). For this reason, the sole reliance on RCT

evidence is *scientifically* unwarranted (Frieden, 2017), and while it may sometimes be challenging to summarize a more diverse body of scientific evidence, that is precisely how *scientific* conclusions are derived. This reasoning process most frequently follows the foundational schema of "aspects" of causal reasoning laid out by Sir Austin Bradford Hill more than 50 years ago (Hill, 1965) and is discussed at length in the "Reference Manual" (Committee on the Development of the Third Edition of the Reference Manual on Scientific Evidence, 2011). In consideration of conclusions of efficacy or harm, all relevant evidence needs to be evaluated.

In sum, this Brief will reason from epidemiologic studies and evidence pertaining to safety and efficacy in preventing hospitalization and mortality with early HCQ+ use in high-risk COVID-19 outpatients. The Brief is organized into four sections: A. Outpatient studies non-compliant with the defining conditions of hospitalization or mortality with early HCQ+ use in high-risk COVID-19 outpatients, i.e., reasons for their non-consideration in this Brief; B. Outpatient studies bearing upon hospitalization or mortality risks with early HCQ+ use in high-risk COVID-19 outpatients; C. Population "natural experiments" bearing upon efficacy of population use of HCQ in mortality reduction; D. Studies of safety and adverse endpoints with outpatient HCQ+ use.

A. Outpatient studies non-compliant with the defining conditions of hospitalization or mortality with early HCQ+ use in high-risk COVID-19 outpatients

Seven studies not relevant for further discussion have been published or released to-date concerning HCQ use in outpatients, as follows.

1. The Boulware University of Minnesota study (Skipper et al., 2020) in which symptomatic, non-hospitalized adults with laboratory-confirmed or probable COVID-19 and high-likelihood of exposure were randomized and started treatment within 6 days of symptom onset with HCQ (n=212) or masked placebo (n=211). The original paper stated a medication-start 4-day limit from symptom onset but was later clarified not to include medication shipping time (Wiseman et al., 2020). This study is non-informative because its study subjects were mostly low-risk individuals, median age 40 years. The low risk is demonstrated by 8 COVID-19-related hospitalizations among the 211 placebo patients (3.8%). In spite of this flawed study design, hospitalizations in treated subjects (4/212 = 1.9%) were half of that in the placebo group. Though not statistically significant and thus possible to have occurred by chance, this 50% cut in risk of hospitalization (the outcome of relevance) is consistent with all of the informative studies to be considered herein. The author conclusion in this study, "Hydroxychloroquine did not substantially reduce symptom severity or prevalence over time in nonhospitalized persons

with early COVID-19" is technically correct but misleading because symptom severity or prevalence is a minor issue compared to hospitalization and mortality, and the study did demonstrate a nonsignificant 50% reduction in hospitalization risk. The authors reported that there were no serious adverse events attributable to HCQ, even with the higher-than-recommended HCQ doses used in the study.

2. The Boulware University of Minnesota prevention study (Boulware et al., 2020), in which 821 asymptomatic healthcare workers with presumed exposure to SARS-CoV-2-infected individuals were randomized to HCQ (n=414) or placebo (n=407) a few days after exposure and followed-up for confirmed or probable COVID-19 as well as for hospitalization. This study is also non-informative because its study subjects were again mostly low-risk individuals, median age 40-41 years. The low risk is demonstrated by 1 COVID-19-related hospitalization among the 407 placebo patients (0.25%). This low a placebo-group risk limits how much better the HCQ arm can do, which was 1 hospitalization among the 414 treated subjects. Serious adverse reactions were reported in the study as zero.

3. The Catalonia non-blinded randomized trial (Mitjà et al., 2020a) in which 136 COVID-19 patients were assigned to HCQ and 157 control patients to no treatment, i.e., no placebo. Median time from onset of symptoms to enrolment was 3 days in both groups. This study is noninformative because its subjects were mostly low-risk individuals, median age 42 years. The low risk is demonstrated by 11 COVID-19-related hospitalizations among the 157 control patients (7.0%). In spite of the composition of low-risk subjects in the study, the treated subjects had even lower risk of hospitalization (8/136 = 5.9%). There were no cardiac disorders observed among the treated subjects, and no serious adverse events adjudicated by the pharmacovigilance consultants in the study as related to HCQ.

4. The small non-randomized but controlled Marseille trial (Gautret et al., 2020). The Marseille COVID-19 research group conducted large, city-wide population screening for COVID-19 based out of the Institut Hospitalier Universitaire. This 60-bed hospital served as a clinic base for screening, work-up, day-patient medication provision, and where necessary, overnight hospital inpatient care. In this study, 42 tested-positive screenees were assigned to control (standard-of-care; n=16), HCQ (n=14) and HCQ+azithromycin (n=6) regimens; 6 patients started on medication but left the trial prior to completing the full course. Some of the controls were identified in other Marseille hospitals, making the comparison of HCQ vs control uncertain. The outcome of this study was day-6 test-positive viral carriage, not hospitalization or mortality, thus not relevant to hospitalization or mortality risks.

5. The Catalonia, Spain, cluster-randomized study (Mitjà et al., 2020b). Another randomized trial in predominantly low-risk patients. Mean patient age 49 years. Mortality in the control group 8/1300, 0.62%. Mortality reduced by HCQ monotherapy by 32%. This study incidentally included 293 nursing-home residents who are by definition high-risk. In them, the "primary

outcome," new PCR-confirmed symptomatic COVID-19 infection within 14 days, was cut in half. This reduction was borderline statistically significant at p=.050. Aside from this result, for all of the low-risk subjects in this study, the results again do not bear upon hospitalization or mortality risks of high-risk outpatients.

6. The Health-Care Workers RCT (Abella et al., 2020). This trial randomized 132 hospital-based health-care workers to equal groups of 8 weeks of 600mg daily HCQ and placebo. The primary outcome was nasal swab viral PCR positivity and seropositivity at 4 and 8 weeks of the study. Median age of study participants was 33 years. No hospitalizations occurred in this study and no serious adverse events were observed. The young age and obvious low risks of the study subjects makes this study uninformative about effect of HCQ on risks of hospitalization or mortality.

7. The US Multicenter PEP Study (Barnabas et al., 2020). This study recruited households with likely COVID-19 cases through advertising and social media. Seemingly unaffected household members were recruited to participate. Subjects were approximately equally randomized to HCQ vs vitamin C as control. I note that vitamin C has been considered as playing a role in outpatient COVID-19 treatment (Carr and Rowe, 2020). The dose of HCQ, 400 mg/d for 3 days, then 200 mg/d for an additional 11 days, takes 5 days to build up tissue levels sufficient to be preventative (Chatterjee et al., 2020; Goenka et al., 2020; Khurana et al., 2020; Yadav et al., 2020). Subjects provided daily nasal swabs for viral PCR testing for outcome determination by day-14. Subjects were considered positive for PCR positivity at cycle threshold (Ct) of 40 or less. It should be noted that positivity at Ct values of 35-40 reflects infections 3-6 weeks in the past and that half of PCR sample positivities at threshold Ct less than 40 reflect such old infections (Singanayagam et al., 2020). The median age of study subjects was 39 years. One treated and one control subject were each briefly hospitalized for COVID-19-related reasons. One person in each group was also briefly hospitalized for treatment-unrelated reasons. This is again a study of low-risk individuals and uninformative about effect of HCQ on hospitalization or mortality risks. No serious adverse events related to the HCQ treatment were observed.

B. Outpatient studies bearing upon hospitalization or mortality risks with early HCQ+ use in high-risk COVID-19 outpatients

1. São Paulo, Brazil study (Barbosa Esper et al., 2020). This study involved consecutive outpatients with two days of flu-like symptoms suspected to be COVID-19. Subjects were

examined by a telemedicine team or emergency-room physicians and those without contraindications were offered treatment with HCQ+azithromycin. Of these, 224 declined treatment and served as the control group, and 412 accepted treatment. The study outcome was hospitalization, based upon worsening condition or PO_2 <90%. Even though the severities of all of the recorded flu-like signs and symptoms and of important comorbidities (diabetes, hypertension, asthma, stroke) were substantially greater in the treated patients than the controls, the need for hospitalization was significantly lower, 1.2% in patients starting treatment before day 7 of symptoms, 3.2% for patients starting treatment after day 7, and 5.4% for controls, reported P-value<.0001. The average age of the patients was 62.5 years, thus the majority were a priori classified as high-risk. No cardiac arrhythmias were reported in the 412 treated patients. The most common side effect of treatment was diarrhea (16.5%), but 12.9% of treated patients presented with diarrhea before treatment began.

2. The larger Marseille screening study (Lagier et al., 2020). The Marseille investigators report on their cohort of 3,737 COVID-19 patients treated with HCQ, azithromycin and other medications. In the pertinent analysis of this study, 199 patients treated with HCQ+azithromycin for 3+ days were matched by medication propensity score (involving categories of combined comorbidity index and NEWS-score symptom intensity) to 199 patients given the medications for less than 3 days, or given only the individual medications, or not given either one. All of the patients in the mortality analysis were 60 years of age or older and a large fraction had comorbidities, thus at a priori high-risk. The stratified Cox-regression analysis showed a mortality hazard ratio of 0.41 (95% CI 0.17-0.99), p=.048, for this comparison. It should be noted that the “unexposed” group included an appreciable number of patients that had used HCQ+azithromycin but for shorter duration, or had used HCQ alone, thus likely biasing the observed hazard ratio nullward. As well, the propensity-score matching did not match for age, however comorbidities tend to increase with age and matching on comorbidity index likely accounted for some of an age association, and in any event all of the patients in the mortality analysis were age 60 or older.

3. The Hapvida Brazil outpatient treatment study (Szente Fonseca et al., 2020). This study involved 717 consecutively numbered tested-positive symptomatic patients over age 40 presenting at the 42 outpatient clinics and emergency rooms of the 6-million-member Hapvida HMO in Brazil between May 11 and June 3 of this year. The mean age of included patients was 51 years. Hapvida services a number of Brazil states with large indigenous populations and higher frequencies of diabetes, heart disease and other chronic conditions, thus the HMO defines age 40 to be the threshold of high-risk at which to consider actively treating COVID-19 outpatients. In the new protocol initiated by the HMO, treatment specifics were chosen ad lib from 7 medications by the attending physician and monitored for quality assurance. The COVID-19 protocol included (all as oral medications): HCQ as first-line treatment, if used (400 mg bid day 1, 400 mg qd days 2-5), prednisone (1 mg/kg qd x 5 days, started on symptom day-6, no taper), azithromycin (500 mg qd x 5 days), ivermectin (12 mg qd x 2 days), plus symptom

relievers. Zinc sulfate, oseltamivir and nitazoxanide were also available to be prescribed but were used infrequently. Doctors quickly found that most of the prescribed HCQ was not available at common drugstores, thus if prescribed it was offered free of charge to all patients who only had to sign informed consent to receive it. The study showed, adjusted for age, gender, dyspnea at presentation, obesity, diabetes, and heart disease, that use of both HCQ and prednisone together was associated with an odds ratio for hospitalization of 0.40 (95% CI 0.21-0.75), p=.0042; use of HCQ only, odds ratio=0.45 (95% CI 0.25-0.80), p=.0065; and use of prednisone only, odds ratio=0.51 (95% CI 0.26-0.99), p=.049. In this model, use of azithromycin conveyed a small additional though not significant benefit, odds ratio=0.85 (95% CI 0.54-1.34), p=.48, and ivermectin offered no additional benefit. Similar magnitudes of association as these were seen for the medications among the 717 subjects with death as the outcome, but the small numbers of deaths (n=11) precluded statistical significance of these associations. No cardiac arrhythmia events requiring medication termination for any of the medications used in the 717 patients were observed, and thus there were no deaths attributable to such arrhythmias.

4. A matched retrospective cohort study was carried out among outpatients within the Hackensack Meridian Health Network, New Jersey (Ip et al., 2020). Between March 1 and April 22, 2020, 1,274 patients with non-admission ER visits were identified and confirmed infected with SARS-CoV-2 by PCR testing. Of these, 97 received prescriptions for or had started taking HCQ, and from the remaining 1,177, 970 were propensity-score matched by age, demographic variables and a host of comorbidity factors, presenting symptoms, indicators of disease severity, baseline laboratory tests, and ER-visit and follow-up times. After the matching, HCQ-treated subjects were slightly older and had more frequent cancer histories than untreated subjects. More than three-quarters of the subjects had comorbidities or were over age 60, making them high-risk. In the matched multivariate analysis, treatment with HCQ significantly cut the risk of hospitalization by 47% (p=.038).

5. A study was conducted in 23 nursing homes in Marseille (Ly et al., 2020), in which of 226 infected residents, 37 were detected because of COVID-19 symptoms and 189 through mass screening. In multivariate analysis adjusted for sex, age and detection modality (symptoms vs screening), receipt of HCQ+azithromycin for at least three days was associated with 59% reduced mortality risk (p=.017).

6. A study in Andorra was carried out at a public nursing home from March 15 to June 5, 2020 (Heras et al., 2020). This study identified 100 PCR-confirmed COVID-19 patients during this interval. Patients received HCQ+azithromycin, HCQ with other antibiotics such as beta-lactam or quinolone types, or other antibiotics alone. Median age was 85 years. In multivariate analysis of mortality risk adjusted for sex, Barthel's index of activities of daily living, and fact of lymphocytopenia, treatment with HCQ+azithromycin vs only other antibiotics had OR=0.044 (95%CI 0.006-0.35), p=.004. Treatment with HCQ+other antibiotics vs other antibiotics alone

had OR=0.32, p=.37.

7. A study of COVID-19 mortality was performed in a nursing home in Milan, Italy (Cangiano et al., 2020). Ninety-eight of the 157 residents tested positive for SARS-CoV-2 by nasal swab PCR or serology and were followed over time. The average age of study patients was 90 years. Subjects who have been receiving vitamin D in their usual health care had reduced mortality. In logistic regression models adjusted for age, sex, Barthel's index and BMI, regular vitamin D supplementation was associated with 5-fold reduced mortality risk, p=0.04. In addition, in the adjusted model, receipt of HCQ was associated with 7-fold reduced mortality, p=.03. These authors noted that "Hydroxychloroquine was prescribed only in patients with better ECG tracings and those receiving less drugs that might induce QT interval prolongation, such as antipsychotic and antidepressant agents, thus being probably fitter then those who did not receive this therapy." However, antipsychotic and antidepressant medications have not been shown to provide 7-fold mortality reduction in treatment of COVID-19 outpatients, thus these medications cannot fully explain the large reduction in mortality risk seen with HCQ use. It is also unclear whether patients receiving such medications would be likely to have physiologically higher risks of mortality.

8. The national Saudi Arabia Study (Sulaiman et al., 2020). In this study, all mild-moderate cases of PCR-positive COVID-19 presenting at national outpatient treatment clinics between 5-26 June were recruited for enrollment. Treated patients (n=3,320) received 400 mg HCQ bid on day-1 and 200 mg bid for an additional four days. Both treated and control (n=4,572) patients received zinc sulfate 60 mg qd for five days, cetirizine 10 mg qd for 10 days, and paracetamol as-needed. Treated and control patients were comparable in distributions of age, sex and nine comorbidities reported. In multivariate modeling adjusted for age, gender and comorbidities, HCQ receipt cut mortality some 3-fold, OR= 0.36 (95%CI 0.16-0.80). However, the Saudi health-care system involves unique national personal identifiers and all of the almost 8,000 study subjects were followed for occurrence of hospitalization and mortality. Thus, the 7 deaths of patients in the HCQ group and 54 in the standard-of-care control group represent a more than 5-fold reduction in mortality with HCQ+zinc treatment vs zinc only. It should be noted that a major fraction of the patients in the Saudi study were of low-risk, however the 61 deaths and 788 hospital admissions make the study informative for those risks.

9. The national Iran study (Mokhtari et al., 2021). This study comprised a multicenter, population-based national retrospective-cohort investigation of 28,759 adults with mild COVID-19 seen within 7 days of symptom onset at a network of Comprehensive Healthcare Centers throughout the country between March and September 2020. Patients were diagnosed by nasal swab RT-PCR (79%) or by clinical parameters and chest imaging (21%). Treated patients (n=7,295) received free of charge HCQ 400mg bid on day 1 and 200mg bid over days 2-5. Control subjects were treated with supportive care only. Treated and control patients were comparable in distributions of age and sex, but treated subjects had slightly

higher frequencies of comorbidities. Adjusted for age, sex, BMI, hypertension, respiratory diseases, diabetes mellitus and cardiovascular diseases other than hypertension, treatment with HCQ was associated with a 38% reduction in risk of hospitalization (95%CI 31-44%) and a 70% reduction in mortality risk (95%CI 55-80%). Both of these risk reductions were highly statistically significant, and were equally so in patients diagnosed by PCR vs by clinical factors and chest imaging.

10. Case-series studies of high-risk outpatients. Case reports comprise truly anecdotal information because of lack of information about the representativeness of the subject for a particular disease or exposure group. On the other hand, organized systematic collections of sequentially eligible patients can be representative of their disease status, just as well-collected case subjects are in a case-control study. Thus, a common characteristic of a representative case series, such as hospitalization or mortality proportion, is a valid estimate of that characteristic for the disease as represented by the particular cases. In a case-control study, such an estimate would be compared to a parallel estimate in its control sample of individuals chosen to be representative of both a relevant underlying population and of the other characteristics of the cases, such as age, gender, race, etc. However, a case series by definition has no control sample, thus does not seemingly allow for estimation of a quantitative relative measure of the case characteristic to the control or population characteristic. This is the situation in general, when a numerical relative measure is needed. It is a different question however when a large discrepancy exists between the frequency of the case characteristic and the known population characteristic, and the goal is to determine evidence for the fact of the discrepancy rather than to estimate the numerical amount or ratio of the discrepancy. In this instance, systematic case-series data can indeed provide evidence.

As a point of reference, mortality risk in Connecticut residents age 60 and older who have tested positive for carriage of SARS-CoV-2, through December 30, 2020, is 12.8% (5,577 deaths out of 43,506 patients) (Connecticut Department of Public Health). Other states may have risks higher or lower than this, but this risk is still substantial. In comparison: the initial cohort of 405 high-risk outpatients treated with HCQ+azithromycin+zinc sulfate by Dr. Vladimir Zelenko, patients resident in the Village of Kiryas Joel, NY, had 2 deaths (Zelenko, 2020). Dr. Zelenko's second series of 400 high-risk outpatients from the same village and treated with the same regimen had zero deaths (Risch, 2020a). Dr. Lawrence Kacmar, in Aurora IL, has treated 68 high-risk outpatients with HCQ+azithromycin and observed zero deaths (Risch, 2020a). Dr. Brian Procter, in McKinney, TX, treated 50 high-risk outpatients with HCQ+ azithromycin+ zinc sulfate+losartan+aspirin and observed zero deaths in his first series, and another 320 with one death in his second series (Procter et al., 2020), and 549 high-risk outpatients and one death in his third series (Procter et al., 2021). Dr. Steven Crawford, in a Festus, MO nursing home, has treated 52 high-risk outpatients with HCQ+rehydration and observed zero deaths (Risch, 2020a). Dr. Brian Tyson, in El Centro CA, has treated approximately 2,000 high-risk outpatients with HCQ+azithromycin and observed zero deaths (Risch, 2020a; Tyson B, personal

communication, 2020). In total, these physicians have reported in the literature or to me, treatment of 3,844 high-risk outpatients with HCQ+azithromycin etc. and observed among them 4 COVID-19-related deaths, for mortality of 0.10%. This low mortality can only be described as stupendous and a tribute to the clinical engagement of these physicians, and completely distinguishable from the CT 12.8% mortality or similar risks of untreated high-risk outpatients in other US states. None of the physicians reported any cardiac arrhythmias either necessitating stopping the medications or fatal.

A theoretical counterargument to these substantial series of successfully treated outpatients is that they were self-selected and came to my attention because of their outstanding results and not because they were typical or representative of doctors treating COVID-19 patients across the US. However, two of these doctors were specifically asked to provide updates of their clinical experiences, Drs. Zelenko and Procter. Statistical evidence for benefit is in these replications. Even if the mortality risk in high-risk patients were as low as 1% (it is probably at least 10%), the likelihood that only two or fewer of these 400+320+549 patients would have died if left untreated would be p=.00024. That is the p-value for the hypothesis that these two series had at most two deaths by chance with as low as an unrealistic 1% mortality risk untreated.

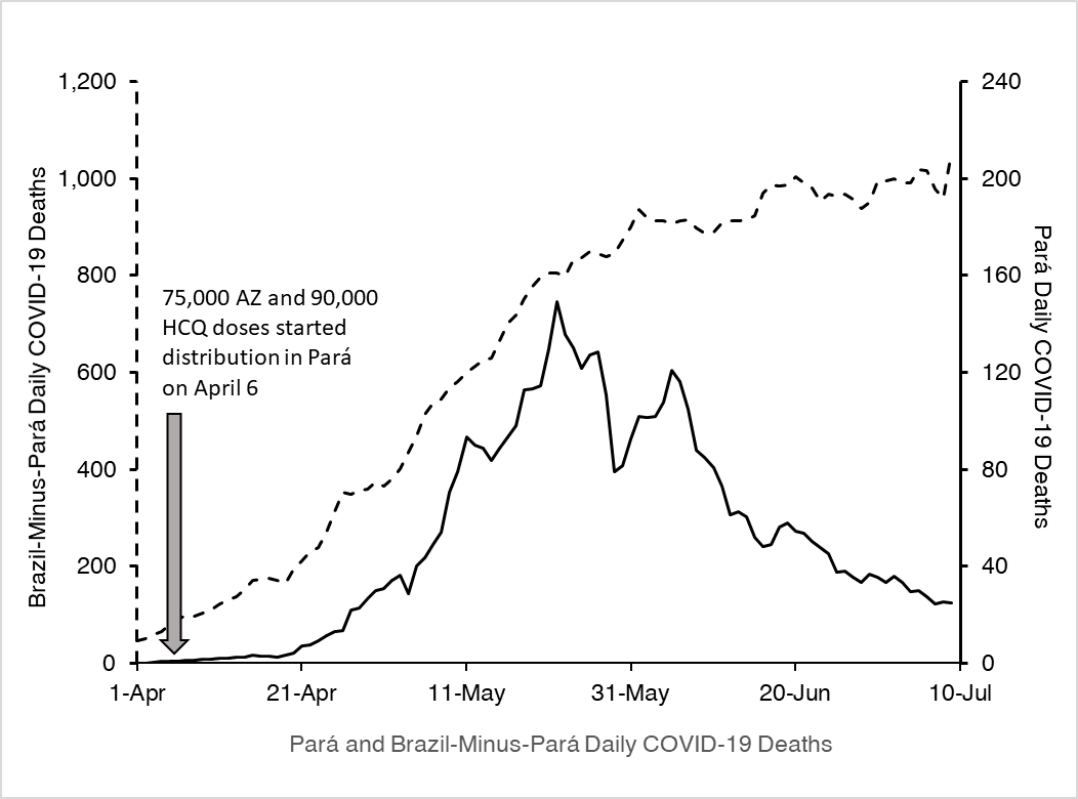
In summary, these numerous case series reports provide overwhelming evidence of the efficacy of HCQ in early outpatient treatment of high-risk COVID-19 disease. These are not anecdotal numbers but multiple systematic samples of real-world effective usage of these medications.

C. Population "natural experiments" bearing upon efficacy of population use of HCQ in mortality reduction

1. The Vadodara, India study (Raja, 2020). In this study, public health authorities administered HCQ to 342,000 residents of the western India city of Vadodara, including health workers and other frontline personnel. Each person completed a full course of HCQ, 400mg bid for the first dose and 400 mg per week for at least three weeks. The investigators sampled 100,000 persons in the city, including 48,873 close contacts of positive patients, contacts who had taken one dose of HCQ, among whom 102 afterward became COVID-19 positive and 12 died from the infection; 17,776 close contacts of positive patients among which contacts 48 took two doses of HCQ, turned positive and one died; and 33,563 close contacts of patients among which contacts took three HCQ doses, 43 tested positive and one died. Aside from the 39% reduction in case occurrence with three doses, among these tested-positive individuals, there is an inverse trend in mortality risk with number of doses of HCQ taken, odds ratio = 0.32 (95%

CI 0.11-0.94), p=.011, for each successive dose after the first, i.e., odds ratio = 0.32^2 = 0.10 for two doses after the first. This study is not yet fully described, so details about its methods are not available, and is small (but statistically significant), limiting its evidential weight, though dose-response trends in risk can be particularly informative.

2. In the northern Brazil state of Pará, COVID-19 deaths were increasing exponentially (Ministério da Saúde Brasil). On April 6, the public-hospital network purchased 75,000 doses of azithromycin and 90,000 doses of hydroxychloroquine (Alexandre Wolkoff, Hapvida Saúde HMO, Fortaleza, Brazil, personal communication, 2020). Over the next few weeks, authorities began distributing these medications to infected individuals. Even though new cases continued to occur, on May 22 the death rate started to plummet and is now about one-eighth what it was at the peak. This is shown in the figure below. Pará daily mortality is the solid line, Brazil-minus-Pará daily mortality is the dashed line.



D. Studies of safety and adverse endpoints with outpatient HCQ+ use.

There is ample evidence that HCQ, especially in high doses, can cause nausea, vomiting, abdominal discomfort and diarrhea. While unpleasant, these complaints are not life-

threatening and can generally be managed medically or with dose reduction. HCQ also has a spectrum of very rare adverse events that have little practical ramification except as suggested in cases such as G6PD deficiency, though a study of chronic HCQ use in such individuals shows no reported episodes of hemolysis during more than 700 months of HCQ usage among G6PD-deficient patients (Mohammad et al., 2018).

The major issue raised by the FDA and others concerns risks of cardiac arrhythmia, especially when HCQ is given in combination with azithromycin. Both HCQ and AZ can produce QTc prolongation, rare instances of fatal Torsades de Pointes and long QT-interval syndrome. Numerous studies have demonstrated QTc prolongation in hospitalized COVID-19 patients treated with HCQ and azithromycin (Bessière et al., 2020; Chorin et al., 2020; Mercuro et al., 2020; Ramireddy et al., 2020; Sridhar et al., 2020). Such physiologic QTc prolongation is typically 18-55ms and QTc can exceed 500ms in some individuals. Based on a large elevated *relative* risk of Torsades de Pointes for QTc>500ms, cardiologists generally regard exceeding this threshold as a contraindication for using HCQ or HCQ+azithromycin. However, large relative risks in the context of rare baseline *absolute* risks are not necessarily actionable, depending upon the absolute risk among the exposed, which can be estimated by multiplying the exposure relative risk times the baseline absolute risk. If the baseline absolute risk is many orders of magnitude smaller than the exposure relative risk is large, the absolute risk among the exposed will still be small. This is the reason why 10-fold or 20-fold relative risks of Torsades de Pointes for QTc>500ms, that seem very large as associations in observational studies, are still essentially unimportant for HCQ and HCQ+azithromycin treatment in general, except in patients who have additional comorbidity, medicine interaction or rare genetic contraindications. These contraindications, for example personal or family history of cardiac arrhythmia, are well documented and part of the standard workup physicians routinely perform when considering use of these medications.

Thus, the question of the frequency of occurrence of fatal Torsades de Pointes and long QT-interval syndrome must be evaluated by empirical data rather than by theoretical reasoning from physiologic observations. Even if these events were to occur with large-scale HCQ monotherapy or HCQ+ treatment of high-risk COVID-19 outpatients, the sole issue concerning the application proposed herein is whether they would occur in frequency as great as or greater than mortality in such patients not treated. It is in fact obvious that such would not be the case: there is no epidemic of fatal arrhythmias occurring among the millions of older, multicomorbid individuals chronically treated with HCQ for lupus erythematosus, rheumatoid arthritis and other autoimmune diseases. The FDA long ago approved HCQ on-label as indicated for these diseases and that approval has been borne out in the long safety record of this drug. While it has been observed that sporadic individual cases of COVID-19-associated myocarditis have occurred, these have been in hospitalized patients and thus does not provide a rationale for an increased arrhythmia risk in early outpatient medication use.

There are three useful ways to evaluate arrhythmia occurrence and mortality in COVID-19 patients treated with HCQ or HCQ+: treated case-series reports, adverse events database analyses, and observational studies of these outcomes.

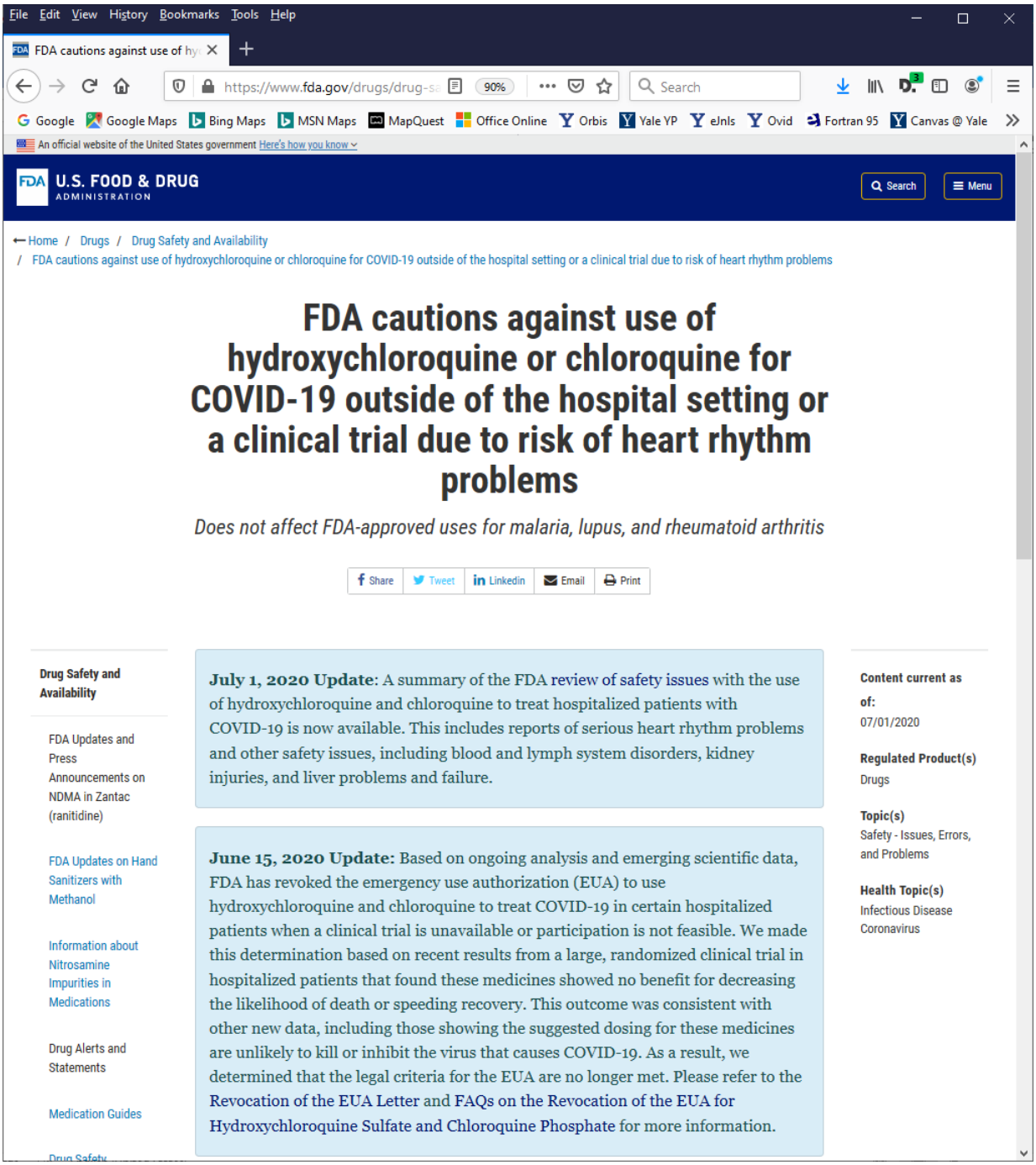
1. Treated case-series reports. As described earlier, in the totality of 3,844 high-risk outpatients treated early with HCQ, most with azithromycin as well, no cardiac arrhythmias were reported. In 202 high-risk outpatients treated early with HCQ+doxycycline, no cardiac arrhythmias were reported. In the Marseille cohort study (Lagier et al., 2020), among 3,737 treated outpatients, QTc prolongation (>60 ms) was observed in 25 (0.67%), including 2 treated with HCQ, 3 with azithromycin and 20 with HCQ+azithromycin (0.54%). Those investigators chose to terminate treatment for 3 cases with QTc of 500ms or longer (2 treated with azithromycin and 1 with HCQ+azithromycin). No cases of sudden death or Torsades de Pointes were observed in the 3,737. In the first Brazil study (Barbosa Esper et al., 2020), among 412 patients treated with HCQ+azithromycin, no arrhythmias were reported; two treated patients subsequently died, one from “acute coronary syndrome” and another from metastatic cancer. In the new Brazil study (Szente Fonseca et al., 2020), 521 high-risk outpatients were treated early with HCQ, azithromycin or both and no arrhythmias were reported among them. In the Hackensack Meridian Health Network study, 2 of the 97 treated subjects showed prolonged QTc intervals; neither had their medications stopped; and there were no arrhythmias. In total, these 3,844+202+3,737+412+521+97 = 8,813 early treated outpatients had no occurring or fatal arrhythmia events.

2. Adverse events database analyses. A search of the FDA Adverse Event Reporting System (FAERS) public dashboard for cardiac rhythm or cardiac sudden-death adverse events related to hydroxychloroquine (all forms named) and Plaquenil from 1968 through January 31, 2021 demonstrates 1,064 serious events including 200 deaths attributed to the hydroxychloroquine use. Of these, 57 events including 10 deaths were attributed to Torsades de Pointes and long QT-interval syndrome combined. This concerns the entirety of HCQ use over more than 50 years of data, over 1 billion uses and of longer-term use than the 5 days recommended for COVID-19 high-risk outpatient treatment. Since the MedWatch reporting system requires physicians, pharmacists or patients to initiate contact with the FDA, it appreciably undercounts drug side-effects. This undercounting may be 10- or 20-fold, and the FDA has stated that FAERS data cannot be used to calculate the incidence of adverse events in the US population, nor are internal odds-ratio calculation studies in the database meaningful (Swank et al., 2020). Nevertheless, even if the true numbers were 20-fold larger, they would still be minuscule compared to the amounts of medication usage, and minuscule compared to the numbers of deaths that have been and are continuing to occur among untreated high-risk outpatients.

The FDA has presented information on serious adverse events in the FAERS data combined with other sources in the FDA Pre-decisional, Deliberative, Internal Draft 16 July 2020 (FDA). The numbers given in the Draft do not give the dates over which they apply, nor whether the

patients were inpatients or outpatients, nor whether the patients were in the US or other countries, nor whether they pertained to HCQ or chloroquine use, nor whether azithromycin was also used. However, the Draft states, “On July 1st, 2020, FDA posted a summary of the agency’s review review [duplication in the original] of safety issues with the use of hydroxychloroquine and chloroquine to treat *hospitalized patients* [my italics] with COVID-19.”

The fda.gov website (https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or) (see image below) is titled “FDA cautions against use of hydroxychloroquine or chloroquine for



COVID-19 *outside of the hospital setting* [my italics] or a clinical trial due to risk of heart rhythm problems" and includes directly underneath the title a text box saying, "July 1, 2020 Update: A summary of the FDA review of safety issues with the use of hydroxychloroquine and chloroquine to treat *hospitalized patients* [my italics] with COVID-19 is now available. This includes reports of serious heart rhythm problems and other safety issues, including blood and lymph system disorders, kidney injuries, and liver problems and failure." The text box on the FDA website plainly says that the FDA review concerned medication usage in *hospitalized* patients. This Brief concerns application of medication use in high-risk *outpatients*, therefore as I have discussed in depth, efficacy and adverse events in *hospitalized* patients do not apply to and cannot be extrapolated to outpatient use (Risch, 2020b). It is patently obvious that had the FDA had systematic adverse events data for outpatients, the subject of the warning, it would have said so as the justification of the warning. This alone is proof that FDA has no systematic adverse events data in outpatients treated with HCQ.

I now turn to the FDA Pharmacovigilance Memorandum May 19, 2020 (Swank et al., 2020) that appears to comprise the principal information upon which FDA relied for its HCQ EUA decisions prior to July 1. On the bottom of page 5, it says that in total 97 adverse events were identified between December 2019 and May 6, 2020 in the US as pertaining to COVID-19 disease. There is no description as to the severity of these events. The EUA restricting HCQ use was instituted on March 28, at which point the FDA's position was that all HCQ use was to be for severely sick hospitalized patients, or RCTs (which at the time were largely hospital-based). Between December 1, 2019 and May 6, 2020, 1,268,819 COVID-19 cases were registered in the US (https://www.worldometers.info/coronavirus/country/us/). However, between December 1, 2019 and March 28, 2020, the date of the EUA, 125,250 cases had been registered. This means that of the COVID-19 cases that the FDA examined for adverse events through May 6, 1,143,569/1,268,819=90.1% occurred during the time of the EUA, i.e., at a time when HCQ would have only been officially available in hospital inpatient settings. This leaves 9.9% of the described 97 US adverse events, 10 events, as possibly pertaining to outpatient HCQ use. The FDA memo states that 5 of the 97 US events were reported through the EUA. However, this number cannot be taken as indicative of patient hospitalization status, because the MedWatch consumer form has no questions related to application of the EUA, and data provided by physicians on MedWatch health professionals forms are frequently incomplete. It seems highly unlikely that at a time when the FDA EUA restriction of HCQ use to hospitalized patients was in force, that physicians would have prescribed 92/97 = 95% of HCQ use to outpatients. Thus, the 97 US adverse events described in the FDA memo can be reasonably assumed to apply largely to hospitalized patients. How many of these adverse events were fatalities is unstated, but likely around 20%. Regardless, the fact that the FDA repeatedly described its adverse events data as pertaining to hospitalized inpatients, first in its internal memo, FDA Pre-decisional, Deliberative, Internal Draft 16 July 2020, and second on the official FDA website of July 1, confirms that all or essentially all of US adverse events data used by the FDA to declare HCQ unsafe for outpatient use (including the 97 US events in the May 19 Memo) were

inappropriate as based on hospital inpatient data. This invalid and outrageous conclusion has been the publicly stated position by the FDA since at least July 1 of 2020.

As well, the FDA states in its June 15, 2020 EUA revocation letter to Dr. Gary L. Disbrow PhD, Deputy Assistant Secretary, BARDA (Hinton, 2020), that it reviewed outcome data reported to BARDA for 1,762 patients as of May 26, 2020. In the description of clinical characteristics of these patients, "68.3% of patients were discharged," implying that the data concerned hospitalized inpatients only. The revocation letter also says that the FDA conducted a literature search and review at the CDC Stephen B. Thacker Library of COVID-19 research articles. The search identified 11 studies. The report of the search says, "All 11 studies were cohort studies conducted in hospitalized COVID-19 populations."

3. Observational studies of adverse outcomes. Three studies have examined adverse event outcomes associated with use of HCQ and HCQ+azithromycin. I have discussed the Oxford University study of 14 large medical records databases (Lane et al., 2020) in depth elsewhere (Risch, 2020b). That analysis shows that in more than 320,000 older rheumatoid arthritis patients with various comorbidities and who took HCQ+azithromycin, cardiac arrhythmia events were at no significant increase (relative risk 1.08, p=.36) vs similar numbers of patients who took HCQ+amoxicillin, demonstrating that the addition of azithromycin to HCQ does not enhance arrhythmia risk. The same study compared HCQ monotherapy to sulfasalazine use and again found no difference in cardiac arrhythmia risk: for HCQ, a slightly lower RR=0.89, P-value=.13. Further, among 306,106 people taking sulfasalazine (which is known not to produce QT prolongation), 877 with cardiac arrhythmias were identified, 0.287%. In 320,589 people taking HCQ+AZ, 1,068 had arrhythmias, 0.333%. The difference, 0.047% (95%CI 0.019%-0.074%) or 47/100,000 older multicomorbidity patients taking HCQ+AZ, is attributable to the HCQ+AZ use. These are events, not fatalities. As I have shown above (200/1,064), fatalities according to the FAERS comprise <20% of HCQ-related arrhythmia events, 9/100,000 (95%CI 4-15)/100,000. The maintenance HCQ dose in the Oxford study patients, 200 mg/day, gives as large or larger average circulating drug levels as five days of HCQ at 400 mg/day, the recommended dose for outpatient COVID-19. These very small numbers of arrhythmias, as well as the null relative-risk results in this very large empirical study, should therefore put to rest the anxieties about population excess mortality of HCQ+AZ outpatient use.

The second study of HCQ adverse events, in outpatients, comprises the Boulware studies (Lofgren et al., 2020). This analysis included data from 2,795 outpatient participants, of whom 2,324 reported data on medication side-effects. The most common side effects were gastrointestinal disturbances. Two individuals were hospitalized for atrial arrhythmias, one on placebo and one on twice weekly HCQ. The patient taking HCQ recovered. No sudden deaths occurred. The medication use in this study caused no arrhythmia-related deaths.

The third study describes clinical characteristics of almost 8,000 COVID-19 patients treated in

the Yale-New Haven Health System between March 1 and April 30, 2020 (McPadden et al., 2020). Median age of these patients was 52 years. Of these patients, 1,633 were hospitalized and of those, 227 (13.9%) died. 95.8% of hospitalized patients received HCQ and 32.7% azithromycin. There was no association between cardiac arrhythmia and mortality: odds ratio = 0.86 (95% CI 0.58-1.28), p=.46.

Conclusions

It is readily apparent that every one of the studies of high-risk outpatient HCQ use has shown 2-fold or better risk reduction for hospitalization or mortality, and that the numerous systematic case-series studies have shown exceedingly good treatment benefit vs mortality. The "natural experiment" studies of population responses provide compelling evidence of temporal relations between medication use and mortality. The RCT studies proclaimed as definitively showing no benefit of HCQ use in outpatients have all involved almost entirely low-risk subjects with virtually no information about risks of hospitalization and mortality and are irrelevant for bearing upon HCQ use in high-risk outpatients. The totality of fatal cardiac arrhythmia events among more than 8,000 patients treated with HCQ and HCQ+azithromycin is zero. The large database study of more than 320,000 older patients taking HCQ+azithromycin shows no excess all-cause mortality (Risch 2020b) and minuscule excess fatal arrhythmia frequency, 9/100,000 patients, compared to the large number of patients whose lives will be saved by outpatient use of these medications. I have not discussed all of the other even lesser-frequent adverse events than the arrhythmias, but these are equally minuscule, and the FDA did not invoke them for its warning about outpatient use in the title statement of the warning. The FDA has stated publicly that it relied upon adverse event data from hospital inpatients to make policy applying to outpatient use. There are no systematic adverse event arrhythmia data of US outpatients from the beginning of 2020 through the present. The FDA website also publicly cautions that only (i.e., "due to") arrhythmia data are relevant to its warning, by omitting from the title any assertions that other potential adverse events were important or frequent enough to be determinative. The FDA's extrapolation from adverse events in hospitalized patients to supposed risks in outpatients is flagrantly unwarranted. Outpatient viral replication is an entirely different disease than inpatient florid cytokine-driven pneumonia (Park et al., 2020) and the treatments are different. The need for outpatient use of HCQ is crucial for saving the lives of high-risk COVID-19 patients. The most recent published recommendations for early treatment of COVID-19 outpatients (McCullough et al., 2020) consider HCQ use and related medications of critical importance and is authored by some 50 clinicians providing this treatment. There is no comparison between the number of lives to be saved with early outpatient treatment and the minuscule numbers addressed in the analyses of adverse events, even what would be postulated to occur with widespread outpatient use. All of these data have been available to the FDA for some time. The improper

warning on the FDA website must be removed immediately, and widespread early outpatient treatment must start immediately.

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Exhibit "E"

This is the Affidavit of [redacted]

Dr. Harvey Risch

affirmed before me this 12th day of April, 2021.

[redacted]

Commissioner of Oaths

Court File No. CV-20-00652216-000

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Applicant/Respondent

AND

ADAMSON BARBECUE LIMITED
AND WILLIAM ADAMSON SKELLY

Respondents/Applicants

COMPENDIUM to the AFFIDAVIT OF Dr. Harvey Risch

Cochrane Library

Cochrane Database of Systematic Reviews

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials (Review)

Anglemyer A, Horvath HT, Bero L

Anglemyer A, Horvath HT, Bero L.
Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials.
Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: MR000034.
DOI: 10.1002/14651858.MR000034.pub2.

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[Methodology Review]

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials

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Editorial group: Cochrane Methodology Review Group.
Publication status and date: New, published in Issue 4, 2014.

Citation: Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: MR000034. DOI: 10.1002/14651858.MR000034.pub2.

ABSTRACT

Background

Researchers and organizations often use evidence from randomized controlled trials (RCTs) to determine the efficacy of a treatment or intervention under ideal conditions. Studies of observational designs are often used to measure the effectiveness of an intervention in 'real world' scenarios. Numerous study designs and modifications of existing designs, including both randomized and observational, are used for comparative effectiveness research in an attempt to give an unbiased estimate of whether one treatment is more effective or safer than another for a particular population.

A systematic analysis of study design features, risk of bias, parameter interpretation, and effect size for all types of randomized and non-experimental observational studies is needed to identify specific differences in design types and potential biases. This review summarizes the results of methodological reviews that compare the outcomes of observational studies with randomized trials addressing the same question, as well as methodological reviews that compare the outcomes of different types of observational studies.

Objectives

To assess the impact of study design (including RCTs versus observational study designs) on the effect measures estimated.

To explore methodological variables that might explain any differences identified.

To identify gaps in the existing research comparing study designs.

Search methods

We searched seven electronic databases, from January 1990 to December 2013.

Along with MeSH terms and relevant keywords, we used the sensitivity-specificity balanced version of a validated strategy to identify reviews in PubMed, augmented with one term ("review" in article titles) so that it better targeted narrative reviews. No language restrictions were applied.

Selection criteria

We examined systematic reviews that were designed as methodological reviews to compare quantitative effect size estimates measuring efficacy or effectiveness of interventions tested in trials with those tested in observational studies. Comparisons included RCTs versus

observational studies (including retrospective cohorts, prospective cohorts, case-control designs, and cross-sectional designs). Reviews were not eligible if they compared randomized trials with other studies that had used some form of concurrent allocation.

Data collection and analysis

In general, outcome measures included relative risks or rate ratios (RR), odds ratios (OR), hazard ratios (HR). Using results from observational studies as the reference group, we examined the published estimates to see whether there was a relative larger or smaller effect in the ratio of odds ratios (ROR).

Within each identified review, if an estimate comparing results from observational studies with RCTs was not provided, we pooled the estimates for observational studies and RCTs. Then, we estimated the ratio of ratios (risk ratio or odds ratio) for each identified review using observational studies as the reference category. Across all reviews, we synthesized these ratios to get a pooled ROR comparing results from RCTs with results from observational studies.

Main results

Our initial search yielded 4406 unique references. Fifteen reviews met our inclusion criteria; 14 of which were included in the quantitative analysis.

The included reviews analyzed data from 1583 meta-analyses that covered 228 different medical conditions. The mean number of included studies per paper was 178 (range 19 to 530).

Eleven (73%) reviews had low risk of bias for explicit criteria for study selection, nine (60%) were low risk of bias for investigators' agreement for study selection, five (33%) included a complete sample of studies, seven (47%) assessed the risk of bias of their included studies,

Seven (47%) reviews controlled for methodological differences between studies,

Eight (53%) reviews controlled for heterogeneity among studies, nine (60%) analyzed similar outcome measures, and four (27%) were judged to be at low risk of reporting bias.

Our primary quantitative analysis, including 14 reviews, showed that the pooled ROR comparing effects from RCTs with effects from observational studies was 1.08 (95% confidence interval (CI) 0.96 to 1.22). Of 14 reviews included in this analysis, 11 (79%) found no significant difference between observational studies and RCTs. One review suggested observational studies had larger effects of interest, and two reviews suggested observational studies had smaller effects of interest.

Similar to the effect across all included reviews, effects from reviews comparing RCTs with cohort studies had a pooled ROR of 1.04 (95% CI 0.89 to 1.21), with substantial heterogeneity (I^2 = 68%). Three reviews compared effects of RCTs and case-control designs (pooled ROR: 1.11 (95% CI 0.91 to 1.35)).

No significant difference in point estimates across heterogeneity, pharmacological intervention, or propensity score adjustment subgroups were noted. No reviews had compared RCTs with observational studies that used two of the most common causal inference methods, instrumental variables and marginal structural models.

Authors' conclusions

Our results across all reviews (pooled ROR 1.08) are very similar to results reported by similarly conducted reviews. As such, we have reached similar conclusions; on average, there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions. Factors other than study design *per se* need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies. Our results underscore that it is important for review authors to consider not only study design, but the level of heterogeneity in meta-analyses of RCTs or observational studies. A better understanding of how these factors influence study effects might yield estimates reflective of true effectiveness.

PLAIN LANGUAGE SUMMARY

Comparing effect estimates of randomized controlled trials and observational studies

Researchers and organizations often use evidence from randomized controlled trials (RCTs) to determine the efficacy of a treatment or intervention under ideal conditions, while studies of observational designs are used to measure the effectiveness of an intervention in non-experimental, 'real world' scenarios. Sometimes, the results of RCTs and observational studies addressing the same question may have different results. This review explores the questions of whether these differences in results are related to the study design itself, or other study characteristics.

This review summarizes the results of methodological reviews that compare the outcomes of observational studies with randomized trials addressing the same question, as well as methodological reviews that compare the outcomes of different types of observational studies.

The main objectives of the review are to assess the impact of study design--to include RCTs versus observational study designs (e.g. cohort versus case-control designs) on the effect measures estimated, and to explore methodological variables that might explain any differences.

We searched multiple electronic databases and reference lists of relevant articles to identify systematic reviews that were designed as methodological reviews to compare quantitative effect size estimates measuring efficacy or effectiveness of interventions of trials with observational studies or different designs of observational studies. We assessed the risks of bias of the included reviews.

Our results provide little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, inclusion of pharmacological studies, or use of propensity score adjustment. Factors other than study design *per se* need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies.

BACKGROUND

Researchers and organizations often use evidence from randomized controlled trials (RCTs) to determine the efficacy of a treatment or intervention under ideal conditions. Studies of observational design are used to measure the effectiveness of an intervention in non-experimental, 'real world' scenarios at the population level. The Institute of Medicine defines comparative effectiveness research (CER) as: “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels" (Institute of Medicine 2009). Comparative effectiveness research has also been called "comparative clinical effectiveness research" and "patient centered outcomes research" (Kamerow 2011). Regardless of what this type of research is called, it should give an unbiased estimate of whether one treatment is more effective or safer than another for a particular population. Debate about the validity of observational studies versus randomized trials for estimating effectiveness of interventions has continued for decades.

Numerous study designs and modifications of existing designs, both randomized and observational, are used for comparative effectiveness research. These include, but are not limited to, head-to-head randomized trials, cluster-randomized trials, adaptive designs, practice/pragmatic/explanatory trials, PBE-CPI “practice based evidence for clinical practice improvement,” natural experiments, observational or cross-sectional studies of registries and databases including electronic medical records, meta-analysis, network meta-analysis, modeling and simulation. Modifications can often include newer observational study analysis approaches employing so-called causal inference techniques, which can include instrumental variables, marginal structural models, propensity scores, among others. Non-randomized experimental designs (e.g., non-randomized trials), also play a role in comparative effectiveness research, but this review focuses on comparing randomized trials with non-experimental observational designs. As noted in the *Cochrane Handbook for Systematic Reviews of Interventions*, potential biases for all non-randomized studies are likely to be greater than for randomized trials (Higgins 2011). A systematic analysis of study design features, risk of bias, and effect size for all the types of studies used for comparative effectiveness research is needed to identify specific differences in design types and potential biases.

This review summarizes the results of methodological reviews that compare the outcomes of observational studies with randomized trials addressing the same question, as well as methodological reviews that compare the outcomes of different types of observational studies. A number of reviews comparing the effect sizes and/or biases in RCTs and observational studies (or non-randomized controlled trials) have been conducted (Benson 2000; Britton 1998; Concato 2000; Deeks 2003; Ioannidis 2001; Kunz 1998; Kunz 2002; MacLehose 2000; Odgaard-Jensen 2011; Oliver 2010; Sacks 1982; Wilson 2001).These reviews examined whether certain types of study designs report smaller or larger treatment effects, or change the direction of effects. Some reviews found that a lack of randomization or inadequate randomization is associated with selection bias, larger treatment effects, smaller treatment effects, or reversed direction of treatment effects (Deeks 2003; Ioannidis 2001; Kunz 1998; Odgaard-Jensen 2011), while others found little to no difference in treatment effect sizes between study designs (Benson 2000; Britton 1998; Concato 2000; MacLehose 2000; Oliver 2010). However, there has been no systematic review of comparisons of all study designs currently being used for comparative effectiveness research. Reviews that compared RCTs with observational studies most often limited the comparison to cohort studies, or the types of observational designs included were not specified. In addition, most of the reviews were published between 1982 and 2003 and the methodology for observational studies has evolved since that time. One Cochrane review, first published in 2002 (Kunz 2002), has been archived and superseded by later versions. The most recent version of that review, published in 2011, compared random allocation versus non-random allocation or adequate versus inadequate/unclear concealment of allocation in randomized trials (Odgaard-Jensen 2011). This review included comparisons of randomized trials ("randomized controlled trials" or "RCTs"); non-randomized trials with concurrent controls, and non-equivalent control group designs. The review excluded comparisons of studies using historical controls (patients treated earlier than those who received the intervention being evaluated, frequently called "historically controlled trials" or "HCTs"); classical observational studies, including cohort studies, cross-sectional studies, case-control studies and ’outcomes studies’ (evaluations using large administrative or clinical databases). Another recent review assessing the relationship between randomized study designs and estimates of effect has focused only on policy interventions (Oliver 2010).

Why it is important to do this review

Despite the need for rigorous comparative effectiveness research, there has been no systematic comparison of effect measure estimates among all the types of randomized and non-experimental observational study designs that are being used to assess effectiveness of interventions. The findings of this review will inform the design of future comparative effectiveness research and help prioritize the types of context-specific study designs that should be used to minimize bias.

OBJECTIVES

To assess the impact of study design - to include RCTs versus observational study designs on the effect measures estimated.

To explore methodological variables that might explain any differences identified. Effect size estimates may be related to the underlying risk of bias (i.e., methodological variables) of the studies, and not the design *per se*. A flawed RCT may have larger effect estimates than a rigorous cohort study, for example. If the methodological reviews we included assessed the risk of bias of the study designs they included, we attempted to see if the differences in risk of bias explain any differences in effect size estimates.

To identify gaps in the existing research comparing study designs.

METHODS

Criteria for considering studies for this review

Types of studies

We examined systematic reviews that were designed as methodological reviews to compare quantitative effect size estimates measuring efficacy or effectiveness of interventions tested in trials with those tested in observational studies. For the purposes of this review, a methodological review is defined as a review that is designed to compare outcomes of studies that vary by a particular methodological factor (in this case, study design) and not to compare the clinical effect of an intervention to no intervention or a comparator. Comparisons included RCTs and observational studies (including retrospective cohorts, prospective cohorts, case-controls, and cross-sectional designs) that compared effect measures from different study designs or analyses. For this review, the only non-experimental studies we analyzed were observational in design. Therefore, we use the term "observational" in presenting the findings of our review. However, it should be noted that the terminology used in the literature to describe study designs is not consistent and can lead to confusion.

We included methodological reviews comparing studies described in the review as head to head randomized trials, cluster randomized trials, adaptive designs, practice / pragmatic / explanatory trials, PBE-CPI “practice based evidence for clinical practice improvement,” natural experiments, prospective and retrospective cohort studies, case-control studies, observational or cross-sectional studies of registries and databases including electronic medical records, or observational studies employing so-called causal inference techniques (e.g. briefly, analytical techniques that attempt to estimate a true causal relationship from observational data), which could include instrumental variables, marginal structural models, or propensity scores. Specifically, we included comparisons of estimates from RCTs with any of the above types of observational studies.

Our focus is on reviews of effectiveness or harms of health-related interventions. We included two types of reviews: a) systematic reviews of primary studies in which the review's main objective was pre-defined to include a comparison of study designs and not to answer one specific clinical research question; and b) methodological reviews of reviews that included existing reviews or meta-analyses that compared RCTs with observational designs. We excluded comparisons of study designs where the included studies were measuring the effects of putative harmful substances that are not health-related interventions, such as environmental chemicals, or diagnostic tests, as well as studies measuring risk factors or exposures to potential hazards. We excluded studies that compared randomized trials to non-randomized trials. For example, we excluded studies that compared studies with random allocation to those with non-random allocation or trials with adequate versus inadequate/unclear concealment of allocation. We also excluded studies that compared the results of meta-analyses with the results of single trials or single observational studies. Lastly, we excluded meta-analyses of the effects of an intervention that included both randomized trials and observational studies with an incidental comparison of the results.

Types of data

It was our intention to select reviews that quantitatively compared the efficacy or effectiveness of alternative interventions to prevent or treat a clinical condition or to improve the delivery of care. Specifically, our study sample included reviews that have effect estimates from RCTs or cluster-randomized trials and observational studies, which included, but were not limited to, cohort studies, case-control studies, cross-sectional studies.

Types of methods

We identified reviews comparing effect measures between trials and observational studies or different types of observational studies to include the following.

- RCTs/cluster-randomized trials versus prospective/ retrospective cohorts
- RCTs/cluster-randomized trials versus case-control studies
- RCTs/cluster-randomized trials versus cross-sectional studies
- RCTs/cluster-randomized trials versus other observational design
- RCTs/cluster-randomized trials versus observational studies employing so-called causal inference analytical methods

Types of outcome measures

The direction and magnitude of effect estimates (e.g. odds ratios, relative risks, risk difference) varied across meta-analyses included in this review. Where possible, we used odds ratios as the outcome measure in order to conduct a pooled odds ratio analysis.

Search methods for identification of studies

Electronic searches

To identify relevant methodological reviews we searched the following electronic databases, in the period from 01 January 1990 to 06 December 2013.

- Cochrane Methodology Register
- Cochrane Database of Systematic Reviews
- MEDLINE (via PubMed)
- EMBASE (via EMBASE.com)
- Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS)
- PsycINFO
- Web of Science/Web of Social Science

Along with MeSH terms and a wide range of relevant keywords, we used the sensitivity-specificity balanced version of a validated strategy to identify reviews in PubMed (Montori 2004), augmented with one term ("review" in article titles) so that it better targeted reviews. We anticipated that this strategy would retrieve all relevant reviews. See Appendix 1 for our PubMed search strategy, which was modified as appropriate for use in the other databases.

The search strategy was iterative, in that references of included reviews were searched for additional references. We used the "similar articles" and "citing articles" features of several of the databases to identify additional relevant articles. All languages were included.

Prior to executing the electronic searches, the search strategy was peer reviewed by a second information specialist, according to the Peer Review of Electronic Search Strategies (PRESS) guidance (Sampson 2009).

Data collection and analysis

The methodology for data collection and analysis was based on the guidance of *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

After removing duplicate references, one review author (THH) screened the results, excluding those that were clearly irrelevant (e.g. animal studies, editorials, case studies).

Two review authors (AA and LB) then independently selected potentially relevant reviews by scanning the titles, abstracts, and descriptor terms of the remaining references and applying the inclusion criteria. Irrelevant reports were discarded, and the full article (or abstract if from a conference proceeding) was obtained for all potentially relevant or uncertain reports. The two review authors independently applied the inclusion criteria. Reviews were reviewed for relevance based on study design, types of methods employed, and a comparison of effects based on different methodologies or designs. THH adjudicated any disagreements that could not be resolved by discussion.

Data extraction and management

After an initial search and article screening, two review authors independently double-coded and entered information from each selected study onto standardized data extraction forms. Extracted information included the following.

- **Study details***:* citation, start and end dates, location, eligibility criteria, (inclusion and exclusion), study designs compared, interventions compared.
- **Comparison of methods details:** effect estimates from each study design within each publication.
- **Outcome details:** primary outcomes identified in each study.

Assessment of risk of bias in included studies

We included systematic reviews of studies therefore, The Cochrane Collaboration tool for assessing the risk of bias for individual studies does not apply. We used the following criteria to appraise the risk of bias of included reviews, which are similar to those used in the methodology review by Odgaard-Jensen and colleagues (Odgaard-Jensen 2011).

- Were explicit criteria used to select the studies?
- Did two or more investigators agree regarding the selection of studies?
- Was there a consecutive or complete sample of studies?
- Was the risk of bias of the included studies assessed?
- Did the review control for methodological differences of included studies (for example, with a sensitivity analysis)?
- Did the review control for heterogeneity in the participants and interventions in the included studies?
- Were similar outcome measures used in the included studies?
- Is there an absence of risk of selective reporting?
- Is there an absence of evidence of bias from other sources?

Each criterion was rated as yes, no or unclear.

We summarized the overall risk of bias of each study as: low risk of bias, unclear risk of bias or high risk of bias.

Measures of the effect of the methods

In general, outcome measures included relative risks or rate ratios (RR), odds ratios (OR), hazard ratios (HR).

Dealing with missing data

This review is a secondary data analysis and did not incur the missing data issues seen in most systematic reviews. However, for a select, small number of reviews we needed more information from the publishing authors regarding methods or other details, therefore, we contacted the corresponding authors.

Assessment of heterogeneity

We synthesized data from multiple reviews to compare effects from RCTs with observational studies. We had a wide variety of outcomes and interventions synthesized, increasing the amount of heterogeneity between reviews. We assessed heterogeneity using the χ^2 statistic with a significance level of 0.10, and the I^2 statistic. Together with the magnitude and direction of the effect, we interpreted an I^2 estimate between 30% and 60% as indicating moderate heterogeneity, 50% to 90% substantial heterogeneity, and 75% to 100% as a high level of heterogeneity. Furthermore, if an included study was, in fact, a review article that already assessed heterogeneity, we reported the authors' original assessment of heterogeneity.

Assessment of reporting biases

We attempted to minimize the potential for publication bias by our comprehensive search strategy that included evaluating published and unpublished literature. In cases where we were missing specific information or data, we contacted authors and requested additional data.

Data synthesis

We examined the relationship between study design type and the affiliated estimates. Using results from observational studies as the reference group, we examined the published estimates to see whether there was a relative smaller or larger effect. We explored whether the RCT comparators showed about the same effects, larger treatment effects, or smaller treatment effects compared to the observational study reference group. Furthermore, in the text we qualitatively described the reported results from each included review. Within each identified review, if an estimate comparing results from RCTs with observational studies was not provided, we pooled the estimates for observational studies and RCTs. Then, using methods described by Altman (Altman 2003), we estimated the ratio of ratios (hazard ratio or risk ratio or odds ratio) for each included review using observational studies as the reference group. Across all reviews, we synthesized these ratios to get a pooled ratio of odds ratios (ROR) comparing results from RCTs to results from observational studies. Our results varied considerably by comparison groups, outcomes, interventions, and study design, which contributed greatly to heterogeneity. To avoid overlap of

data between included studies, we did not include data previously included in another included review.

Subgroup analysis and investigation of heterogeneity

Reducing bias in comparative effectiveness research is particularly important for studies comparing pharmacological interventions with their implications for clinical care and health care purchasing. Since a number of the studies comparing study designs used for comparative effectiveness research focused on pharmacological comparisons, we decided, *a priori*, to conduct a subgroup analysis of these pharmacological studies. Specifically, we hypothesized that studies of pharmacological comparisons in a randomized design may have smaller effect estimates than studies of pharmacological comparisons in an observational study.

Additionally, we performed a subgroup analysis by heterogeneity of the included methodological reviews to compare the differences between RCTs and observational studies from the subgroup of methodological reviews with high heterogeneity (as measured in their respective meta-analysis) to those with moderate-low heterogeneity. As such, we stratified the reviews by the heterogeneity *within* each methodology review.

RESULTS

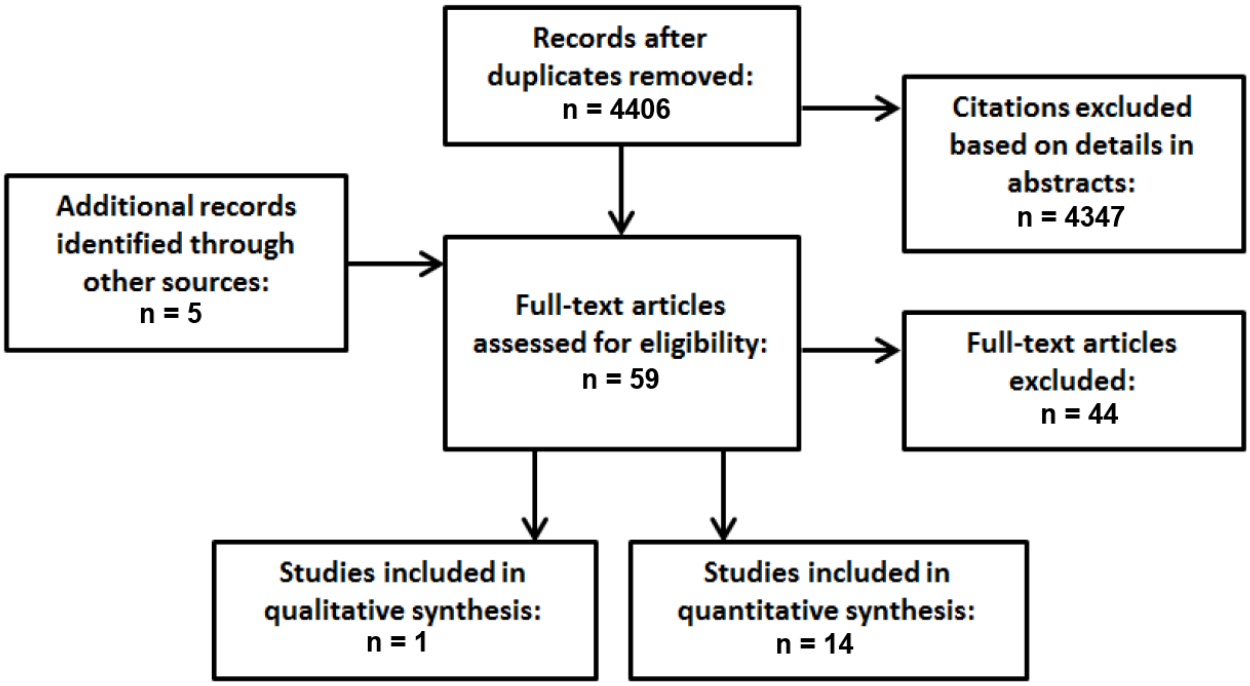
Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Our initial search yielded 4406 unique references. An additional five references were identified from checking the reference lists of included publications. We selected 59 full-text articles for further review, of which 44 were excluded because they did not meet our inclusion criteria. Fifteen reviews met our inclusion criteria for this review; 14 of these reviews were included in the quantitative analysis. See Figure 1 for study selection chart.

Figure 1. Flow chart depicting screening process



Included studies

See Characteristics of included studies. Fifteen reviews, published between 01 January 1990 and 06 December 2013, met the inclusion criteria for this review. Fourteen papers compared RCTs with observational designs; two reviews focused exclusively on pharmacological interventions (Beynon 2008; Naudet 2011), while four focused on pharmacological and other interventions, but provided data on drugs that could be analyzed separately (Benson 2000; Concato 2000; Golder 2011; Ioannidis 2001).

The included reviews analyzed data from 1583 meta-analyses that covered 228 different medical conditions. The mean number of included studies per paper was 178 (range 19 to 530).

Of the 15 reviews, 14 were included in the quantitative analysis and had data, or we were able to obtain quantitative data from the authors, that allowed us to calculate RORs. One study (Papanikolauo 2006) was included in a previously published review (Golder 2011), therefore we have described it, but did not include it in the meta-analysis.

Benson 2000 et al searched the Abridged Index Medicus and Cochrane databases for observational studies published between 1985 and 1998 that compared two or more treatments. To identify RCTs and observational studies comparing the same treatment, the researchers searched MEDLINE and Cochrane databases. One hundred and thirty-six publications were identified that covered 19

different treatments. Benson 2000 et al found little evidence that treatment effect estimates obtained from observational studies were consistently larger than estimates from RCTs.

Beynon 2008 et al attempted to identify all observational and randomized studies with all-cause mortality as the outcome for a sample of topics selected at random from the medical literature. One hundred and fourteen RCTs and 19 observational studies on 19 topics were included. The ratio of RRs for RCTs compared to observational studies was 0.88 (0.8 to 0.97), suggesting that observational studies had larger treatment effects by 12% on average.

Bhandari 2004 et al conducted a MEDLINE search for both observational and randomized studies comparing internal fixation and arthroplasty in patients with femoral neck fractures in publications between 1969 and 2002. The authors found 27 studies that met the criteria. Bhandari 2004 et al found that observational studies underestimated the relative benefit of arthroplasty by 19.5%.

Concato 2000 et al searched MEDLINE for meta-analyses of RCTs and observational studies of the same intervention published in five major journals between 1991 and 1995. From 99 reports on five clinical topics, observational studies, on average, were similar to RCTs. The authors concluded that well-designed observational studies generally do not have larger effects of treatment when compared to results of RCTs.

Edwards 2012 et al performed a systematic review and meta-analysis comparing effect estimates evaluating the effects of surgical procedures for breast cancer in both RCTs and observational studies. A search of MEDLINE, EMBASE, and Cochrane Databases (2003 to 2008) yielded 12 RCTs covering 10 disparate outcomes. In two of 10 outcomes the pooled estimates from RCTs and observational studies differed, though none significantly. The authors conclude that RCTs comparing breast surgery procedures may yield different estimates in 20% to 40% of cases compared with estimates from observational studies.

Furlan 2008 et al searched for comparative studies of low-back pain interventions published in MEDLINE, EMBASE, or *The Cochrane Library* through May 2005 and included interventions with the highest numbers of non-randomised studies. Seventeen observational studies and eight RCTs were identified and, in general, results from observational studies either agreed with results from RCTs or underestimated the effects when compared to RCTs.

Golder 2011 et al performed a meta-analysis of meta-analyses comparing estimates of harm derived from meta-analysis of RCTs with meta-analyses of observational studies. Fifty-eight meta-analyses were identified. Pooled relative measures of adverse effect (odds ratio (OR) or risk ratio (RR)) suggested no difference in effect between study type (OR = 1.03; 95% confidence interval (CI) 0.93-1.15). The authors conclude that there is no evidence on average in effect estimate of adverse effect of interventions from meta-analyses of RCTs when compared to observational studies.

Ioannidis 2001 et al performed an analysis of meta-analyses comparing effect estimates evaluating medical interventions from meta-analysis of RCTs to meta-analyses of observational studies. A search of MEDLINE (1966to 2000) and *The Cochrane Library* (2000, Issue 3) and major journals yielded 45 diverse topics from 240 RCTs and 168 observational studies. Observational studies tended to show larger treatment effects (P = 0.009). The authors conclude that despite good correlation between RCTs and observational studies, differences in effect sizes are present.

Kuss 2011 et al performed a systematic review and meta-analysis comparing effect estimates from RCTs with observational studies employing propensity scores The included studies examined the effects of off-pump versus on-pump surgery in similar populations. A MEDLINE search yielded 29 RCTs and 10 propensity score analyses covering 10 different outcomes. For all outcomes, no differences were noted between RCTs and propensity score analyses.

The authors conclude that RCTs and propensity score analyses will likely yield similar results and propensity score analyses may have only a small remaining bias compared to RCTs.

Lonjon 2013 et al performed a systematic review and meta-analysis comparing effect estimates from RCTs with observational studies employing propensity scores studying the effects of surgery addressing the same clinical question. A MEDLINE search yielded 94 RCTs and 70 propensity score analyses covering 31 clinical questions. For all-cause mortality the authors noted no differences between RCTs and propensity score analyses (ROR = 1.07; 95% CI 0.87 to 1.33).

The authors conclude that RCTs and propensity score analyses will likely yield similar results in surgery studies.

Müeller 2010 et al searched PubMed for RCTs and observational studies comparing laparoscopic versus open cholecystectomy. A total of 162 studies were identified for inclusion (136 observational and 26 RCTs). Among the 15 outcomes of interest, three yielded significant discrepancies in effect sizes between study designs. As such, the authors conclude that the results from observational studies and RCTs differ significantly in at least 20% of outcomes variables.

Naudet 2011 et al identified published and unpublished studies from 1989 to 2009 that examined fluoxetine and venlafaxine as first line treatment for major depressive disorder. The authors identified 12 observational studies and 109 RCTs and produced meta-regression estimates for outcomes of interest. The standardized treatment response in RCTs was greater by a magnitude of 4.59 compared to observational studies and the authors conclude that the response to antidepressants is greater in RCTs than in observational studies.

Oliver 2010 et al identified systematic reviews that compared results of policy interventions, stratifying estimates by observational study and RCT study design published between 1999 and 2004. A total of 16 systematic reviews were identified, with a median of 11.5 RCTs and 14.5 observational studies in each systematic review. Observational studies published in systematic reviews were pooled separately from RCTs published in the same systematic reviews. Results that were stratified by study design were heterogeneous with no clear differences in magnitude of effects; the authors found no evidence for clear systematic differences in terms of results between RCTs and observational studies.

Shikata 2006 et al identified all meta-analyses of RCTs of digestive surgery published between 1966 and 2004. Fifty-two outcomes for 18 disparate topics were identified from 276 articles (96 RCTs and 180 observational studies). Pooled odds ratios and relative risks were extracted for each outcome, using the same indicator that had been used in the meta-analysis of interest and approximately 25% of all outcomes of interest yielded different results between observational studies and RCTs.

Papanikolauo 2006 et al compared evidence from RCTs with observational studies that explored the effects of interventions on the risk of harm. Harms of interest were identified from RCTs with more than 4000 patients. Observational studies of more than 4000 patients were also included for comparison. Fifteen harms of interest were identified and relative risks were extracted for 13 topics. Data from 25 observational studies were compared with results from RCTs. Relative risks for each outcome/harm were calculated for both study types. The estimated increase in RR differed by more than two-fold between observational studies and RCTs for 54% of the topics studied. The authors conclude that observational studies usually under-estimate the absolute risk of harms. These data were included in Golder 2011 and consequently were not re-analyzed in the current quantitative analysis.

Excluded studies

See Characteristics of excluded studies. Following full-text screening, 44 studies were excluded from this review. The main reasons for exclusion included the following: the studies were meta-analyses that did an incidental comparison of RCTs and observational studies, but were not designed for such a comparison (n = 14); the studies were methodological or statistical papers that did not conduct a full systematic review of the literature (n = 28); or the studies included quasi- or pseudo-randomized studies, or provided no numerical data that would allow a quantitative comparison of effect estimates (n = 7).

Risk of bias in included studies

Eleven reviews had low risk of bias for explicit criteria for study selection (Benson 2000; Beynon 2008; Bhandari 2004; Edwards 2012; Furlan 2008; Ioannidis 2001; Kuss 2011; Müeller 2010; Naudet 2011; Oliver 2010; Papanikolauo 2006); nine (60%) had low risk of bias for investigators' agreement for study selection (Bhandari 2004; Concato 2000; Edwards 2012; Golder 2011; Kuss 2011; Naudet 2011; Oliver 2010; Papanikolauo 2006; Shikata 2006); five (33%) included a complete sample of studies (Bhandari 2004; Müeller 2010; Naudet 2011; Oliver 2010; Shikata 2006); seven (47%) assessed the risk of bias of their included studies (Bhandari 2004; Furlan 2008; Golder 2011; Lonjon 2013; Müeller 2010; Naudet 2011; Oliver 2010); seven (47%) controlled for methodological differences between studies (Furlan 2008; Ioannidis 2001; Kuss 2011; Lonjon 2013; Müeller 2010; Naudet 2011; Oliver 2010); eight (53%) controlled for heterogeneity among studies (Beynon 2008; Edwards 2012; Furlan 2008; Ioannidis 2001; Lonjon 2013; Müeller 2010; Naudet 2011; Oliver 2010); nine (60%) analyzed similar outcome measures (Benson 2000; Beynon 2008; Bhandari 2004; Edwards 2012; Ioannidis 2001; Lonjon 2013; Müeller 2010; Oliver 2010; Shikata 2006); and only four (27%) were judged to be at low risk of reporting bias (Bhandari 2004; Furlan 2008; Ioannidis 2001; Naudet 2011).

We rated reviews that were coded as adequate for explicit criteria for study selection, complete sample of studies, and controlling for methodological differences and heterogeneity as having a low risk of bias and all others as having a high risk of bias. Two reviews, Müeller 2010 and Naudet 2011, met all four of these criteria and, thus, had an overall low risk of bias.

See Figure 2; Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

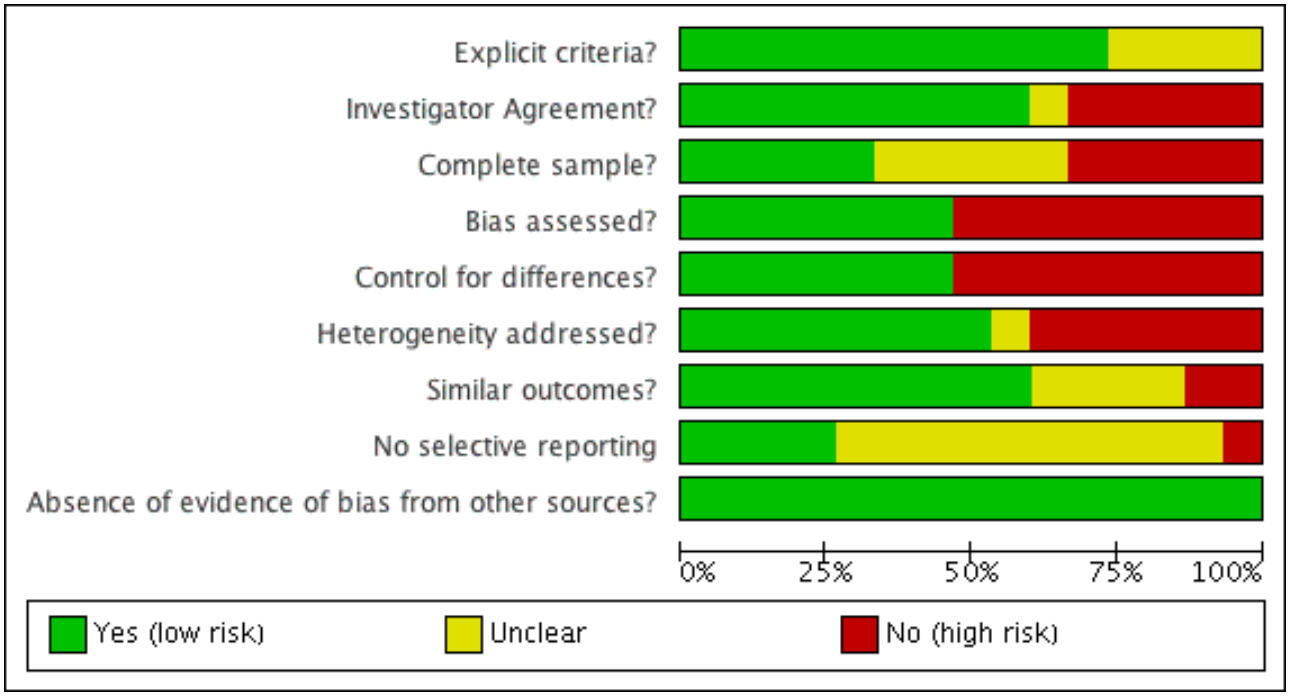
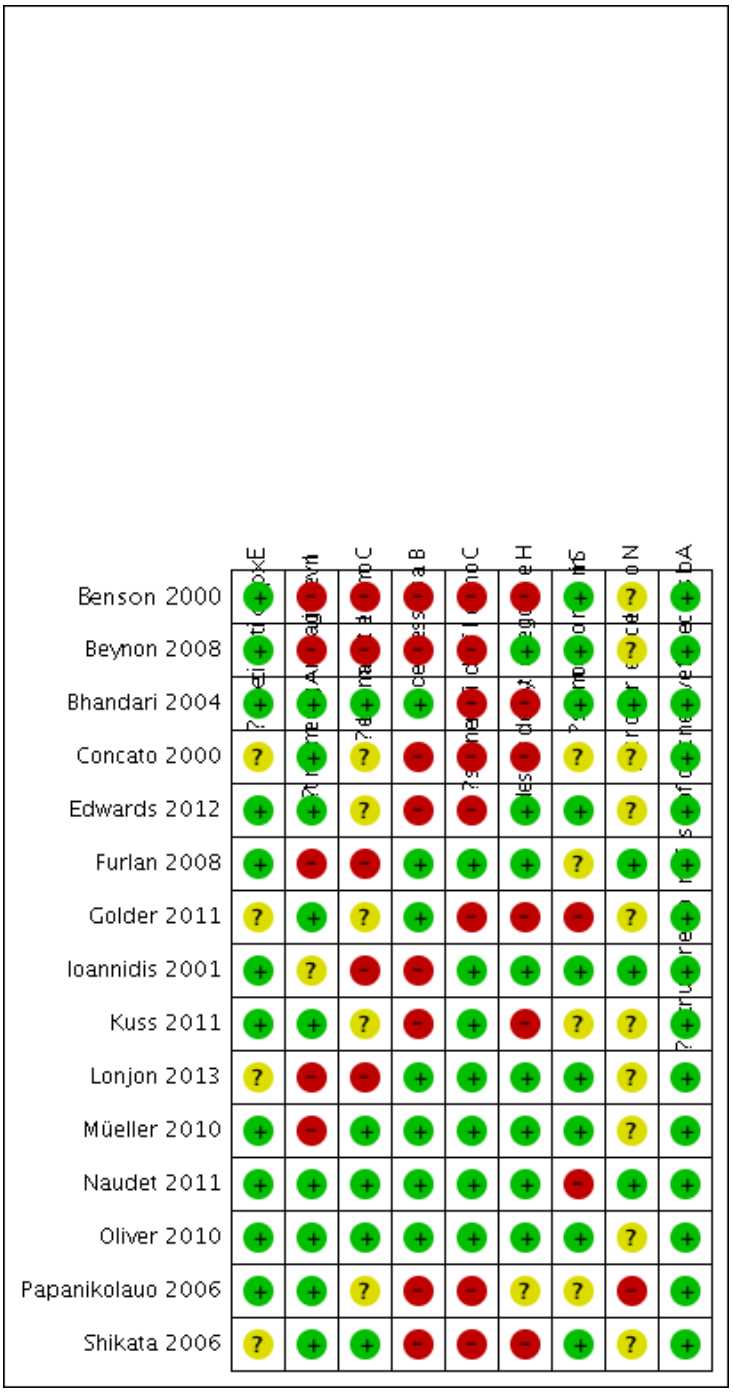


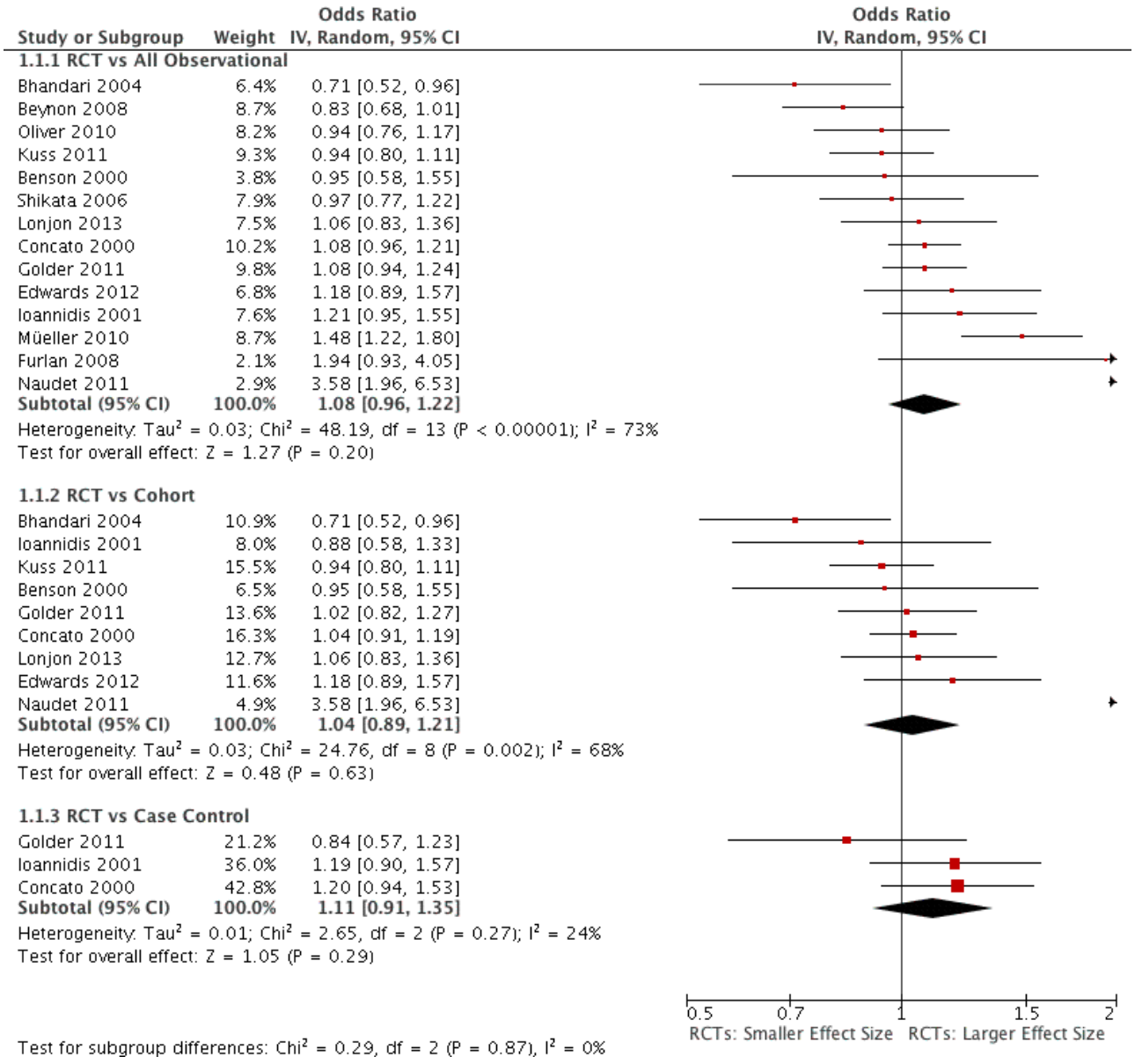
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Effect of methods

Our primary quantitative analysis (Analysis 1.1), including 14 reviews, showed that the pooled ratio of odds ratios (ROR) comparing effects from RCTs with effects from observational studies was 1.08 (95% confidence interval (CI) 0.96 to 1.22) (see Figure 4). There was substantial heterogeneity for this estimate (I^2 = 73%). Of the 14 reviews included in this analysis, 11 (71%) found no significant difference between observational studies and RCTs. However, one review suggested observational studies have larger effects of interest (Bhandari 2004), while two other reviews suggested observational studies have smaller effects of interest (Müeller 2010; Naudet 2011).

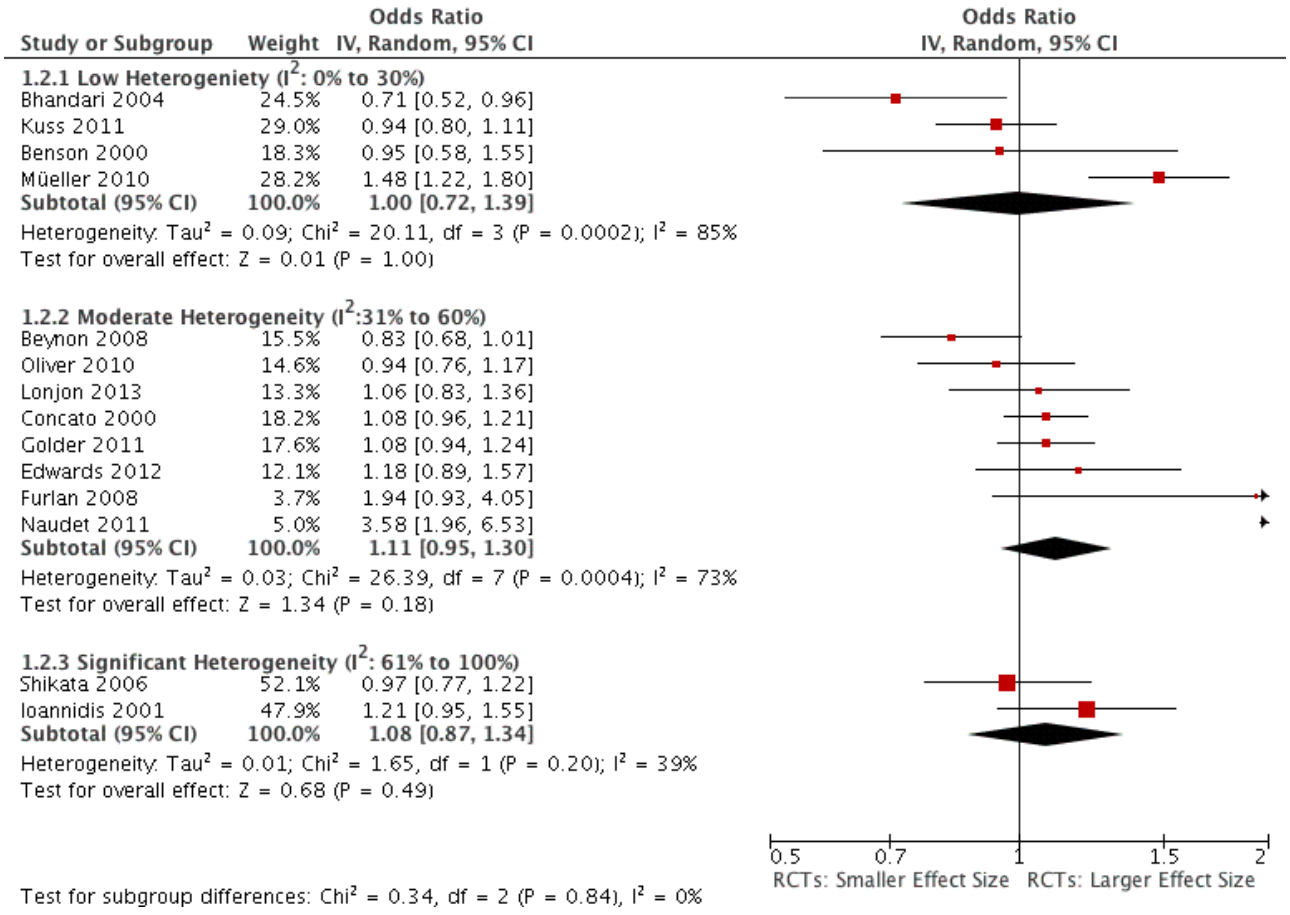
Figure 4. Forest plot of comparison: 1 RCT vs Observational, outcome: 1.2 Pooled Ratio of Odds Ratios--Study Design.



When possible or known, we isolated our results to reviews that specifically compared cohort studies and RCTs. Nine reviews either provided adequate data or performed these analyses in their publication (Benson 2000; Bhandari 2004; Concato 2000; Edwards 2012; Golder 2011; Ioannidis 2001; Kuss 2011; Lonjon 2013; Naudet 2011) Similar to the effect across all included reviews, the effects from RCTs compared with cohort studies was pooled ROR = 1.04 (95% CI 0.89 to 1.21), with substantial heterogeneity (I^2 = 68%) (Analysis 1.1.2). In lieu of a sensitivity analysis removing case-control studies, we performed a subgroup analysis of reviews that compared the effects of case-controls versus RCTs (Concato 2000; Golder 2011; Ioannidis 2001). The pooled ROR comparing RCTs with case-control studies was 1.11 (95% CI 0.91 to 1.35), with minor heterogeneity (I^2 = 24%). There was no significant difference between observational study design subgroups (P value = 0.61).

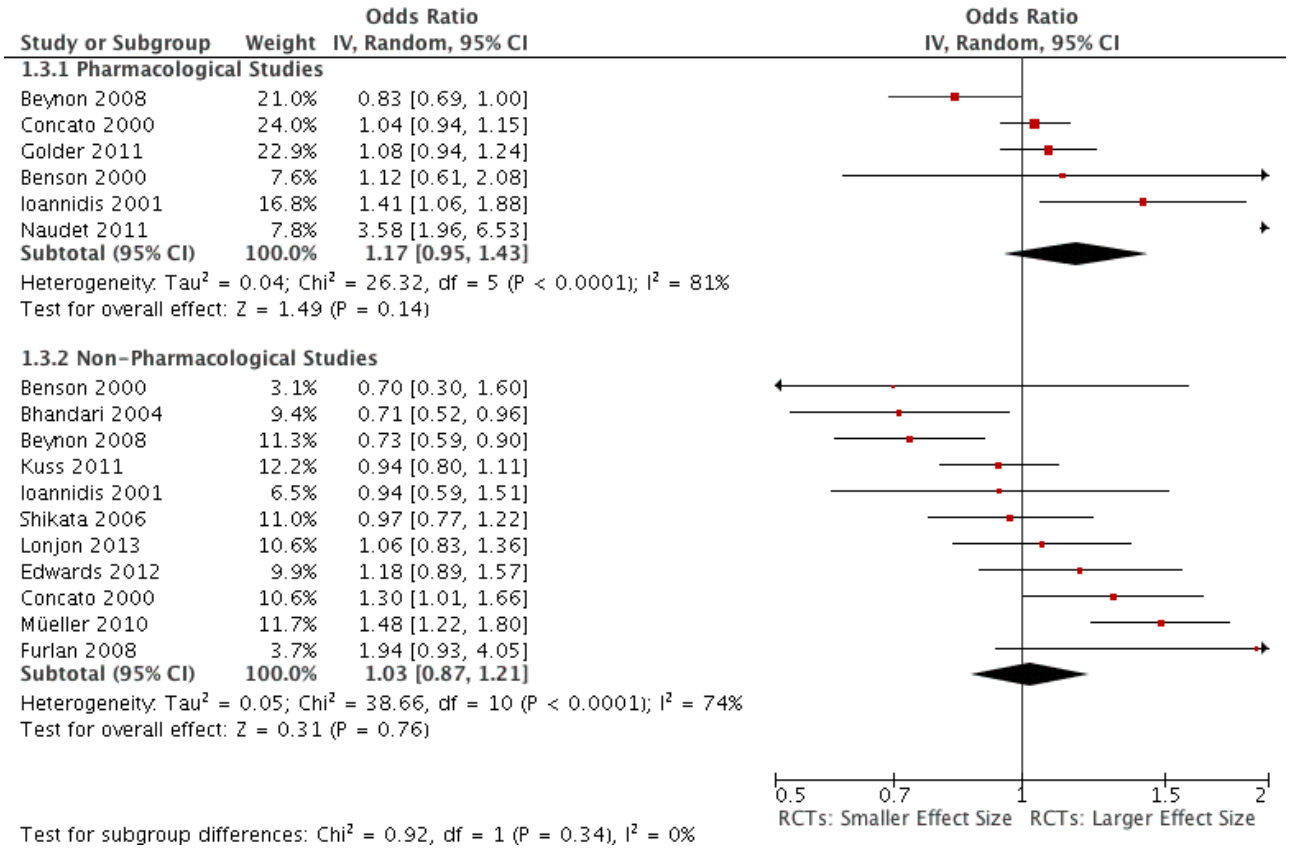
We also performed a subgroup analysis of all reviews stratified by levels of heterogeneity of the pooled RORs from the respective reviews (Analysis 1.2). No significant difference in point estimates across heterogeneity subgroups were noted (see Figure 5). Specifically, comparing RCTs with observational studies in the low heterogeneity subgroup yielded a pooled ROR of 1.00 (95% CI 0.72 to 1.39). The pooled ROR comparing RCTs with observational studies in the moderate heterogeneity group was also not significantly different (OR = 1.11; 95% CI 0.95 to 1.30). Similarly, the pooled ROR comparing RCTs with observational studies in the significant heterogeneity group was 1.08 (95% CI 0.87 to 1.34).

Figure 5. Forest plot of comparison: 1 RCT vs Observational, outcome: 1.3 Pooled Ratio of Odds Ratios--Heterogeneity Subgroups.



Additionally, we performed a subgroup analysis of all included reviews stratified by whether they compared pharmacological studies or not (Analysis 1.3). Though the pooled ROR for comparisons of pharmacological studies was higher than the pooled ROR for reviews of non-pharmacological studies, this difference was not significant (see Figure 6) (P value = 0.34). Namely, the pooled ROR comparing RCTs with observational studies in the pharmacological studies subgroup of six reviews was 1.17 (95% CI 0.95 to 1.43), with substantial heterogeneity (I^2 = 81%). The pooled ROR comparing RCTs with observational studies in the non-pharmacological studies subgroup of 11 reviews was 1.03 (95% CI 0.87 to 1.21), with substantial heterogeneity (I^2 = 74%).

Figure 6. Forest plot of comparison: 1 RCT vs Observational, outcome: 1.4 Pooled Ratio of Odds Ratios--Pharmacological Studies Subgroups.



Lastly, we performed an analysis of all included reviews that compared RCTs and observational studies that employed propensity score adjustments (Analysis 1.4). The pooled ROR comparing estimates from RCTs with the estimates from observational studies using propensity scores was not significant. Namely, the pooled ROR comparing RCTs with observational studies with propensity scores (two reviews) was 0.98 (95% CI 0.85 to 1.12), with no heterogeneity (I^2 = 0%). There was no difference between the pooled ROR of RCTs versus observational studies with propensity score adjustment and the pooled ROR of RCTs versus observational studies without propensity score adjustment (P value = 0.22).

DISCUSSION

Summary of main results

Our results showed that, on average, there is little difference between the results obtained from RCTs and observational studies. In addition, despite several subgroup analyses, no significant differences between effects of study designs were noted. However, due to high statistical heterogeneity, there may be important differences between subgroups of reviews that we were unable to identify, Our primary quantitative analysis showed that the pooled ROR comparing effects from RCTs with effects from observational studies was 1.08 (95% CI 0.96 to 1.22). The effects from RCTs compared with cohort studies only was pooled ROR = 1.04 (95% CI 0.89 to 1.21), while the pooled ROR comparing RCTs with only case-control studies was1.11 (95% CI 0.91 to 1.35).

Though not significant, the point estimates suggest that observational studies may have smaller effects than those obtained in RCTs, regardless of observational study design. Furthermore, it is possible that the difference between effects obtained from RCTs and observational studies has been somewhat attenuated in more recent years due to researchers' improved understanding of how to handle adjustments in observational studies. In the present study, it was not always very clear which observational studies included adjusted estimates and which did not in the included reviews. Bhandari et al reported that no observational study adjusted for all nine confounders the authors felt were important (Bhandari 2004). In fact, they adjusted for as few as two and as many as six. Mueller et al reported that of the 136 non-RCTs included in their review, 19 population-based studies and 22 other studies adjusted their results for baseline imbalances (Müeller 2010). Two reviews included only observational studies with propensity score adjustments (Kuss 2011; Lonjon 2013). Other included reviews note the importance of adjustment in the estimates from observational studies, but do not specifically list the studies with and without adjusted estimates. Our results suggest that although observational designs may be more biased than RCTs, this does not consistently result in larger or smaller intervention effects.

We also found that the effect estimate differences between observational studies and RCTs were potentially influenced by the heterogeneity within meta-analyses. Though subgroup analyses comparing heterogeneity groups were not statistically significant, meta-analyses comparing RCTs and observational studies may be

particularly influenced by heterogeneity and researchers should consider this when designing such comparisons. However, with so few reviews, spurious effects between heterogeneity subgroups cannot be ruled out.

The risks of bias in the included reviews were generally high. In particular, two-thirds of all included reviews either did not include a complete sample or there was not enough information provided to make a determination, and more than half of the reviews did not assess the risk of bias of their included studies. Furthermore, nearly three-quarters of the included reviews were judged to be at high or unclear risk of reporting bias.

We note that our results may be influenced by the different comparison arms in all the studies included in the reviews. Often the specific types of comparison arms in the meta-analyses were not identified in the review. However, among included reviews with reported details about comparison arms in the RCTs in the meta-analyses (n = 519 meta-analyses), 84% (n = 454) compared one intervention (e.g., drug or surgery) with another intervention (drug or surgery), 11% (n = 55) used a placebo or sham, 3% (n = 13) used an unspecified control arm, and 2% (n = 15) compared one intervention with no intervention or treatment.

Lastly, though not statistically significant, there appears to be a difference in effect comparing RCTs and observational studies when considering studies with pharmacological-only interventions or studies without pharmacological interventions. More specifically, the difference in point estimates between pharmacological RCTs and observational pharmacological studies is greater than the difference in point estimates from non-pharmacological studies. Perhaps this is a reflection of the difficulties in removing all potential confounding in observational pharmacological studies; or, perhaps this is an artifact of industry or selective reporting bias in pharmacological RCTs. The most recent study quantifying pharmaceutical industry support for drug trials found that the pharmaceutical industry funded 58% of drug trials in 2007 and this was the largest source of funding for these trials (Dorsey 2010). This is not surprising as RCTs must be submitted to regulatory agencies to obtain regulatory approval of drugs, whereas observational studies of drugs are conducted after drug approval. Funding and selective reporting bias have been well documented in industry-sponsored RCTs (Lundh 2012) and less is known about the extent of these biases in observational studies.

Potential biases in the review process

We reduced the likelihood for bias in our review process by having no language limits for our search and having two review authors independently screen abstracts and articles for selection. Nevertheless, we acknowledge the potential for introduction of unknown bias in our methods as we collected a myriad of data from 14 reviews (1583 meta-analyses covering 228 unique outcomes).

Agreements and disagreements with other studies or reviews

Our results across all reviews (pooled ROR 1.08; 95% CI 0.96 to 1.22) are very similar to results reported by Concato 2000 and Golder 2011. As such, we have reached similar conclusions--there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of drug studies.

Golder 2011 (and consequently, Papanikolauo 2006) and Edwards 2012) were the only reviews that focused on harm outcomes. Golder's findings do not support the notion that observational studies are more likely to detect harm than randomized controlled trials, as no differences in RCTs and observational studies were detected. However, this finding may be related to the short-term nature of the adverse events studied where one would expect shorter-term trials to be as likely to detect harm as longer-term observational studies.

AUTHORS' CONCLUSIONS

Implication for methodological research

In order to understand why RCTs and observational studies addressing the same question sometimes have conflicting results, methodological researchers must look for explanations other than the study design *per se*. Confounding is the greatest bias in an observational study compared to an RCT and methods for accounting for confounding in meta-analyses of observational studies should be developed (Reeves 2013). The Patient-Centered Outcomes Research Institute is finalizing methodological standards and calling for more research on measuring confounding in observational studies(PCORI 2012). PCORI has also called for empirical data to support the constitution of propensity scores and the validity of instrumental variables, two methods used to control for confounding in observational studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Benson 2000

Methods	Searched for all RCTs and observational studies that compared 2 or more treatments between 1985 and 1998
Data	136 reports about 19 disparate treatments and interventions
Comparisons	Combined magnitude of effects from RCTs vs combined magnitude of effects from observational studies for same treatment
Outcomes	17 of 19 analyses yielded no difference in magnitude of effects comparing methods

Benson 2000 *(Continued)*

Notes	Little evidence that estimates of treatment effects in observational studies are larger than effects from RCTs

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Yes	Had four inclusion criteria for observational studies matched to RCTs
Investigator Agreement?	No	No mention of this
Complete sample?	No	They could have missed observational studies due to poor indexing
Bias assessed?	No	Not done
Control for differences?	No	Methodological differences noted, but not controlled for
Heterogeneity addressed?	No	Noted, but not controlled for
Similar outcomes?	Yes	The few exceptions where outcomes were not similar were noted
No selective reporting?	Unclear	Not discussed in detail
Absence of evidence of bias from other sources?	Yes	

Beynon 2008

Methods	Searched for RCTs and observational studies with all-cause mortality as the outcome for a sample of topics randomly selected from the medical literature
Data	114 RCTs and 71 observational studies on19 diverse topics identified
Comparisons	Ratio of relative risks (RRR) calculated comparing RCT vs observational studies for each outcome
Outcomes	16 of 19 analyses yielded no difference in RRRs comparing methods
Notes	Little evidence that estimates of treatment effects in observational studies are larger than effects from RCTs

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Yes	Identified by outcome, then observational studies were matched to an RCT
Investigator Agreement?	No	No mention of this
Complete sample?	No	Topics selected at random
Bias assessed?	No	Not done
Control for differences?	No	Mentioned selection bias of observational studies but did not control for this

Beynon 2008 *(Continued)*

Heterogeneity addressed?	Yes	Controlled for heterogeneity
Similar outcomes?	Yes	All mortality
No selective reporting?	Unclear	Not discussed in detail
Absence of evidence of bias from other sources?	Yes	

Bhandari 2004

Methods	An analysis of all studies, observational studies and RCTs, published between 1962 and 2002 which compared internal fixation and arthroplasty in femoral neck fracture patients
Data	27 studies eligible for inclusion:14 RCTs and 13 observational studies
Comparisons	Pooled data across studies for each outcome and calculated relative risks
Outcomes	Observational studies underestimated the relative benefit of arthroplasty by 19.5% (the risk reduction for revision surgery with arthroplasty compared with internal fixations was 77% for RCTs and 62% for NRS)
Notes	Observational studies provide results that are dissimilar to results provided by RCTs specifically for arthroplasty vs internal fixation for revision rates and mortality in femoral neck fracture patients

Risk of bias

Item	**Authors' judgement**	**Description**
Explicit criteria?	Yes	4 explicit criteria on focused topics
Investigator Agreement?	Yes	Two reviewed
Complete sample?	Yes	Complete sample on focused topic
Bias assessed?	Yes	Yes, table 1
Control for differences?	No	Discussed, but not controlled for
Heterogeneity addressed?	No	No mention
Similar outcomes?	Yes	Part of selection criteria
No selective reporting?	Yes	Thorough search included seeking unpublished studies
Absence of evidence of bias from other sources?	Yes	

Concato 2000

Methods	Identified all meta-analyses published between 1991 and 1995 in five major journals

Concato 2000 *(Continued)*

Data	72 RCTs and 24 observational studies were identified, in addition to 6 meta-analyses of both study method types, which covered 5 clinical topic areas. A total of 1,871,681 study participants were included in all analyses.
Comparisons	Pooled data across studies for each outcome and calculated relative risks
Outcomes	Effectiveness of Bacille Calmette-Guerin vaccine and TB (no difference between study design); Mammography and mortality (no difference); cholesterol levels and death due to trauma (no difference); treatment of hypertension and stroke (no difference between study design); treatment of hypertension and coronary heart disease (no difference)
Notes	No noted difference in point estimates between observational study results and RCT study results.

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Unclear	Studies were identified from published meta-analyses in 5 journals
Investigator Agreement?	Yes	2 reviewed the MA for inclusion
Complete sample?	Unclear	Depended on how the MA was done
Bias assessed?	No	Stated it was assessed, but not reported or controlled for except in a few cases
Control for differences?	No	Discussed, but not controlled for
Heterogeneity addressed?	No	No mention
Similar outcomes?	Unclear	For some comparisons not clear what outcomes were measured
No selective reporting?	Unclear	Depends on the included MA
Absence of evidence of bias from other sources?	Yes	

Edwards 2012

Methods	RCTs of breast cancer treatment published between 2003-2008 were identified and similar observational studies of the same topics were also identified.
Data	37 studies selected (26 observational studies and 12 RCTs) for inclusion. A total of 32,969 study participants were included in all analyses.
Comparisons	Pooled data across studies for each outcome and calculated relative risks
Outcomes	Nerve dissection versus preservation on sensory deficit (no difference between study designs); axillary lymph node dissection vs sentinel lymph node biopsy on death (no difference between designs); axillary lymph node dissection vs sentinel lymph node biopsy on local recurrence (observational studies may have shown larger effect than RCTs); axillary lymph node dissection vs sentinel lymph node biopsy on numbness (no difference between designs); mastectomy vs breast conserving therapy on death (no difference between designs); mastectomy vs breast conserving therapy on local recurrence (no difference between designs); pectoral minor dissection vs preservation on number of lymph nodes removed (no difference between designs)

Edwards 2012 *(Continued)*

Notes	RCT and observational study results were inconsistently different (3 out of 10 comparisons were different in the authors' presented analyses).

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Yes	All studies had to meet clear, specific, inclusion criteria
Investigator Agreement?	Yes	2 reviewers assessed titles for inclusion
Complete sample?	Unclear	The selective search may have introduced bias by not selecting all available literature
Bias assessed?	No	This was not assessed
Control for differences?	No	Discussed, but not controlled for
Heterogeneity addressed?	Yes	The authors calculated the heterogeneity within each meta-analysis.
Similar outcomes?	Yes	The analyses were stratified by topic type
No selective reporting?	Unclear	RCTs were selected from a 5 year window
Absence of evidence of bias from other sources?	Yes	

Furlan 2008

Methods	Found comparative studies of low back pain published before May 2005. Studies of similar interventions were synthesized
Data	17 observational studies and 8 RCTs identified which covered 3 outcomes of interest
Comparisons	Observational studies were synthesized and compared to the synthesized estimates from RCTs, producing ORs for each outcome
Outcomes	For all 3 outcomes covering comparing study design, observational studies underestimated the effects when compared to RCTs
Notes	Across all studies and outcomes, there is only slight evidence that observational study estimates are different than RCT estimates

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Yes	Observational studies identified according to specific criteria then matched to RCTs
Investigator Agreement?	No	No mention
Complete sample?	No	Selected interventions with the most observational studies

Furlan 2008 *(Continued)*

Bias assessed?	Yes	Assessed RoB plus other characteristics
Control for differences?	Yes	Subgrouped
Heterogeneity addressed?	Yes	Sensitivity analysis
Similar outcomes?	Unclear	Grouped by intervention not outcome
No selective reporting?	Yes	Thorough search included seeking unpublished studies
Absence of evidence of bias from other sources?	Yes	

Golder 2011

Methods	Meta-analysis of meta-analyses comparing estimates of harm derived from meta-analysis of RCTs to meta-analyses of observational studies
Data	58 meta-analyses identified
Comparisons	Effect estimates of meta-analyses of RCTs compared to effect estimates of meta-analyses of observational studies. drug and non-drug studies included in comparisons.
Outcomes	Pooled relative measures of adverse effect (odds ratio or risk ratio)
Notes	No evidence, on average, in risk estimate of adverse effect of interventions from meta-analyses of RCTs vs observational studies

Risk of bias

Item	**Authors' judgement**	**Description**
Explicit criteria?	Unclear	Studies were identified from published meta-analyses in 5 journals
Investigator Agreement?	Yes	Consensus
Complete sample?	Unclear	Depended on how the MA was done
Bias assessed?	Yes	Described in text
Control for differences?	No	Done descriptively
Heterogeneity addressed?	No	Done descriptively
Similar outcomes?	No	Only one outcome had multiple studies addressing it
No selective reporting?	Unclear	Depends on the included MA
Absence of evidence of bias from other sources?	Yes	

Ioannidis 2001

Methods	Identified meta-analyses that considered both RCTs and observational studies published before 2000
Data	45 topics identified from 240 RCTs and 168 observational studies
Comparisons	Effect estimates of meta-analyses of RCTs compared to effect estimates of meta-analyses of observational studies.
Outcomes	Observational studies tended to show larger treatment effect sizes, and in 7 outcomes of 45 studied, differences between RCTs and observational studies were significantly different
Notes	Differences between RCTs and observational studies are present (about 16% of the time)

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Yes	Very explicit for meta-analyses identified and studies within the meta-analyses
Investigator Agreement?	Unclear	Says "we" but not explicit
Complete sample?	No	Could have missed identifying some MA that contained both observational studies and RCTs
Bias assessed?	No	Assessed some study characteristics but not RoB specifically
Control for differences?	Yes	Subgrouped
Heterogeneity addressed?	Yes	Subgrouped
Similar outcomes?	Yes	Grouped by outcomes
No selective reporting?	Yes	Did identify extent of trials that had been published after the included meta-analysis
Absence of evidence of bias from other sources?	Yes	

Kuss 2011

Methods	Performed a systematic review and meta-analysis that compared RCTs and propensity score analyses in similar populations
Data	10 topics identified from 51 RCTs and 28 observational studies that employed propensity scores
Comparisons	Effect estimates of meta-analyses of RCTs compared to effect estimates of meta-analyses of propensity score analyses
Outcomes	Propensity score analyses across all outcomes were no different than estimates from RCTs
Notes	Only a small bias, if any, may remain in propensity score analyses estimating the effects of off-pump versus on-pump surgery

Risk of bias

Kuss 2011 *(Continued)*

Item	Authors' judgement	Description
Explicit criteria?	Yes	The authors included all studies with propensity score analyses comparing off and on pump CABG
Investigator Agreement?	Yes	Two reviewers selected studies independently
Complete sample?	Unclear	It is possible that RCTs that were not previously identified in systematic reviews may have been missed
Bias assessed?	No	Bias not assessed
Control for differences?	Yes	Confounder data were extensively collected
Heterogeneity addressed?	No	Heterogeneity not addressed
Similar outcomes?	Unclear	All analyses were evaluating similar comparisons for disparate outcomes
No selective reporting?	Unclear	Their search was simple and used only MEDLINE for RCTs
Absence of evidence of bias from other sources?	Yes	

Lonjon 2013

Methods	Performed a systematic review and meta-analysis that compared RCTs and prospective observational studies using propensity scores addressing the same clinical questions
Data	31 clinical topics identified from 94 RCTs and 70 observational studies that employed propensity scores
Comparisons	Effect estimates of meta-analyses of RCTs compared to effect estimates of meta-analyses of propensity score analyses
Outcomes	Propensity score analyses across all outcomes were no different than estimates from RCTs
Notes	Prospective observational studies are reliable for providing evidence in the absence of RCTs

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Unclear	31 different clinical questions were included, though it is unclear if these questions were conceived a priori
Investigator Agreement?	No	One reviewer extracted data and one reviewer selected studies based on clinical expertise
Complete sample?	No	Not all RCTs were selected for each research question--restricted to last 5 years
Bias assessed?	Yes	Performance, detection, and attrition biases were all assessed
Control for differences?	Yes	Sensitivity analyses performed
Heterogeneity addressed?	Yes	For all analyses, heterogeneity assessed using I^2 statistic

Lonjon 2013 *(Continued)*

Similar outcomes?	Yes	The authors' primary outcome was all-cause mortality
No selective reporting?	Unclear	As a result of not including all RCTs, selective reporting is possible
Absence of evidence of bias from other sources?	Yes	

Müeller 2010

Methods	Identified studies, including RCTs and observational studies that compared laparoscopic vs open cholecystectomy
Data	162 studies were identified, including 136 observational studies and 26 RCTs, covering 15 outcomes of interest
Comparisons	Effect estimates of RCTs were compared to estimates from observational studies
Outcomes	In 3 of 15 outcomes there were significant differences between results from observational studies and RCTs
Notes	Differences between RCTs and observational studies are present (about 20% of the time)

Risk of bias

Item	**Authors' judgement**	**Description**
Explicit criteria?	Yes	Identified RCTs and observational studies (cohorts) on a specific topic
Investigator Agreement?	No	No mention of this
Complete sample?	Yes	Complete sample on focused topic
Bias assessed?	Yes	Cochrane RoB criteria plus additional
Control for differences?	Yes	Sensitivity analysis
Heterogeneity addressed?	Yes	Sensitivity analysis
Similar outcomes?	Yes	Included studies with different outcomes, analyzed by outcome
No selective reporting?	Unclear	Their search was simplistic (NEDLINE)
Absence of evidence of bias from other sources?	Yes	

Naudet 2011

Methods	Identified published and unpublished studies from 1989 to 2009 that examined fluoxetine and venlafaxine as first line treatment for major depressive disorder
Data	12 observational studies and 109 RCTs were identified

Naudet 2011 *(Continued)*

Comparisons	Meta-regression estimates for outcomes of interest
Outcomes	The standardized treatment response in RCTs is greater by a magnitude of 4.59 compared to observational studies
Notes	Response to antidepressants is greater in RCTs than in observational studies

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Yes	PICO specified
Investigator Agreement?	Yes	2 reviewed independently, consensus
Complete sample?	Yes	Searched for all studies on a specific topic, seems thorough
Bias assessed?	Yes	Different instruments for RCTs and observational studies
Control for differences?	Yes	Some RoB items included in meta-regression, also did sensitivity analysis
Heterogeneity addressed?	Yes	Meta-regression
Similar outcomes?	No	Converted to standardized scores
No selective reporting?	Yes	Limited evidence of publication bias based on funnel plots
Absence of evidence of bias from other sources?	Yes	

Oliver 2010

Methods	Identify systematic reviews that compareD results of policy interventions, stratifying estimates by observational study and RCT study design published between 1999 and 2004
Data	16 systematic reviews identified, with a median of 11.5 RCTs and 14.5 observational studies in each systematic review
Comparisons	Observational studies published in systematic reviews were pooled separately from RCTs published in the same systematic reviews.
Outcomes	Results stratified by study design were heterogeneous with no clear direction of magnitude
Notes	Overall, the authors found no evidence for clear systematic differences in terms of results between RCTs and observational studies.

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Yes	Identified systematic reviews including observational studies and RCTs on a specific topic
Investigator Agreement?	Yes	All disagreements were settled by consensus or referral to third reviewer

Oliver 2010 *(Continued)*

Complete sample?	Yes	Searched for all studies on a specific topic,
Bias assessed?	Yes	Bias was discussed in detail
Control for differences?	Yes	Sensitivity analyses were detailed in the results
Heterogeneity addressed?	Yes	Heterogeneity was discussed in detail
Similar outcomes?	Yes	Various outcomes from policy interventions analyzed by intervention type
No selective reporting?	Unclear	Not discussed in detail
Absence of evidence of bias from other sources?	Yes	

Papanikolauo 2006

Methods	The authors compareD evidence from RCTs to observational studies that have explored the effects of interventions on the risk of harm. Harms of interest were identified from RCTs with more than 4000 patients. Observational studies of more than 4000 patients were also included for comparison
Data	15 harms of interest were identified and relative risks were extracted for 13 topics
Comparisons	Data from 25 observational studies were compared to results from RCTs. Relative risks for each outcome/harm were calculated for both study types
Outcomes	The estimated increase in RR differed by more than two-fold between observational studies and RCTs for 54% of the topics studied.
Notes	Observational studies usually under-estimated the absolute risk of harms.

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Yes	Matched observational studies to published RCTs on particular topics
Investigator Agreement?	Yes	2 independently, consensus
Complete sample?	Unclear	Unclear whether they were able to match observational studies to all the RCTs
Bias assessed?	No	Not done
Control for differences?	No	Not done
Heterogeneity addressed?	Unclear	Did assess mathematical heterogeneity between reviews of RCT and observational studies
Similar outcomes?	Unclear	"Harms" broadly defined, could include multiple outcomes
No selective reporting?	No	Selection of observational studies could have missed some
Absence of evidence of bias from other sources?	Yes	

Shikata 2006

Methods	The authors identified all meta-analyses of RCTs and observational studies of digestive surgery published between 1966 and 2004.
Data	52 outcomes for 18 disparate topics were identified from 276 articles (96 RCTs and 180 observational studies)
Comparisons	Pooled odds ratios and relative risks were extracted for each outcome, using the same indicator that had been used in the meta-analysis of interest
Outcomes	Approximately 1/4 of all outcomes of interest yielded different results between observational studies and RCTs
Notes	

Risk of bias

Item	Authors' judgement	Description
Explicit criteria?	Unclear	MA were identified, if meta-analysis did not include observational studies, then searched for them separately
Investigator Agreement?	Yes	2 reviewed independently, then consensus
Complete sample?	Yes	Complete sample on focused topic
Bias assessed?	No	Not done
Control for differences?	No	Not done
Heterogeneity addressed?	No	Not done
Similar outcomes?	Yes	Grouped by outcomes, noted that measures were similar
No selective reporting?	Unclear	Search strategy comprehensive but odd (MA + OBS)
Absence of evidence of bias from other sources?	Yes	

CABG: **c**oronary artery bypass graft
NRS: non-randomized study
PICO: population, intervention, comparison and outcome
RCT: randomized controlled trial
RoB: risk of bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ather 2011	An original meta-analysis with an incidental comparison of RCTs and observational studies.
Begg 1991	This is a statistical methods paper that did not have a systematic selection of studies for identified outcomes or interventions.

Study	Reason for exclusion
Beyersmann 2008	This is a statistical methods paper that did not have a systematic selection of studies for identified outcomes or interventions.
Bosco 2010	This is not a meta-analysis or review of meta-analyses. There is no comparison of RCTs and observational data.
Britton 1998	The authors chose to include uncontrolled trials in their data collection.
Chambers 2010	This is a methods paper that did not have a systematic selection of studies for identified outcomes or interventions. There was no meta-analysis of observational data performed.
Coulam 1994	From this study it was not possible to separate out uncontrolled, quasi-, or pseudo-randomized studies from other studies.
Dahabreh 2012	Not a comprehensive or systematic search of RCT data. RCT data matched selectively to observational data.
Deeks 2002	This study was unique in that it created non-randomised studies through resampling of RCTs. This is a statistical methods paper that did not have a systematic selection of studies for identified outcomes or interventions.
Deeks 2003	The authors included quasi-experimental and quasi-randomized studies.
Diehl 1986	Not designed to specifically compare the effect sizes of RCT and observational studies.
Diez 2010	Not designed to specifically compare the effect sizes of RCT and observational studies, but to test new analytic methods that takes study design into account
Flossmann 2007	An original meta-analysis with an incidental comparison of RCTs and observational studies.
Hallstrom 2000	An original meta-analysis with an incidental comparison of RCTs and observational studies.
Henry 2001	Not designed to specifically compare the effect sizes of RCT and observational studies, but to qualitatively assess agreement between designs.
Hlatky 1988	Did not have a systematic selection of studies for identified outcomes or interventions.
Ioannidis 2005	This is a qualitative comparison of high cited RCTs and observational studies and their initially stronger effects that are often later contradicted.
Labrarere 2006	This is a methods paper that did not have a systematic selection of studies for identified outcomes or interventions.
LaTorre 2009	An original meta-analysis of harms outcomes among only observational studies.
Linde 2007	An incidental comparison of RCTs and observational studies; did not have a systematic selection of studies for identified outcomes or interventions.
Lipsey 1993	From this study it was not possible to separate out uncontrolled, quasi-, or pseudo-randomized studies from other studies.
Loke 2011	An original meta-analysis with an incidental comparison of RCTs and observational studies.
MacLehose 2000	The authors included quasi-experimental studies.
Mak 2009	An original meta-analysis with an incidental comparison of RCTs and observational studies.

Study	Reason for exclusion
McCarron 2010	This is a statistical methods paper that did not have a systematic selection of studies for identified outcomes or interventions; the authors re-analyzed previously published data.
McKee 1999	A commentary and/or descriptive analysis.
Moreira 2012	No meta-analysis; RCT data included quasi-experimental.
Ni Chroinin 2013	An original meta-analysis with an incidental comparison of RCTs and observational studies.
Nixdorf 2010	An original meta-analysis with an incidental comparison of RCTs and observational studies.
Ottenbacker 1992	A commentary and/or descriptive analysis.
Papanastassiou 2012	An original meta-analysis with an incidental comparison of RCTs and observational studies.
Phillips 1999	This study had no systematic selection of meta-analyses; only included three large prospective studies that were the focus of the analysis.
Pratt 2012	No meta-analysis performed.
Pyorala 1995	An original meta-analysis with an incidental comparison of RCTs and observational studies.
Schmoor 2008	This study had no systematic selection of meta-analyses; only an embedded prospective study within an RCT that was the focus of the analysis.
Scott 2007	An original meta-analysis with an incidental comparison of RCTs and observational studies.
Shah 2005	No meta-analysis, only a quantitative comparison of results between observational studies with different designs.
Shepherd 2006	A commentary and/or descriptive analysis.
Steinberg 1994	An analysis of previously published meta-analyses that aimed to compare effects between sources of controls within observational study designs.
Stukel 2007	A primary analysis; this is a statistical methods paper that did not have a systematic selection of studies for identified outcomes or interventions; no RCT data.
Ward 1992	This is a statistical methods paper that did not have a systematic selection of studies for identified outcomes or interventions; not a review of meta-analyses.
Watson 1994	An original meta-analysis with an incidental comparison of RCTs and observational studies; the authors include non-randomized as observational studies.
Williams 1981	This is a statistical methods paper that did not have a systematic selection of studies for identified outcomes or interventions; not a review of meta-analyses and no meta-analysis performed.
Wilson 2001	From this study it was not possible to separate out uncontrolled, quasi-, or pseudo-randomized studies from other studies.

RCT: randomized controlled trial

DATA AND ANALYSES

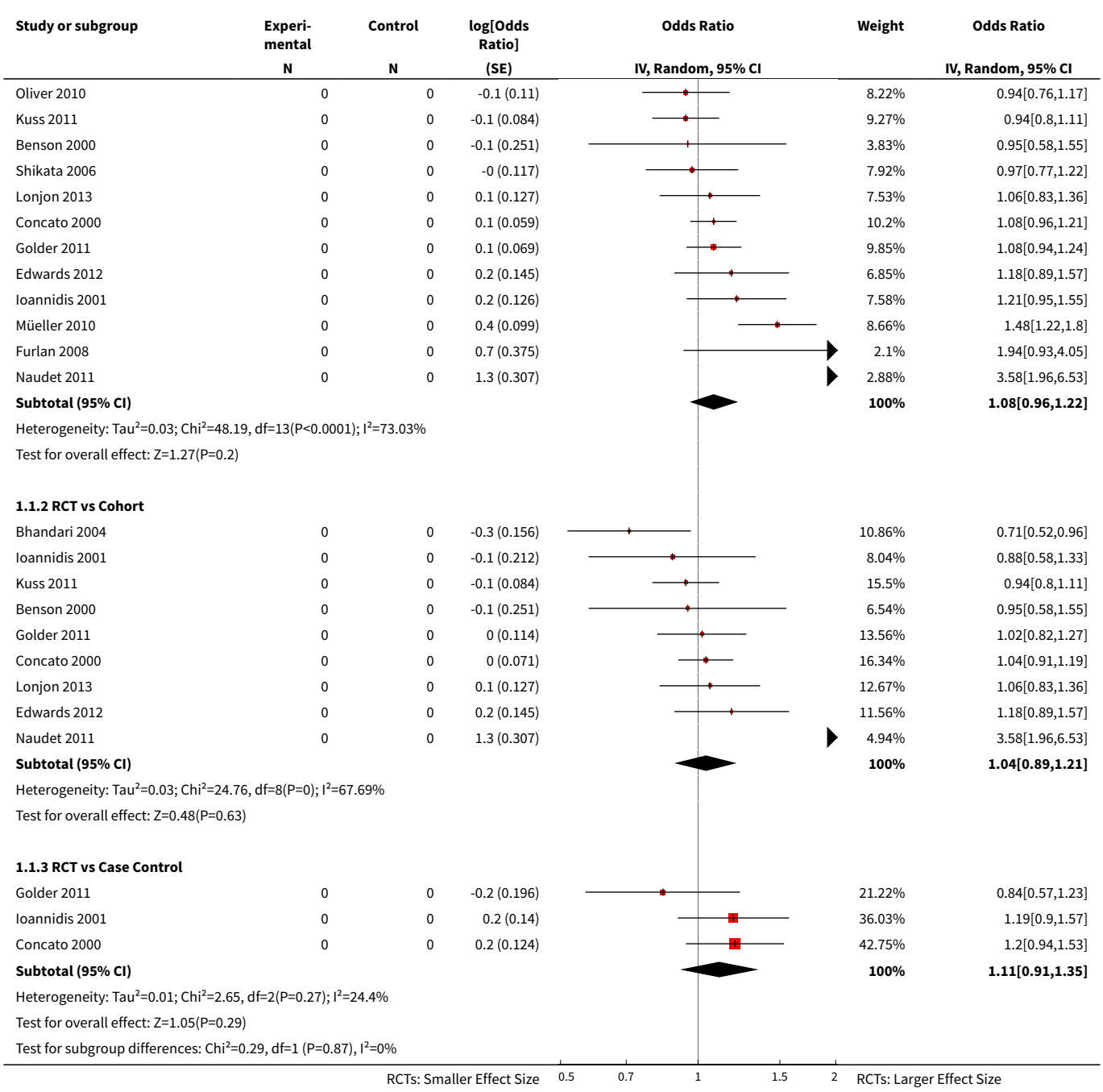
Comparison 1. RCT vs Observational

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Summary Ratios of Ratios: RCTs vs Observational Studies	14		Odds Ratio (Random, 95% CI)	Subtotals only
1.1 RCT vs All Observational	14		Odds Ratio (Random, 95% CI)	1.08 [0.96, 1.22]
1.2 RCT vs Cohort	9		Odds Ratio (Random, 95% CI)	1.04 [0.89, 1.21]
1.3 RCT vs Case Control	3		Odds Ratio (Random, 95% CI)	1.11 [0.91, 1.35]
2 Summary Ratios of Ratios: RCTs vs Observational Studies (Heterogeneity Subgroups)	14		Odds Ratio (Random, 95% CI)	Subtotals only
2.1 Low Heterogeniety (I^2: 0% to 30%)	4		Odds Ratio (Random, 95% CI)	1.00 [0.72, 1.39]
2.2 Moderate Heterogeneity (I^2:31% to 60%)	8		Odds Ratio (Random, 95% CI)	1.11 [0.95, 1.30]
2.3 Significant Heterogeneity (I^2: 61% to 100%)	2		Odds Ratio (Random, 95% CI)	1.08 [0.87, 1.34]
3 Summary Ratios of Ratios: RCTs vs Observational Studies (Pharmacological Studies vs non-Pharmacological Studies)	13		Odds Ratio (Random, 95% CI)	Subtotals only
3.1 Pharmacological Studies	6		Odds Ratio (Random, 95% CI)	1.17 [0.95, 1.43]
3.2 Non-Pharmacological Studies	11		Odds Ratio (Random, 95% CI)	1.03 [0.87, 1.21]
4 Summary Ratios of Ratios: RCTs vs Observational Studies (Propensity Scores)	14		Odds Ratio (Random, 95% CI)	Subtotals only
4.1 RCTs vs Observational Studies (propensity score adjustment)	2		Odds Ratio (Random, 95% CI)	0.98 [0.85, 1.12]
4.2 RCTs vs Observational Studies (no propensity score adjustment)	12		Odds Ratio (Random, 95% CI)	1.10 [0.96, 1.27]

Analysis 1.1. Comparison 1 RCT vs Observational, Outcome 1 Summary Ratios of Ratios: RCTs vs Observational Studies.

Study or subgroup	Experimental N	Control N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 RCT vs All Observational						
Bhandari 2004	0	0	-0.3 (0.156)		6.43%	0.71[0.52,0.96]
Beynon 2008	0	0	-0.2 (0.098)		8.69%	0.83[0.68,1.01]

RCTs: Smaller Effect Size — RCTs: Larger Effect Size



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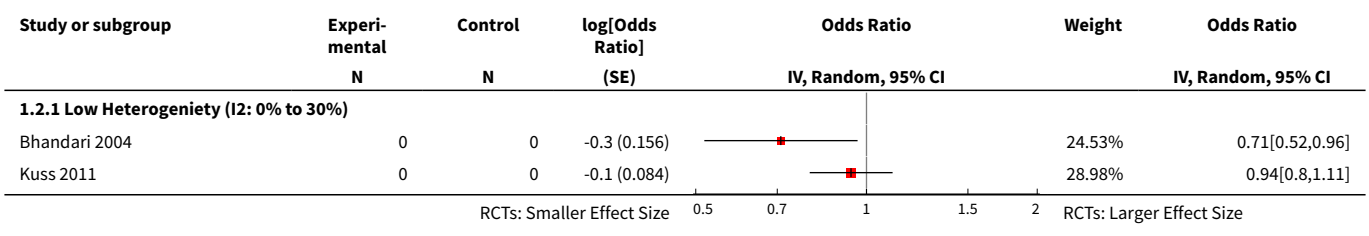

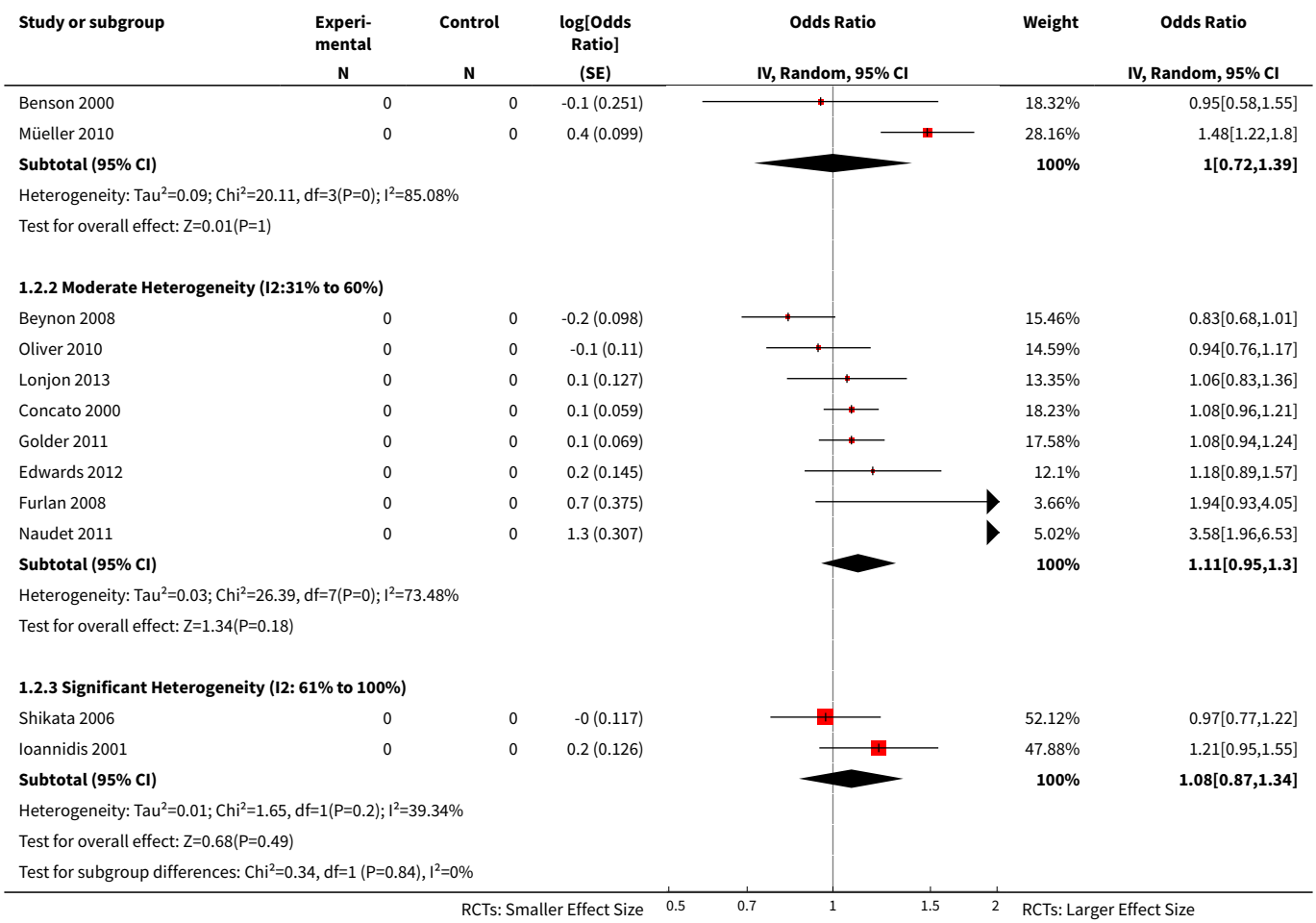

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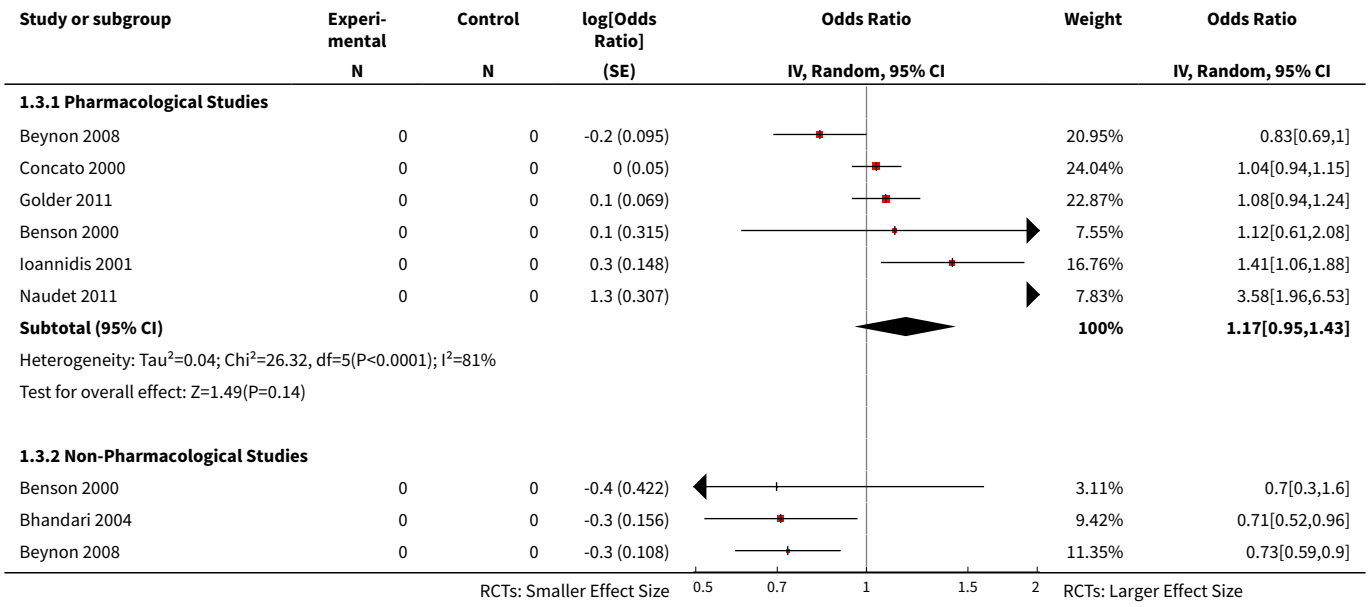
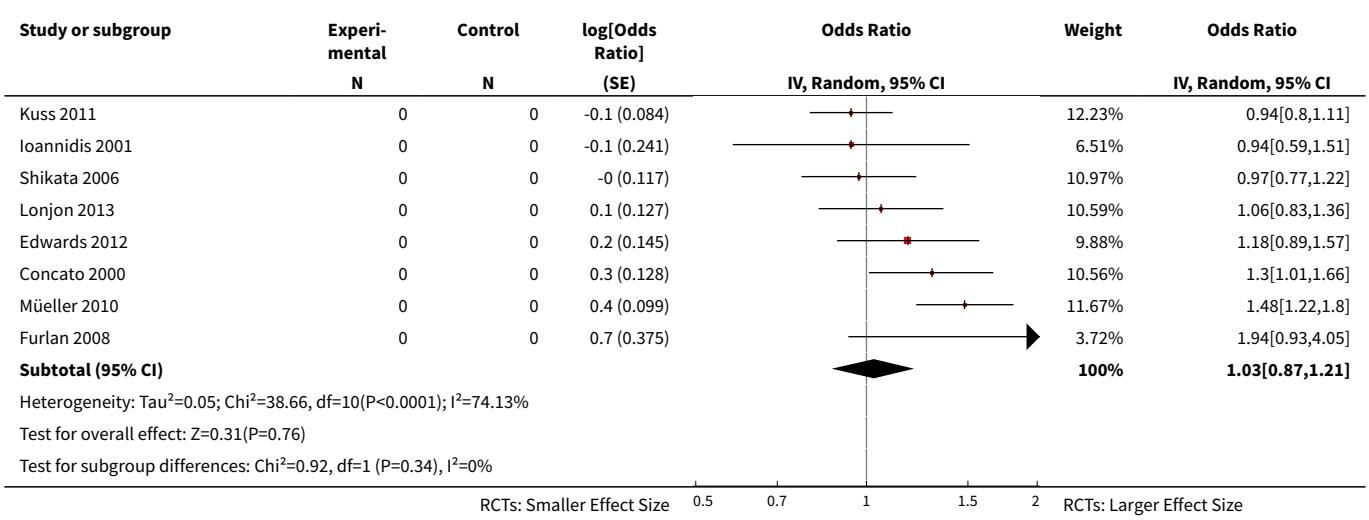
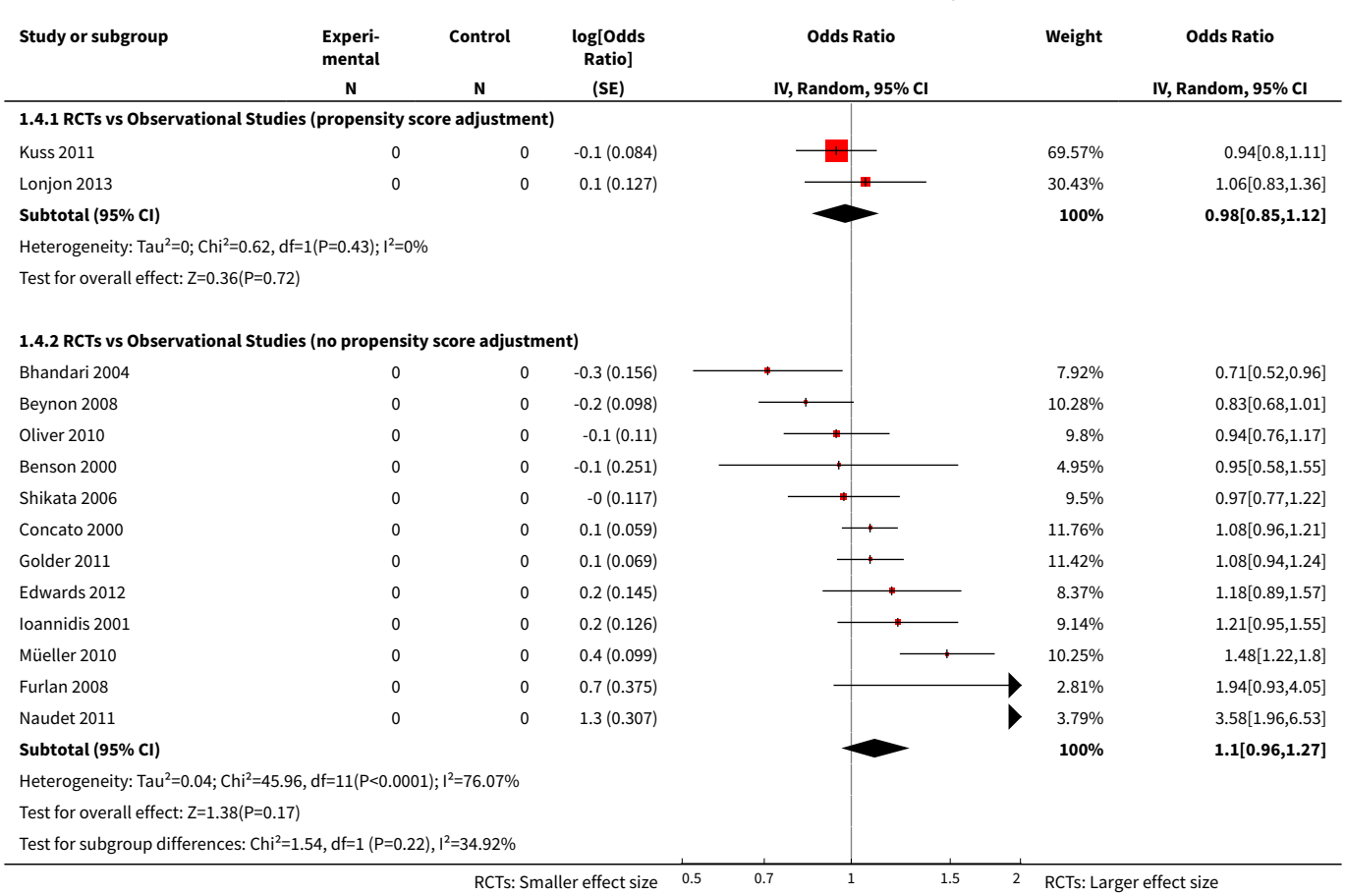




Analysis 1.4. Comparison 1 RCT vs Observational, Outcome 4 Summary Ratios of Ratios: RCTs vs Observational Studies (Propensity Scores).



APPENDICES

Appendix 1. PubMed strategy, which was modified as appropriate for use in the other databases

Search	Terms
#4	(((#1) AND #2) AND #3)
#3	compara*[tiab] OR comparison*[tiab] OR contrast*[tiab] OR similar*[tiab] OR consistent*[tiab] OR inconsistent*[tiab] OR dissimilar*[tiab] OR differen*[tiab] OR concordan*[tiab] OR discordan*[tiab] OR heterogene*[tiab] OR "Research Design"[mh]
#2	"Observation"[mh] OR "Cohort Studies"[mh] OR "Longitudinal Studies"[mh] OR "Retrospective Studies"[mh] OR "Prospective Studies"[mh] OR observational[tiab] OR cohort*[tiab] OR crosssectional[tiab] OR crossectional[tiab] OR cross-sectional[tiab] OR cross sectional[tiab] OR longitudinal[tiab] OR causal inference*[tw] OR causality[tw] OR “instrumental variable”[tw] OR “structural model”[tw] OR practice-based[tw] OR propensity score*[tw] OR natural experiment*[tw] OR case-control[tw] OR before-after[tw] OR pre-post[tw] OR case-cohort[tw] OR case-crossover[tw] OR serial[tiab] OR nonexperimental[tiab] OR non-experimental[tiab] OR “nonrandomized”[tiab] OR “non-randomised”[tiab] OR “non-randomised”[tiab] OR “nonrandomised”[tiab] OR “study designs”[tiab] OR “newcastle ottawa”[tiab] OR overestimat*[tiab] OR over-estimat*[tiab] OR bias[tiab] OR "are needed"[tiab] OR (evidence[tiab] AND quality[tiab])
#1	Cochrane Database Syst Rev [TA] OR search[tiab] OR meta-analysis[PT] OR MEDLINE[tiab] OR PubMed[tiab] OR (systematic*[tiab] AND review*[tiab]) OR review[ti]

CONTRIBUTIONS OF AUTHORS

All authors contributed to drafting of the review. LB conceived the idea for the study. THH conducted all searches and reviewed the final manuscript. LB and AA screened titles, wrote the final manuscript, and revised the manuscript in response to peer review comments. AA conducted all analyses.

DECLARATIONS OF INTEREST

None to declare.

SOURCES OF SUPPORT

Internal sources

- Clinical and Translational Sciences Institute (CTSI), University of California, San Francisco (UCSF), USA.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were unable to conduct subgroup analyses by topic area of the research, or differences in interventions and conditions, as proposed, because these parameters were too diverse to permit grouping of studies. For the same reasons, we were unable to explore the impact of confounding by indication.

INDEX TERMS

Medical Subject Headings (MeSH)

*Observational Studies as Topic; *Randomized Controlled Trials as Topic; Meta-Analysis as Topic; Outcome Assessment, Health Care [*methods]

MeSH check words

Humans

Published online: December 30, 2020

IMR Press

Review

Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)

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DOI:10.31083/j.rcm.2020.04.264

Rev. Cardiovasc. Med. 2020 vol. 21(4), 517–530

Reviews in Cardiovascular Medicine

The SARS-CoV-2 virus spreading across the world has led to surges of COVID-19 illness, hospitalizations, and death. The complex and multifaceted pathophysiology of life-threatening COVID-19 illness including viral mediated organ damage, cytokine storm, and thrombosis warrants early interventions to address all components of the devastating illness. In countries where therapeutic nihilism is prevalent, patients endure escalating symptoms and without early treatment can succumb to delayed in-hospital care and death. Prompt early initiation of sequenced multidrug therapy (SMDT) is a widely and currently available solution to stem the tide of hospitalizations and death. A multipronged therapeutic approach includes 1) adjuvant nutraceuticals, 2) combination intracellular anti-infective therapy, 3) inhaled/oral corticosteroids, 4) antiplatelet agents/anticoagulants, 5) supportive care including supplemental oxygen, monitoring, and telemedicine. Randomized trials of individual, novel oral therapies have not delivered tools for physicians to combat the pandemic in practice. No single therapeutic option thus far has been entirely effective and therefore a combination is required at this time. An urgent immediate pivot from single drug to SMDT regimens should be employed as a critical strategy to deal with the large numbers of acute COVID-19 patients with the aim of reducing the intensity and duration of symptoms and avoiding hospitalization and death.

Keywords

SARS-CoV-2; COVID-19; hospitalization; mortality; ambulatory treatment; anti-infective; anti-inflammatory; antiviral; corticosteroid; antiplatelet agent; anticoagulant; sequenced multidrug therapy

The pandemic of SARS-CoV-2 (COVID-19) is advancing unabated across the world with each country and region developing distinct epidemiologic patterns in terms of frequency, hospitalization, and death. There are four pillars to an effective pandemic response: 1) contagion control, 2) early treatment, 3) hospitalization, and 4) vaccination to assist with herd immunity (Fig. 1). Additionally, when feasible, prophylaxis could be viewed as an additional pillar since it works to reduce the spread as well as incidence of acute illness. Many countries have operationalized all four pillars including the second pillar of early home-based treatment with distributed medication kits of generic medications and supplements as shown in Table 1. In the US, Canada, United Kingdom, Western European Union, Australia, and some South American Countries there has been three major areas of focus for pandemic response: 1) containment of the spread of infection (masking, social distancing, etc., 2) late hospitalization and delayed treatments (remdesivir, convalescent plasma, antiviral antibodies), and 3) vaccine development (Bhimraj et al., 2020; COVID-19 Treatment Guidelines, 2020). Thus the missing pillar of pandemic response is early home-based treatment (as seen in Fig. 1).

The current three-pronged approach has missed the predominant opportunity to reduce hospitalization and death given the practice of directing patients to self-isolation at home. Early sequential multidrug therapy (SMDT) is the only currently available method by which hospitalizations and possibly death could be reduced in the short term (McCullough et al., 2020a). Most COVID-19 patients with progressive symptoms who arrive to hospital by emergency medical services do not require intubation or pressors initially in the field (Yang et al., 2020). Once hospitalized, if oxygen is required the mortality rate rises to ~12% (Palazzuoli et al., 2020). Approximately one quarter require mechanical ventil ation, advanced circulatory support, or renal replacement therapy and in that group the mortality exceeds 25% (S. Gupta et al., 2020a,b). Our observations suggest a majority of hospitalizations could be avoided with a first treat-at-home strategy with appropriate telemedicine monitoring and access to oxygen and therapeutics. Patients will have the best chance of therapeutic gain when trea ted before there is significant progression of disease (Argenziano et al., 2020; McCullough et al., 2020b; Rhodes et al., 2017).

The majority serious viral infections require early treatment with multiple agents and this approach has not been applied in trials of COVID-19 sponsored by governments or industry. Since COVID-19 syndrome is characterized by early exponential viral proliferation, cytokine-mediated organ damage and dysfunction, and endothelial injury with proximal platelet aggregation with thrombosis, (Fig. 2) it is not realistic to assume a single drug or antibody could comprehensively handle all of these manifestations. At this time there are no reports of conclusive randomized trials of oral ambulatory therapy for COVID-19 and none are expected in the short term. Most oral therapy trials reported to date have been small, underpowered, unblinded, relied on biased physician assigned endpoints, or in some cases, have been administratively stopped early without scientific justification or safety concerns.

Because COVID-19 is highly communicable, many U.S. ambulatory clinics do not care for patients with COVID-19 and studies suggest there has been little or no attempt to provide outpatient therapy to patients in the period before hospitalization (Price-Haywood et al., 2020). As the most notable early closure of a critically needed trial was U.S. National Institutes of Health study of hydroxychloroquine (HCQ) and azithromycin in ambulatory COVID-19 patients after 30 days with only 20 of 2000 budgeted patients enrolled (National Institutes of Health, 2020a,b). There has been no substantive federal effort since then on ambulatory trials and thus any future results are not expected in a time frame to influence public health policy (World Health Organisation, 2020). At the time of this writing, there are no planned trials of SMDT regimens designed to manage early viral replication, cytokine storm, and thrombosis in ambulatory patients with COVID-19 (Fig. 3). Hence, there is an urgent need for innovative early SMDT in COVID-19 to achieve the goal of reducing the intensity and severity of symptoms and lessening the risk of hospitalization or death. This outpatient ambulatory push could have a dramatic impact on reducing the strain on healthcare systems.

In the absence of evidence from or a commitment to clinical trials of early therapy, other scientific information on the pathophysiology, treated natural history, and clinical judgement together must guide contemporary ambulatory management of COVID-19 (McCullough et al., 2020b). Observational studies reporting outcomes in patient populations managed consistently with empirically derived early intervention regimens currently provide an acceptable level of evidence for safety and efficacy of these widely available, inexpensive and safe alternatives to the current standard of non-intervention (Khan et al., 2020). Based on pathophysiology and observational data, each physician and patient using shared decision making set the course for COVID-19 management: watch-

Table 1. Listing of early home-based treatment kits provided for acute COVID-19 illness by various countries.

Country	Drugs and supplements	References
Algeria	Chloroquine/Hydroxychloroquine	(Belayneh, 2020)
Argentina	Ivermectin	(Mega, 2020)
Brazil	Hydroxychloroquine, Ivermectin, Azithromycin (Vitamin D and zinc only for those who can afford)	(Coronavirus a Tarde, 2020; Ministério da Saúde, 2020)
Bangladesh	Ivermectin, Doxycycline	(Trial Site News, 2020)
Cameroon	Chloroquine/Hydroxychloroquine	(Belayneh, 2020; Bösmüller et al., 2020)
China	Chloroquine/Hydroxychloroquine plus other traditional medicine up to 23 different Chinese herbal medicines	(Fan et al., 2020)
Colombia	Ivermectin	(Mega, 2020)
Egypt	Chloroquine/Hydroxychloroquine	(Mohhamad, 2020)
France	Hydroxychloroquine, Azithromycin, and Lopinavir-Ritonavir	(Gérard et al., 2020)
Ghana	Chloroquine/Hydroxychloroquine	(Isaac, 2020)
India	Hydroxychlorquine, Ivermectin, alone or in combination with other drugs	(Vora et al., 2020)
Korea	Hydroxychloroquine	(Hong et al., 2020)
Mexico	Ivermectin, hydroxychloroquine	(Pacheco, 2020)
Morocco	Chloroquine/Hydroxychloroquine	(Brian, 2020; McFadyen et al., 2020; Mussa, 2020)
Mozanbique	Chloroquine/Hydroxychloroquine	(Belayneh, 2020; McFadyen et al., 2020)
Nigeria	Chloroquine/Hydroxychloroquine	(Felix, 2020; McFadyen et al., 2020)
Peru	Ivermectin, Azithromycin	(Diario oficial del bicentenario, 2020; Trial Site News, 2020)
Senegal	Chloroquine/Hydroxychloroquine	(Huaxia, 2020; McFadyen et al., 2020)
South Africa	Chloroquine/Hydroxychloroquine	(Katharine , 2020; McFadyen et al., 2020)
Spain	Patients who are already taking hydroxychloroquine within or outside of clinical trials for COVID-19 as well as patients undergoing chronic treatment with these drugs should continue taking them and, in any case, maintain their usual follow-ups with their doctors	(Agencia Española de Medicamentos y Productos Sanitarios, 2020)
Taiwan	Hydroxychloroquine	(Sheng, 2020)
Uganda	Chloroquine/Hydroxychloroquine, Azithromycin	(McFadyen et al., 2020; The Independent, 2020)
USA	No kits provided from public health agencies, Association of American Physicians and Surgeons Home COVID-19 Treatment Guide recommendends adjuvant neutraceuticals, and sequenced multidrug therapy by prescription	(AAPS, 2020)

ful waiting in self-quarantine or empiric treatment with the aim of lessening the intensity and duration of symptoms and reducing the risk of hospitalization and death (Gopalakrishnan et al., 2020). Fortunately, most healthy individuals with COVID-19 under age 50 years have a self-limited illness and no specific treatment is advised in the absence of severe symptoms. However, they should be advised that development of lower respiratory symptoms warrant evaluation of oxygenation status and consideration chest imaging which may prompt interventions with documentation of hypoxemia or pulmonary infiltrates.

However, those over age 50 and or those with one or more comorbidity have increased risks for hospitalization and death over 1% which increase substantially up to 40% with advancing age and more medical illnesses (obesity, diabetes mellitus, heart disease, pulmonary disorders, renal disease, and malignancies) and thus, warrant early ambulatory treatment according to best medical judgement weighing the benefits and risks of oral therapy. SARS-CoV-2 as with many viral infections, may be amenable to multiple drugs early in its course but is less responsive to the same treatments when administration is delayed and given in the hospital (Vaduganathan et al., 2020). Innovative SMDT regimens for COVID-19 utilize principles learned from hospitalized patients as well as data from treated ambulatory patients.

For the ambulatory patient with recognized signs and symptoms of COVID-19 on the first day (Fig. 2), often with nasal real-time reverse transcription or oral antigen testing not yet performed, the following three therapeutic principles apply (Centers for Disease Control and Prevention, 2020) : 1) combination anti-infective therapy to attenuate viral replication, 2) corticosteroids to modulate cytokine storm, and 4) antiplatelet agent/antithrombotic therapy to prevent and manage micro- or overt vascular thrombosis. For patients with cardinal features of the syndrome (fever, viral malaise, nasal congestion, loss of taste and smell, dry cough, etc) with pending or suspected false negative testing, therapy is the same as those with confirmed COVID-19.

1. Reducing viral spread and contamination

A major goal of self-quarantine is control of contagion (Nussbaumer-Streit et al., 2020). While there has been a great emphasis on masking and social distancing in congregate settings, many sources of information suggest the main place of viral transmission occurs in the home (respiratory, contact, oral-fecal) (Jef-

Fig. 1. The four pillars of pandemic response to COVID-19. The four pillars of pandemic response to COVID-19 are: 1) contagion control or efforts to reduce spread of SARS-CoV-2, 2) early ambulatory or home treatment of COVID-19 syndrome to reduce hospitalization and death, 3) hospitalization as a safety net to prevent death in cases that require respiratory support or other invasive therapies, 4) natural and vaccination mediated immunity that converge to provide herd immunity and ultimate cessation of the viral pandemic.

ferson et al., 2020; Xu et al., 2020). Masks for all unaffected contacts within the home as well as frequent use of hand sanitizer and hand washing is mandatory in the setting when one or more family members falls ill. Sterilizing surfaces such as countertops, door handles, phones, and other devices is advised. When possible, other close contacts can move out of the house and seek shelter free of SARS-CoV-2. Findings from multiple studies indicate that policies concerning control of the spread SARS-CoV-2 are only partially effective and extension into the home as the most frequent site of viral transfer is reasonable (Hsiang et al., 2020; Xiao et al., 2020). One of the great advantages of home treatment of COVID-19 is the ability of an individual or family unit to maintain isolation and complete contact tracing. If therapy is offered in the home with delivery of medications, then trips to urgent care centers, clinics, and hospitals can be reduced or eliminated. This limits spread to drivers, other patients, staff, and healthcare workers. On the contrary, therapeutic nihilism on the part of primary care physicians and health systems drives anxiety and panic among patients with acute COVID-19 who feel abandoned, making them more likely to break quarantine and seek aid at urgent care centers, emergency rooms and hospitals.

SARS-CoV-2 exists outside the human body in a bioaerosol of airborne particles and droplets. Since exhaled air in an infected person is considered to be "loaded" with particulate inoculum, each exhalation and inhalation in theory reinoculates the nasopharynx and tracheobronchial tree (Chen, 2020). We propose that fresh circulating air could reduce reinoculation and potentially lessen the severity of illness and possibly limit household spread during quarantine (Melikov et al., 2020). This calls for open windows, fans for aeration, or spending long periods of time outdoors away from others with no face covering in order to disperse and not reinhale the viral bioaerosol. These are principles used in the hospital with negative pressure ventilation deployed in isolation rooms to reduce bioaerosol contagion.

2. Adjunctive nutraceuticals

There has been considerable interest and study of the use of micronutrients and supplements for COVID-19 prophylaxis and treatment in combination with anti-infectives as first proposed by Zelenko and colleagues (Derwand et al., 2020). In general these agents are not curative but assist in treatment regimens to augment the therapeutic response. The aim of supplementation is to replenish in those with deficiencies associated with COVID-19 mortality, and to aid in reducing viral replication and tissue damage. Zinc deficiency is common among adults (Sharma et al., 2020). Zinc alone is a potent inhibitor of viral replication. Zinc in combination with hydroxychloroquine (HCQ) is potentially synergistic in reducing viral replication since HCQ is a zinc ionophore facilitating intracellular entry and inhibition of intracellular viral replication (Derwand and Scholz, 2020). This readily available nontoxic therapy could be deployed at the first signs of COVID-19 (Rahman

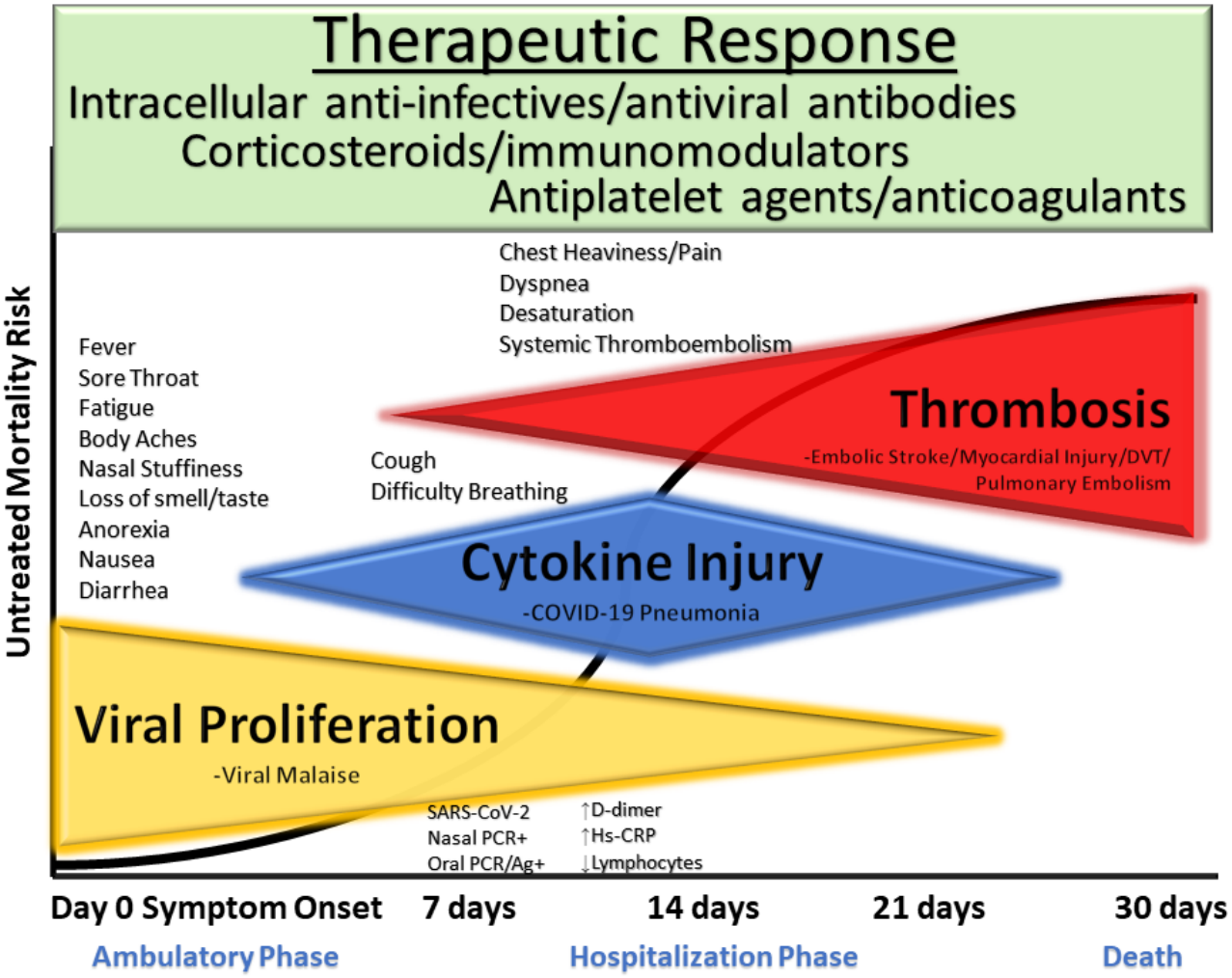

Fig. 2. Major dimensions of COVID-19 infection that call for a multi-drug strategy in the early ambulatory period with available medications including anti-infectives (hydroxychloroquine, ivermectin, azithromycin, doxycycline), corticosteroids, and anti-platelet drugs and anticoagulants. The three dimensions of the infection and their time-course allow for the sequenced multi-drug approach to be utilized with the goal of reducing hospitalization and death.

and Idid, 2020). Zinc sulfate 220 mg (50 mg elemental zinc) can be taken orally per day (Pormohammad et al., 2020).

Vitamin D deficiency has been associated with increased COVID-19 mortality and is commonly confounded by increasing age, obesity, diabetes, darker skin tones, and lack of fitness (Meltzer et al., 2020; Pereira et al., 2020) With good rationale, one small, randomized trial of vitamin D_3 supplementation found reduced mortality in patients with COVID-19 (Entrenas et al., 2020; Zhang et al., 2020a). The suggested dose is 5000 IU of vitamin D_3 per day.

Vitamin C has been used in a variety of viral infections and could be useful in combination with other supplements in COVID-19 (Carr and Rowe, 2020). Multiple randomized trials of vitamin C given intravenously or orally are planned or in progress at the time of this writing (Beigmohammadi et al., 2020; Liu et al., 2020) A reasonable dose would be vitamin C 3000 mg po qd.

Quercetin is a polyphenol that has a theoretical mechanism of action that could reduce the activity of a SARS-CoV-2 entry through the ACE2 receptor, inhibit viral proteases via conveyance of zinc, and attenuate inflammatory responses mediated through interleukin-6 (Bastaminejad and Bakhtiyari, 2020; Cione et al., 2019; Dabbagh-Bazarbachi et al., 2014; Derosa et al., 2020). The mechanisms of action favorably affect viral replication and immune response, so it is conceivable that this agent taken in combination with others discussed could play an assistive role in reducing early viral amplification and tissue damage (Colunga Biancatelli et al., 2020). The suggested dose of quercetin is 500 mg po bid.

3. Anti-infective therapy with intracellular activity

Quickly reducing the rate, quantity, and duration of viral replication, is a goal of antiviral therapy aimed at starting on the first day of symptomatic illness. The compelling rationale for prompt therapy is to minimize the degree of direct viral injury to the respiratory epithelium, vascular endothelium, and organs (Izzedine et al., 2020). Maladaptive host responses dependant on replication of SARS-CoV-2 could be attenuated by early initiation of combination anti-infectives including activation of inflammatory cells, cytokines, endothelial injury, and thrombosis (Singhania et al., 2020). Because SARS-CoV-2 infection is associated with severe disease and increased mortality in patients over age 50 years and those with one or more comorbidities, clinicians should use of at least two commercially available, anti-infective agents where it is

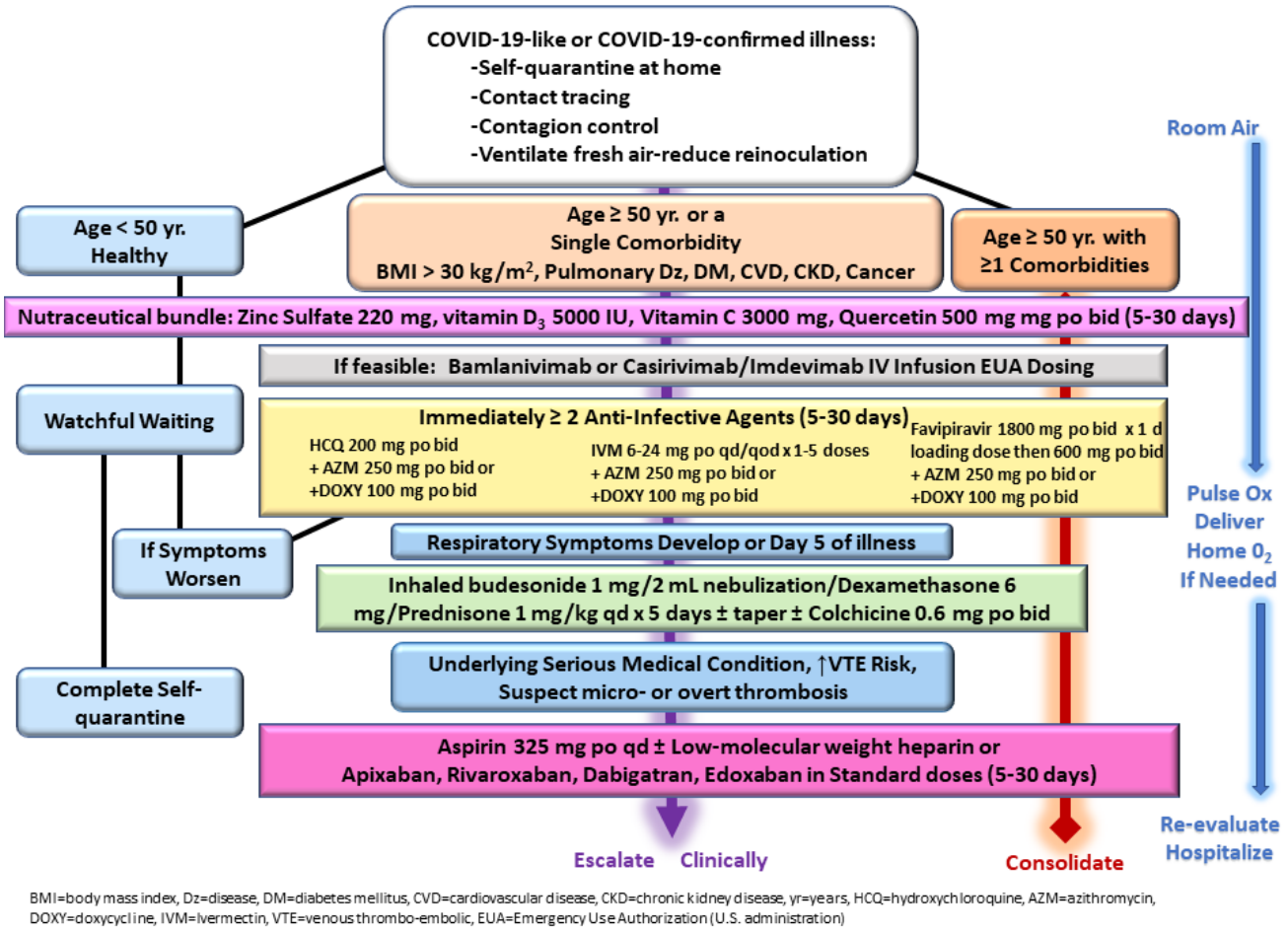

Fig. 3. Sequential multidrug treatment algorithm for ambulatory acute COVID-19 like and confirmed COVID-19 illness in patients in self-quarantine. Yr = year, BMI = body mass index, Dz = disease, DM = diabetes mellitus, CVD = cardiovascular disease, chronic kidney disease, HCQ = hydroxychloroquine, IVM = ivermectin, Mgt = management, Ox = oximetry, reproduced with permission from reference.

appropriately considered clinically indicated, medically necessary "off-label" prescription (Shojaei and Salari, 2020). Conversely, the decision to withhold oral therapy early in a potentially fatal illness should be made in a shared-decision making process with the patient given the full understanding that the natural untreated history of COVID-19 in high risk adults includes the risk of hospitalization, hospital-acquired complications, and death. The physician and patient should understand that the only method by which a hospitalization could be avoided would be the empiric use of SMDT that have a reasonable chance of success with acceptable safety. Recent expanded use authorization of IV administration of bamlanivimab is another option available to a limited number of patients, but supplies will be insufficient to treat everyone who meets the broad criteria for the therapy, so availability of oral alternatives remains essential.

4. Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial/anti-inflammatory drug that impairs endosomal transfer of virions within human cells. HCQ is also a zinc ionophore that conveys zinc intracellularly to block the SARS-CoV-2 RNA-dependent RNA polymerase which is the core enzyme of the virus replication (te Velthuis et al., 2010). A continuously updated synthesis of HCQ studies supports the following (COVID-19 Treatment, 2020): 1) 63% of studies of HCQ administered late in the hospital course have demonstrated benefit, 2) 100% of the early treatment studies have demonstrated benefit with a composite 64% relative risk reduction in the progression of disease, hospitalization, and death (Arshad et al., 2020; Mikami et al., 2020; Prodromos and Rumschlag, 2020; Rosenberg et al., 2020). The small randomized trials to date are inconclusive for the following reasons: 1) no placebo control, 2) unblinded, 3) altered primary endpoints, 4) biased unblinded physician assigned endpoints (such as need for oxygen), 5) markedly truncated sample sizes and administrative termination of trials, 6) pretreatment with other antivirals.

Hydroxychloroquine was approved by the U.S. Food and Drug Administration in 1955, has been used by hundreds of millions of people worldwide since then, is sold over the counter in many countries and has a well characterized safety profile (Fram et al., 2020; Schrezenmeier and Dörner, 2020). Asymptomatic QT prolongation is well-recognized though an infrequent (< 1%) occurrence with HCQ (Prodromos et al., 2020). In those with glucose-6-phosphate dehydrogenase deficiency HCQ should not be used (Aguilar, 2020). In the setting of acute severe COVID-19 illness, symptomatic arrhythmias can develop in the absence of HCQ and are attributed to cytokine storm and critical illness (Elsaid et al., 2020). Data safety and monitoring boards have not declared safety concerns in HCQ clinical trial published to date. Rare pa-

tients with a personal or family history of prolonged QT syndrome, those on additional QT prolonging, contraindicated drugs (e.g. dofetilide, sotalol), should be treated with caution and a plan to monitor the QTc in the ambulatory setting. A typical HCQ regimen is 200 mg bid for 5 to 30 days depending on continued symptoms.

5. Ivermectin

Ivermectin (IVM) is a broad spectrum anti-parasitic agent that has been shown to have anti-viral activity against a range of viruses including recently, SARS-CoV-2 (Heidary and Gharebaghi, 2020). This drug is well tolerated, has a high therapeutic index and proven safety profile with over 3.7 billion treatments, and has been used alone or combined with either doxycycline or azithromycin in early clinical studies of patients with COVID-19 (Rahman et al., 2020). There are a number of randomized and prospective studies and all have shown efficacy in clinical outcomes at the time of this report (Alam et al., 2020; Chowdhury et al., 2020; Gorial et al., 2020; Khan et al., 2020; Nunez et al., 2020). Hence, it is reasonable in patients where HCQ cannot be used and favipiravir is not available, that IVM (200-600 mcg/kg [6-36 mg] single oral dose given daily or every other day for 2-3 administrations) could be the base of SMDT intended to reduce viral replication early in the course of COVID-19. However, uncertainty remains at this time concerning optimal dosing and schedule (Schmith et al., 2020). In the ICON study, IVM use in the hospital was associated with a 48% relative risk reduction in COVID-19 mortality (Rajter et al., 2020). Currently, there are 36 randomized clinical trials of ivermectin alone or in combination for ambulatory and hospitalized patients listed on clinicaltrials.gov.

6. Favipiravir

Favipiravir is an oral selective inhibitor of RNA-dependent RNA polymerase, and is approved for ambulatory use in COVID-19 in multiple countries (Coomes and Haghbayan, 2020). Favipiravir is safe and it shortens viral nasal shedding to less than 7 days in most studies (Ivashchenko et al., 2020; Pilkington et al., 2020). A dose administration could be 1600-1800 mg po bid on day 1, following by 600-800 mg po bid for 14 days depending on the dose sizes available in 30 different countries (Li et al., 2020). At the time of this writing, there are large ambulatory clinical trials in progress but are not expected to report in time to aid in the crisis at hand in the U.S.

7. Antibiotics with intracellular anti-infective activity

Azithromycin (AZM) is a commonly used macrolide antibiotic that has antiviral properties mainly attributed to reduced endosomal transfer of virions as well as established anti-inflammatory effects (Pani et al., 2020). French reports indicated that AZM in combination with HCQ was associated with reduced durations of viral shedding, fewer hospitalizations, and reduced mortality as compared to those untreated (Lagier et al., 2020; Million et al., 2020). In a large observational inpatient study (n = 2451), those who received AZM alone had an adjusted hazard ratio for mortality of 1.05, 95% CI 0.68-1.62, P = 0.83 (Colunga Biancatelli et al., 2020). The combination of HCQ and AZM has been considered a standard of care outside the US for COVID-19 in more than 300,000 older adults with multiple comorbidities (Risch, 2020). AZM like HCQ can prolong the QTc in $< 1\%$ of patients, yet has demonstrated safety in co-administration with HCQ (Huang et al., 2020). A reasonable regimen is 250 mg po bid for 5 to 30 days for persistent symptoms or evidence of bacterial superinfection.

Doxycycline is another common antibiotic with multiple intracellular effects that may reduce viral replication, cellular damage, and expression of inflammatory factors (Malek et al., 2020; Sodhi and Etminan, 2020). It has been shown to have in vitro activity against COVID-19 at clinically used concentrations, acting in post-entry stages of the infection with SARS-CoV-2 in Vero E_6 cells (Gendrot et al., 2020). It has also been shown to concentrate in the lungs at levels twice that of plasma. When combined with ivermectin early in the infection it appears to enhance efficacy to near complete eradication of COVID-19 in less than 10 days. This drug has no effect on cardiac conduction and has the main caveat of gastrointestinal upset and esophagitis. Both AZM and doxycycline has the advantage of offering antibacterial coverage for superimposed bacterial and atypical infection in the upper respiratory tract (Ailani et al., 1999). Doxycycline can be dosed 200 mg po followed by 100 mg po bid for 5 to 30 days for persistent symptoms or evidence of bacterial superinfection.

8. Antibody therapy

Recently, bamlanivimab a monoclonal antibody directed against the SARS-CoV-2 spike protein has been approved for the early ambulatory treatment of COVID-19. In the BLAZE-1 randomized trial, the pooled secondary endpoint of COVID-19 hospitalizations occurred 4/136 and 7/69 of the Bamlanivimab and placebo groups respectively (Chen, 2020). While these results are not considered conclusive nor robust, given the emergency context, bamlanivimab is authorized for COVID-19 patients who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 or hospitalization. The authorized dosage for bamlanivimab is a single IV infusion of 700 mg administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. The infusion should occur over an hour with another hour of monitoring for systemic reactions (expected $< 5\%$).

A humanized antibody blend of casirivimab and imdevimab has also received emergency approval in the United States and for a similar population as bamlanivimab. This pair of antibodies binds at different regions of the SARS-CoV-2 spike protein. This antibody combination is dosed 1,200 mg of casirivimab and 1,200 mg of imdevimab together as a single IV infusion over at least 60 minutes with another hour of monitoring for reactions (Regeneron Pharmaceuticals, Inc., 2020). In the phase II program, the secondary endpoint of hospitalization occurred in 8/434 and 10/231 of casirivimab/imdevimab and placebo groups, respectively. These results should be interpreted with caution and cannot be characterized as being conclusive or robust, yet as with all therapies discussed in this paper, casirivimab/imdevimab can be integrated into an innovative sequenced multi-drug regimen for SARS-CoV-2 infection.

If SARS-CoV-2 is diagnosed by rapid testing in a facility that performs antibody infusion such as an emergency room, urgent care center, or clinic, it is reasonable to start COVID-19 with the antibody infusion. Conversely, if it can be safely arranged by home infusion while maintaining quarantine, physicians may prescribe this therapy to augment the effects of longer courses of oral treat-

ment. At this time, it is unattractive to ask a patient to break quarantine and risk spread of infection to drivers and healthcare personnel in order to receive an outpatient infusion.

9. Corticosteroids

The manifestations of COVID-19 that prompt hospitalization and that may well lead to multi-organ system failure are attributed to a cytokine storm. The characteristic profile of an acutely ill COVID-19 patient includes leukocytosis with a relative neutropenia. Among COVID-19 patients, serum IL-6 and IL-10 levels are elevated in the critically ill (Han et al., 2020). In COVID-19, some of the first respiratory findings are cough and difficulty breathing. These features are attributable to inflammation and cytokine activation. Early use of oral corticosteroids is a rational intervention for COVID-19 patients with these features as they would be in other inflammatory lung disorders (Kolilekas et al., 2020; Singh et al., 2020). Inhaled budesonide 1 mg/2 mL via nebulizer or 200 mcg/inhaler up to every four hours can be utilized however, there are no published reports of efficacy in COVID-19. The RECOVERY trial randomized 6425 hospitalized patients with COVID-19 in a 2 : 1 ratio to open label dexamethasone 6 mg po/IV qd for up to 10 days and found dexamethasone reduced mortality, HR = 0.65, 95% CI 0.51-0.82, $P < 0.001$ (Horby et al., 2020) . Concordantly, a meta-analysis involving 1703 critically ill COVID-19 patients found a 36% relative risk reduction in death (Sterne et al., 2020). Safety concerns regarding prolonged viral replication with steroids have not been substantiated (Masiá et al., 2020). A clinical extension of these findings is administration of steroids in COVID-19 patients at home on day five or beyond with moderate or greater pulmonary symptoms (Szente Fonseca et al., 2020). Dexamethasone 6 mg po qd or prednisone 1 mg/kg can be given orally per day for five days with or without a subsequent taper.

10. Colchicine

Colchicine is a non-steroidal anti-mitotic drug used in gout and pericarditis which blocks metaphase of inflammatory cells by binding to the ends of microtubules preventing their intracellular assembly. The GRECCO-19 randomized open-label trial in 105 hospitalized patients with COVID-19 (treated with HCQ and AZM in 98 and 93% respectively) found that colchicine was associated with a reduction in D-dimer levels and improved clinical outcomes (Deftereos et al., 2020). The clinical primary end point (2-point change in World Health Organization ordinal scale) occurred in 14.0% in the control group (7 of 50 patients) and 1.8% in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95% CI, 0.01-0.96; $P = 0.02$) (World Health Organisation, 2020). Because the short-term safety profile is well understood, it is reasonable to consider this agent along with corticosteroids in an attempt to reduce the effects of cytokine storm and myopericarditis. A dosing scheme of 0.6 mg po bid x 3 days then 0.6 mg po qd for 30 days can be considered.

11. Antiplatelet agents and antithrombotics

Multiple studies have described increased rates of pathological macro and micro-thrombosis (Bösmüller et al., 2020; McFadyen et al., 2020). COVID-19 patients have described chest heaviness associated with desaturation that suggests the possibility of pulmonary thrombosis (Bhandari et al., 2020). Multiple reports have described elevated D-dimer levels in acutely ill COVID-19 patients which has been consistently associated with increased risk of deep venous thrombosis and pulmonary embolism (Artifoni et al., 2020; Chan et al., 2020; Mestre-Gómez et al., 2020). Autopsy studies have described pulmonary micro thrombosis and overt embolism with deep venous thrombus found in over half of fatal COVID-19 cases (Ackermann et al., 2020; Burlacu et al., 2020). These observations support the hypothesis that a unique endothelial injury and thrombosis are playing a role in oxygen desaturation, a cardinal reason for hospitalization and supportive care (Zhang et al., 2020b). Because thromboxane A_2 is markedly upregulated with SARS-CoV-2 infection, early administration of aspirin 325 mg per day is advised for initial antiplatelet and anti-inflammatory effects (Chow et al., 2020; Glatthaar-Saalmüller et al., 2017; A. Gupta et al., 2020a; Turshudzhyan, 2020). Ambulatory patients can also be treated with subcutaneous low-molecular weight heparin or with oral novel anticoagulant drugs (apixaban, rivaroxaban, edoxaban, dabigatran) in dosing schemes similar to those used in outpatient thromboprophylaxis. In a retrospective study of 2773 COVID-19 inpatients, 28% received anticoagulant therapy within 2 days of admission, and despite being used in more severe cases, anticoagulant administration was associated with a reduction in mortality, HR = 0.86 per day of therapy, 95% CI: 0.82-0.89; $P < 0.001$. Contemporary use of in hospital anticoagulants has remained in ~30% of cases (Vahidy et al., 2020) . Pre-emptive use of low molecular weight heparin or novel anticoagulants have been associated with $>$ 50% reduction in COVID-19 mortality (Billett et al., 2020). Anticoagulants also reduce death in COVID-19 hospitalized patients with thrombotic complications, elevated D-dimer levels, and higher comorbidity scores (Tang et al., 2020) . Finally, many acutely ill outpatients also have general indications or risk for cardioembolic/venous thromboembolic prophylaxis applicable to COVID-19 (Moores et al., 2020; Ruocco et al., 2020). There are ambulatory randomized trials of aspirin and novel oral anticoagulants underway. However, given reports of catastrophic stroke and systemic thromboembolism and the large reductions in mortality for both prophylactic and therapeutic use, administration of aspirin 325 mg po qd for all COVID-19 high-risk patients and systemic anticoagulation is prudent in patients with a history of heart, lung, kidney, or malignant disease (Yamakawa et al., 2020).

12. Delivery of oxygen and monitoring

Telemedicine is a tractable means for the initial evaluation and management of COVID-19 allowing the patient to remain in self-quarantine at home. Clinical impressions of the patient can be gained with audio and video feeds. Key supplemental information includes self/family measurement of vital signs and temperature. A significant component of safe outpatient management is maintenance of arterial oxygen saturation on room air or prescribed home oxygen (oxygen concentrators) under direct supervision by daily telemedicine with escalation to hospitalization for assisted ventilation if needed. Self-proning could be entertained for medically sophisticated patients with good at-home monitoring (Westafer et al., 2020) .

The interventions discussed in this review could be extended to seniors in COVID-19 treatment units within nursing homes and other non-hospital settings. In addition to oral medications, these centers could deliver intravenous fluid and parenteral medications (i.e. bamlanivimab, casirivimab/imdevimab), oxygen, and assisted pressure ventilation with the goal of reducing the risk of

hospital transfer.

13. Summary

The SARS-CoV-2 outbreak is a once in a hundred-year pandemic that has not been addressed by rapid establishment of infrastructure amenable to support the conduct of large, randomized trials in outpatients in the community setting. The early flu-like stage of viral replication provides a therapeutic window of tremendous opportunity to potentially reduce the risk of more severe sequelae in high risk patients. Precious time is squandered with a "wait and see" approach in which there is no anti-viral treatment as the condition worsens, possibly resulting in unnecessary hospitalization, morbidity, and death. Once infected, the only means of preventing a hospitalization in a high-risk patient is to apply treatment before arrival of symptoms that prompt paramedic calls or emergency room visits. Given the current failure of government support for randomized clinical trials evaluating widely available, generic, inexpensive therapeutics, and the lack of instructive outpatient treatment guidelines (U.S., Canada, U.K., Western EU, Australia, some South American Countries), clinicians must act according to clinical judgement and in shared decision making with fully informed patients. Early SMDT developed empirically based upon pathophysiology and evidence from randomized data and the treated natural history of COVID-19 has demonstrated safety and efficacy. In newly diagnosed, high-risk, symptomatic patients with COVID-19, SMDT has a reasonable chance of therapeutic gain with an acceptable benefit-to-risk profile. Until the pandemic closes with population-level herd immunity potentially augmented with vaccination, early ambulatory SMDT should be a standard practice in high risk and severely symptomatic acute COVID-19 patients beginning at the onset of illness.

Footnote: To understand which drugs are being used in the early treatment of COVID-19 in these countries' websites of government agencies such as Brazil, Peru, Spain, Taiwan, and USA were searched. We also looked for researchers published in PUBMED by China, France, India, Korea, and African countries. Additional Information was also obtained from reliable sources of internet such as Argentina, Bangladesh, Colombia, Mexico and African Countries.

Author contributions

PAM wrote the first draft and created the figures, all authors provided critical edits and comments, PEA did the final proofreading and key finalization of the text. SR created the first draft of the table.

Acknowledgements

We are indebted to Jeremy Snavely who assisted in manuscript preparation.

Funding

None related.

Conflict of Interest

There is nothing to disclose. Author had access to the data and wrote the manuscript.

Submitted: November 28, 2020
Revised: December 08, 2020
Accepted: December 15, 2020
Published: December 30, 2020

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Journal Pre-proofs

Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting

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PII: S1567-5769(21)00272-1
DOI: https://doi.org/10.1016/j.intimp.2021.107636
Reference: INTIMP 107636

To appear in: *International Immunopharmacology*

Received Date: 25 February 2021
Revised Date: 30 March 2021
Accepted Date: 31 March 2021

Please cite this article as: M. Mokhtari, M. Mohraz, M. Mehdi Gouya, H. Namdari Tabar, K. Tayeri, S. Aghamohamadi, Z. Rajabpoor, M. Karami, A. Raeisi, H. Rahmani, H. Khalili, Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting, *International Immunopharmacology* (2021), doi: https://doi.org/10.1016/j.intimp.2021.107636

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Abstract

The role of hydroxychloroquine (HCQ) in early outpatient management of mild coronavirus disease 2019 (COVID-19) needs further investigation.

This study was a multicenter, population-based national retrospective-cohort investigation of 28,759 adults with mild COVID-19 seen at the network of Comprehensive Healthcare Centers (CHC) between March and September 2020 throughout Iran. The baseline characteristics and outcome variables were extracted from the national integrated health system database.

A total of 7,295 (25.37%) patients who presented with mild COVID-19 within 3 to 7 days of symptoms onset received HCQ (400 mg twice daily on day 1 followed by 200 mg twice daily for the next four days and were then followed for 14 days).

The main outcome measures were hospitalization or death for six months follow-up. COVID-19-related hospitalizations or deaths occurred in 523 (7.17%) and 27 (0.37%) respectively, in HCQ recipients and 2,382 (11.10%) and 287 (1.34%) respectively, in non-recipients. The odds of hospitalization or death was reduced by 38% (odds ratio [OR] = 0.62; 95% confidence interval [CI]: 0.56–0.68, p = < 0.001) and 73% (OR = 0.27; 95% CI: 0.18–0.41, p = < 0.001) in HCQ recipients and non-recipients. These effects were maintained after adjusting for age, comorbidities, and diagnostic modality. No serious HCQ-related adverse drug reactions were reported.

In our large outpatient national cohort of adults with mild COVID-19 disease who were given HCQ early in the course of the disease, the odds of hospitalization or death was reduced significantly regardless of age or comorbidities.

Key Words: COVID-19, Outpatient, Hydroxychloroquine

1. Introduction

Since the start of human transmission of Severe Acute Respiratory Coronavirus-2 (SARS CoV-2) to date (February 5, 2021), the virus has claimed 2,265,354 out of 104,165,006 confirmed cases globally.[1] Despite experiencing a year of the pandemic and the development and deployment of multiple vaccines, efforts to find effective treatment with outcome benefits in patients with coronavirus disease 2019 (COVID-19) have remained futile.

Hydroxychloroquine (HCQ) was one of the first medications that were repurposed for the treatment of COVID-19. Following the publication of *in-vitro* and non-randomized clinical studies, [2-3] HCQ use rapidly increased to the extent that it was prescribed for about 60% of hospitalized patients with COVID-19 in the United States in March 2020.3 This level decreased to 12% in May 2020 owing to the ineffectiveness of HCQ as shown in subsequent studies. [4- 5] Nevertheless, the controversy concerning its efficacy continued until randomized clinical trials (RCTs), such as the randomized evaluation of COVID-19 therapy (RECOVERY) and Solidarity trials confirmed the lack of efficacy of HCQ in hospitalized patients with COVID-19. [6-7]

Currently, most guidelines, such as those from the National Institutes Health (NIH) and infectious diseases society of America (IDSA), recommend against the use of HCQ for hospitalized patients. [8-9] Besides, from the early onset of its use, there was a concern about a potential property of HCQ in QTc interval prolongation as demonstrated on electrocardiography (ECG) tracings, particularly in patients with a history of cardiovascular diseases. Some studies have shown an increased in the risk of arrhythmias and ECG abnormalities following administration of HCQ, especially in combination with azithromycin. [10–12]

However, with the publication of subsequent studies, this concern has been somewhat alleviated. [6, 13-14] Taken together, these factors once again led to attention being paid to HCQ use in outpatient settings.

The first confirmed case of COVID-19 in Iran was diagnosed on February 18, 2020. [15] A scientific COVID-19 taskforce was promptly assembled by the Iranian Ministry of Health (MOH) and five days later, the first national protocol for the management of the COVID-19 in outpatient settings was developed.

On February 29, 2020, the responsibility for providing outpatient services to the COVID-19 patients across a vast span of communities in Iran was assigned to the Comprehensive Health Centers (CHCs). The extensive CHC network of 5,500 centers is the main provider of primary healthcare in Iran. These centers work free of charge in 16- or 24-h rosters and cover both rural and urban populations. These centers are governed by their regional medical science universities and health services authorities under the jurisdiction of the MOH throughout the whole country. [16] The health information of more than 90% of the population in Iran is registered in an electronic network of health records that are maintained by these centers. Allocation of these CHCs to function as the main body for primary care, data collection, and registration centers for COVID-19 facilitates the screening and follow-up of these patients, especially in the high-risk populations.

In this large population-based study, we evaluated the clinical outcomes of mild COVID-19 patients who were treated with HCQ in an outpatient setting.

2. Methods

In this outpatient national retrospective cohort study, the clinical outcomes of patients with mild COVID-19 were followed in two main groups of patients who received or did not receive HCQ.

HCQ was added to the supportive care for patients with mild COVID-19 illness who did not require referral to the hospital. Based on the national COVID-19 protocol, the mild disease was defined as the presence of mild cough, body ache, loss of smell or taste, a body temperature of ≤ 38 °C, peripheral oxygen saturation (SpO2) ≥ 93%, and the absence of shortness of breath, altered hemodynamics, and mental status instability.

HCQ was provided to the patients who presented with no clear contraindications and were not using it for other indications. They were instructed to take 400 mg twice daily on day 1 followed by 200 mg twice daily from days 2 to 5 if they had presented within 3 to 7 days of the initiation of their COVID-19 symptoms.

Patients were followed daily for 5 days and then on day 14, either in-person or by phone, for their disease trajectory, outcome variables, and adverse HCQ-related drug reactions. Baseline characteristics and outcome variables of hospitalization or death for all patients were also collected from the national integrated health system database.

COVID-19 was diagnosed based on the clinical presentation and either reverse transcriptase-polymerase chain reaction (RT-PCR) results from nasopharyngeal swab samples following World Health Organization (WHO) protocols or chest imaging. The clinical outcomes of our study were COVID-19-related hospitalizations or deaths during six-months of follow up.

Continuous and categorical variables are shown as mean ± standard deviation (SD) and frequency (percentage), respectively. OR and 95% CI were estimated for comparison of outcomes of the patients who were treated or not treated with HCQ by binary logistic regression models. The effect

of confounding variables, including age, sex, body mass index (BMI), hypertension, respiratory diseases, diabetes mellitus, and cardiovascular diseases, other than hypertension, on the incidence of outcomes was examined by adjusted logistic regression models. The selection of these factors was based on their effects on the clinical outcomes of the patients with mild to moderate COVID-19 as described in previous studies.[18]

To calculate cost saving of HCQ administration, the probability of hospitalization was estimated using following formulas:

$$\text{Odds ratio} = \frac{\text{odds of hospitalization in the patients treated with HCQ}}{\text{odds of hospitalization in the patients who did not treat with HCQ}}$$

$$\text{Probability} = \frac{\text{odds}}{1 + \text{odds}}$$

3. Results

From March 2020 to September 2020, the COVID-19 related data concerning a total of 28,759 patients who presented to the CHCs were included in the integrated health system for final analysis. COVID-19 diagnosis was made by clinical parameters and RT-PCR in 22,784 (79.22%) and clinical parameters and chest imaging in the remaining patients (Table 1). Upon presentation, evaluation, and a brief education about COVID-19 and possible HCQ adverse reaction, a total of 7,295 (25.37%) patients with mild symptoms consented to receive and use HCQ as prescribed.

The mean age ± SD of the patients was 45 ± 15 and 46 ± 15 years old in those who received and did not receive HCQ, respectively. No significant gender differences in both groups were noted (Table 1). Hypertension, chronic respiratory diseases, and diabetes mellitus were the most common underlying reported diseases. Hospitalization for COVID-19 worsening was required in 7.17% and

11.1% of patients who received and did not receive HCQ, respectively. HCQ reduced the odds of hospitalization by 38% (OR=0.62; 95% CI: 0.56–0.68, p-value=< 0.001).

A total of 314 patients died of COVID-19 complications, 27 (0.37%) and 287 (1.34%) in those who receive and did not receive HCQ respectively, indicating a 73% mortality risk reduction on logistic regression model (OR = 0.27; 95% CI: 0.18–0.41, p ≤ 0.001) in the HCQ group.

The effect of HCQ on the outcome measures was maintained after adjusting for confounding factors and comorbidities. This effect remained significant whether patients were diagnosed based on positive RT-PCR or otherwise (Table 1).

According to the odds of hospitalization of patients who received (0.077) or did not receive (0.124) HCQ, the probability of this outcome was 0.07 and 0.11 respectively. Dividing the difference of these numbers by 0.11 it was estimated that hospitalization costs were reduced by about 36 percent.

Serious HCQ adverse drug reactions were not reported in any of the age groups with or without comorbidities.

4. Discussion

In this large national retrospective cohort study, we examined the clinical outcomes of the patients with mild COVID-19 following early treatment with HCQ in an outpatient setting. Our study demonstrated that a short course of HCQ, given in the outpatient setting and within seven days of symptoms, could significantly reduce hospitalizations and deaths. The odds of COVID-19-related hospitalizations and deaths in our study population who were treated with HCQ were reduced by more than one-third and two-thirds, respectively.

In our study, we included the effects of confounding factors on the occurrence of outcome measures and recorded any serious HCQ adverse reactions.

In the light of severe and prolonged burden caused by SARS-CoV-2, the importance of its early detection and management, and the lack of an effective, available, and cheap therapeutic option, our study along with others [19–21] may convey important messages regarding the outpatient management of mild COVID-19 disease.

In Iran, the mean direct medical cost for each hospitalized patient with COVID-19 was estimated to be 59,203,409 Rials (approximately $ 3,755). [22] Administration of HCQ can reduce the hospitalization cost by about 36 percent. Assuming a population of 100 patients, the total costs of hospitalization are calculated as $ 41,305 (11× 3,755) without administration of HCQ while this cost will decrease to $ 26,285 (7× 3,755) with considering the medication. Of course, if indirect costs are also considered, the effect of HCQ will be far greater. It should be noted that mean indirect cost of each patient with COVID-19 was estimated as $ 11,634. [22]

The impact of triple therapy, including HCQ, azithromycin, and zinc on hospitalization rates and all-cause deaths was examined in a retrospective study. The dose of HCQ was 200 mg twice daily for five days in that study. Use of the triple regimen caused a significant reduction in the incidence rates of hospitalization and all-cause mortality (OR = 0.16 and 0.2, respectively). [19] Although this study was also retrospective, the number of included patients was much smaller than found in our study. In this study, concomitant medications, and adverse effects of HCQ were mentioned. The patients were risk-stratified based on age, symptoms, and comorbidities.

The impact of medications, such as HCQ, prednisolone, azithromycin, ivermectin, and oseltamivir on clinical outcomes of 717 COVID-19 patients was examined retrospectively in an outpatient

setting in Brazil. The main outcomes of the study were the rates of hospitalization and deaths as in our study. The use of HCQ alone was associated with 55% reduction in the rate of hospitalization. While not significant, the same decrease was seen with respect to the incidence of death. Except for prednisolone, other medications had no significant effect on the outcomes. [20] Interestingly, cardiac and ECG abnormalities were not seen in any of the above studies. [19- 20]

Beneficial effects of HCQ in outpatient were also described in a systematic review. [23] Currently, several random clinical trials (RCTs) are ongoing with the aim of evaluating the efficacy of HCQ, specifically in COVID-19 disease outpatient management. [24-25]

However, two recent RCTs for early HCQ use in non-hospitalized patients did not indicate any significant association with a reduction in the risk of hospitalization. [26-27]

Several studies especially RCTs demonstrated that HCQ can be administrated safely and without incidence of serious cardiac adverse events in outpatients and hospitalized patients with mild COVID-19. [14, 28–30]

Some of the limitations of our study are the retrospective design, lack of laboratory data (as the patients were deemed to be mild and not followed for hospital laboratory values), lack of access to other medications received by the patients in each group, absence of data on patients who required hospital admission, and a short initial follow-up period.

However, our large, multicenter, national study and adjustment of the outcome variables for comorbidities are the strengths of our study.

5. Conclusion

Our investigation of a large national cohort appears to support early administration (within the first 3 to 7 days of COVID-19 diagnosis) of HCQ in mild COVID-19 disease in an outpatient setting for reducing hospitalizations and deaths without any serious adverse HCQ-related effects. If this finding is confirmed in future clinical trials, HCQ as a cheap and available drug may still play a role in a specific population with respect to reducing COVID-19 burden, particularly in resource-poor countries.

Acknowledgment

Data were extracted from CHCs affiliated to following Medical Sciences Universities. We appreciate all staffs for data gathering and sharing.

Abadan University of Medical Sciences, Arak University of Medical Sciences, Ardabil University of Medical Sciences, Urmia University of Medical Sciences, Hamedan University of Medical Sciences (Asadabad branch), North Khorasan University of Medical Sciences (Esfarayen branch), Isfahan University of Medical Sciences, Alborz University of Medical Sciences, Iran University of Medical Sciences, Zahedan University of Medical Sciences (Iranshahr), Ilam University of Medical Sciences, Babol University of Medical Sciences, North Khorasan University of Medical Sciences (Bojnourd branch), Kerman North Khorasan University of Medical Sciences (Bam branch), Hormozgan University of Medical Sciences, Ahwaz Jundishapur University of Medical Sciences (Bahbahan branch), Bushehr University of Medical Sciences, Birjand University of Medical Sciences, Tabriz University of Medical Sciences, Mashhad University of Medical Sciences (Torbat Jam branch), Tehran University of Medical Sciences, Jahrom University of Medical Sciences, Jiroft University of Medical Sciences, Ardabil University of Medical Sciences (Khalkhal branch), Khomein University of Medical Sciences, Urmia University of Medical Sciences (Khoy branch), Dezful University of Medical

Sciences, Rafsanjan University of Medical Sciences, Zabol University of Medical Sciences, Zanjan University of Medical Sciences, Mazandaran University of Medical Sciences, Saveh University of Medical Sciences, Sabzevar University of Medical Sciences, Tabriz University of Medical Sciences (Sarab branch), Semnan University of Medical Sciences, Sirjan University of Medical Sciences, Shahrood University of Medical Sciences, Shahrekord University of Medical Sciences, Shahid Beheshti University of Medical Sciences, Ahwaz Jundishapur University of Medical Sciences (Shushtar branch), Shiraz University of Medical Sciences, Fasa University of Medical Sciences, Qazvin University of Medical Sciences, Qom University of Medical Sciences, Kashan University of Medical Sciences, Kordestan University of Medical Sciences, Gonabad University of Medical Sciences, Gilan University of Medical Sciences, Shiraz University of Medical Sciences (Larestan branch), Lorestan University of Medical Sciences, Maragheh University of Medical Sciences, Neyshabur University of Medical Sciences, Yasuj University of Medical Sciences, Yazd University of Medical Sciences

We would like to thank the nurses and other staffs of Imam Khomeini Hospital Complex for their kind supports and also Ms. Ava Khalili for English proofreading the manuscript.

Funding: The authors did not receive any fund for this work.

Declaration of interest: There is no conflict of interest for authors to declare.

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Table 1. Baseline characteristics and clinical outcomes of the patients who received and did not receive hydroxychloroquine

Variable	**Received HCQ (N=7,295)**	**Did not receive HCQ (N=21,464)**	**OR (95% CI)**	**P-Value**
Demographic characteristics				
Median age (IQR) — yr	43 (33-57)	43 (33-58)	-	0.112
Age category — no. (%)				
≤65 yr	6,424 (88.06)	18,557 (86.45)	-	0.001
>65 to ≤85 yr	825 (11.31)	2,710 (12.63)	-	
>85 yr	46 (0.63)	197 (0.92)	-	
Sex — no. (%)				
Male	3,674 (50.36)	10,924 (50.89)	-	0.220
Female	3,621 (49.64)	10,540 (49.11)	-	
COVID-19 risk factors — no. (%)				
Without risk	4,724 (64,76)	14,365 (66.93)	-	<0.001
With at least 1 risk	2,571 (35.24)	7,099 (33.07)	-	
Hypertension	1,023 (14.02)	2,864 (13.34)	-	0.074
Respiratory diseases	636 (8.72)	1,782 (8.30)	-	0.140
Diabetes mellitus	426 (5.84)	982 (4.58)	-	<0.001
Non-hypertensive cardiovascular diseases	308 (4.22)	907 (4.23)	-	0.508

Obesity (BMI >30 kg/m^2)	122 (1.67)	415 (1.93)	-	0.085
History of corticosteroid use	110 (1.51)	281 (1.31)	-	0.114
Malignancy	43 (0.59)	126 (0.59)	-	0.526
Cancer therapy	32 (0.44)	98 (0.46)	-	0.462
Organ transplant recipient	14 (0.19)	33 (0.15)	-	0.292
HIV positive	9 (0.12)	21 (0.10)	-	0.344
COVID-19 diagnosis — no. (%)				
PCR positive	5,964 (81.76)	16,820 (78.36)	-	<0.001
PCR negative	470 (6.44)	1,418 (6.61)	-	
No test	861 (11.80)	3,226 (15.03)	-	
Clinical outcomes — no. (%)				
Hospitalization (unadjusted)	523 (7.17)	2,382 (11.10)	0.62 (0.56-0.68)	<0.001
Hospitalization (adjusted*)	-	-	0.62 (0.56-0.69)	<0.001
Death (unadjusted)	27 (0.37)	287 (1.34)	0.27 (0.18-0.41)	<0.001
Death (adjusted*)	-	-	0.30 (0.20-0.45)	<0.001
Hospitalization in patients with positive PCR	408 (6.84)	1,598 (9.50)	0.70 (0.63-0.78)	<0.001

Hospitalization in patients with negative PCR	24 (5.11)	154 (10.86)	0.44 (0.28-0.69)	<0.001
Hospitalization in patients with no test	91 (10.57)	630 (19.53)	0.49 (0.39-0.62)	<0.001
Death in patients with positive PCR	18 (0.30)	151 (0.90)	0.33 (0.21-0.55)	<0.001
Death in patients with negative PCR	1 (0.21)	4 (0.28)	0.75 (0.08-6.76)	0.801
Death in patients with no test	8 (0.93)	132 (4.09)	0.22 (0.11-0.45)	<0.001

*Adjusted for age, sex, BMI, hypertension, respiratory diseases, diabetes mellitus and cardiovascular diseases other than hypertension

Highlights

- Early administration of HCQ reduced the odds of hospitalization by 38%.

- Early administration of HCQ reduced the odds of death by 73%%.

-In resource-poor countries, HCQ may be still an option for mild COVID-19.

The Effect of Early Hydroxychloroquine-based Therapy in COVID-19 Patients in Ambulatory Care Settings: A Nationwide Prospective Cohort Study

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ABSTRACT

BACKGROUND: Currently, there is no proven effective therapy nor vaccine for the treatment of SARS-CoV-2. Evidence regarding the potential benefit of early administration of hydroxychloroquine (HCQ) therapy in symptomatic patients with Coronavirus Disease (COVID-19) is not clear.

METHODS: This observational prospective cohort study took place in 238 ambulatory fever clinics in Saudi Arabia, which followed the Ministry of Health (MOH) COVID-19 treatment guideline. This guideline included multiple treatment options for COVID-19 based on the best available evidence at the time, among which was Hydroxychloroquine (HCQ). Patients with confirmed COVD-19 (by reverse transcriptase polymerase chain reaction (PCR) test) who presented to these clinics with mild to moderate symptoms during the period from 5-26 June 2020 were included in this study. Our study looked at those who received HCQ-based therapy along with supportive care (SC) and compared them to patients who received SC alone. The primary outcome was hospital admission within 28-days of presentation. The secondary outcome was a composite of intensive care admission (ICU) and/or mortality during the follow-up period. Outcome data were assessed through a follow-up telephonic questionnaire at day 28 and were further verified with national hospitalisation and mortality registries. Multiple logistic regression model was used to control for prespecified confounders.

RESULTS: Of the 7,892 symptomatic PCR-confirmed COVID-19 patients who visited the ambulatory fever clinics during the study period, 5,541 had verified clinical outcomes at day 28 (1,817 patients in the HCQ group vs 3,724 in the SC group). At baseline, patients who received HCQ therapy were more likely to be males who did not have hypertension or chronic lung disease compared to the SC group. No major differences were noted regarding other comorbid conditions. All patients were presenting with active complaints; however, the HCQ groups had higher rates of symptoms compared to the SC group (fever: 84% vs 66.3, headache: 49.8 vs 37.4, cough: 44.5 vs 35.6, respectively). Early HCQ-based therapy was associated with a lower hospital admission within 28-days compared to SC alone (9.4% compared to 16.6%, RRR 43%, *p-value* <0.001). The composite outcome of ICU admission and/or mortality at 28-days was also lower in the HCQ group compared to the SC (1.2% compared to 2.6%, RRR 54%, *p-value* 0.001). Adjusting for age, gender, and major comorbid conditions, a multivariate logistic regression model showed a decrease in the odds of hospitalisation in patients who received HCQ compared to SC alone (adjusted OR 0.57 [95% CI 0.47-0.69], *p-value <0.001*). The composite outcome of ICU admission and/or mortality was also lower for the HCQ group

compared to the SC group controlling for potential confounders (adjusted OR 0.55 [95% CI 0.34-0.91], *p-value* 0.019).

CONCLUSION: Early intervention with HCQ-based therapy in patients with mild to moderate symptoms at presentation is associated with lower adverse clinical outcomes among COVID-19 patients, including hospital admissions, ICU admission, and/or death.

Keywords: COVID-19 Treatment, Hydroxychloroquine, Ambulatory care, Hospitalisation, Mortality, Outcome

INTRODUCTION

COVID-19 has rapidly emerged as a pandemic infection that caused significant morbidity and mortality worldwide. Globally, extensive efforts have been made to explore effective and safe therapeutics against the causative virus, SARS-CoV-2 (1). Several medications, including remdesivir, favipiravir, the combination of ribavirin, interferon-beta, and lopinavir-ritonavir, have been suggested based on promising in-vitro results therapeutic experiences from two other coronavirus diseases; severe acute respiratory syndrome and the Middle East respiratory syndrome. However, none of these medications has yet been translated into clinical benefits in treating patients with COVID-19 (2, 3).

Hydroxychloroquine (HCQ), best known as an antimalarial medication, is prominent on the list of potential COVID-19 treatments, owing to its potent antiviral activity against SARS-CoV-2 in in-vitro studies and the results from several trials (4, 5). In-vitro studies show that HCQ blocks COVID-19 infection at a low-micromolar concentration, with a half-maximal effective concentration (EC50) of 1.13 μM and a half-cytotoxic concentration (CC50) greater than 100 μM. The exact mechanism of HCQ's antiviral activity in HIV is not fully understood, yet several mechanisms have been proposed (7-10). Early theories focused on alterations in post-transcriptional development of the outer HIV surface molecule glycoprotein 120 (gp120), which would render newly formed virions non-infectious (7-12).

To date, studies regarding the efficacy of HCQ, whether alone or in combination with azithromycin, have been contradicting with some pointing towards improved various clinical outcomes (4,5,13-16). In contrast, others failed to demonstrate any benefit (17-21). However, there are major differences amongst these studies in terms of the populations which received HCQ vs a comparator and the timing of initiation of the therapy which may have a significant impact on the variability of these results.

Zinc is a supplement which also has potential antiviral properties that affect the common cold, many of which are due to coronaviruses (22). The combination of HCQ with zinc in the treatment of COVID-19 patients, in an out-or inpatient setting, has been believed to improve the clinical outcome and limit COVID-19 mortality rates, especially if given in early stages of the disease (14). However, evidence regarding the potential therapy of HCQ, whether given alone or in combination with zinc, for COVID-19 patients, is not clear and limited (23) Furthermore, chloroquine and its derivative HCQ may hamper cardiac function at clinically relevant doses, and its safety margin is questionable (20,24). Therefore, further studies are needed to monitor this medication's safety and benefits.

As part of its response to the COVID-19 pandemic, the Saudi Arabian Ministry of Health (MOH) launched a national fever clinic program to support the acute healthcare system. Healthcare providers at these clinics were managing patients according to a national MOH COVID-19 management guideline which included the option of starting HCQ in addition to the supportive care according to disease severity (25). This study aims to assess the effect of the early use of HCQ in addition to supportive care (SC) compared to supportive care SC alone in patients with confirmed COVID-19 (by Polymerase Chain Reaction (PCR) test) presenting with mild or moderate disease at these ambulatory fever clinics on 28-day adverse clinical outcomes.

METHODS

Study setting and design

The national COVID-19 response led by the Ministry of Health (MOH) at Saudi Arabia focused on providing guidance on diagnostic and therapeutic options for COVID-19 as well as improving access to care across the Kingdom. Within that, a comprehensive COVID-19 management guideline was devised by a group of clinical experts according to the best available evidence at the time and was published and periodically reviewed by the MOH (26). This management guideline based the treatment on supportive care therapy in addition to other therapeutics to be considered and included HCQ as a possible option for mild to moderate disease if there was no contraindication.

In line with the national COVID-19 response vision, the MOH also launched a national fever clinic program across all regions of the Kingdom to support the healthcare system. By June 2020, a total of 238 fever clinics were fully operational in assessing patients with symptoms concerning for COVID-19. These fever clinics provided free medical care to all community members regardless of their nationality, insurance status, legal status, and area of residence.

The national fever clinic program included screening all patients using an approved national visual triage checklist from the Saudi Center for Disease Control (26), measuring vital signs, detailed assessment by a trained primary care provider, and considering treatment options per the MOH management guideline (25). The fever clinics were designed to care for patients with mild to moderate symptoms, while unstable patients were referred to emergency care services (**appendix.1**). During the selected study period, HCQ was the only available treatment option along with supportive care at these fever clinics. The final decision for starting HCQ therapy in addition to supportive care was based on the individual provider's discretion after detailed risk assessment (including comorbidity screening, baseline electrocardiogram (ECG), serum electrolytes check) and the shared decision with the patient. Per the ambulatory fever clinic program, patients with baseline abnormal QTc interval or electrolyte imbalances were not prescribed HCQ. Given the overall safety concerns about HCQ therapy in patients above the age of 65 years, the national ambulatory clinic program cautioned providers from prescribing it to this age group. If HCQ was prescribed, patients were required to return for a follow-up visit at day 3 to assess tolerance and to obtain repeat ECG and serum electrolytes to ensure safety. HCQ therapy was discontinued at any time patients reported any medication-related adverse events. All patients who attended these clinics provided consent be enrolled in and allow the use of their clinical data for prospective research purposes at their first visit.

A comprehensive implementation plan was rolled out for this national fever clinic program which included: 1) continuous supply chain of personnel protective equipment, medical devices, and medications; 2) virtual training sessions of 990 primary care providers operating these clinics by an infectious diseases specialist and a senior clinical pharmacist about the clinic program; 3) hotline service to access infectious diseases expertise opinion when needed; 4) standardised ambulatory medication prescription order sets to minimise variability; 5) fever clinics with extended hours of service at 24 hours 7 days a week; 6) extensive media coverage to educate the community about the program; 7) fully equipped call centre to coordinate appointments and answer inquiries around the clock.

This observational prospective cohort study looks at the outcomes of patients presenting to these ambulatory fever clinics during the period between the 5th to 26th of June 2020 who had mild to moderate symptoms and were later confirmed to have COVID-19. All enrolled patients were followed up telephonically at day 28 to record their outcomes (either personally or by a family member).

Study participants

Symptomatic patients with PCR-confirmed COVID-19 who attended the ambulatory fever clinics during the study period were included in this study. Mild to moderate symptoms included fever (> 38 ºC) with or without one or more of the following symptoms: sore throat, cough, diarrhoea, shortness of breath, headache, and myalgia. Patients who were less likely to get HCQ prescriptions were excluded from the study cohort such as paediatrics patients (age < 14 years), pregnant and lactating ladies, patients known to have conductive heart disease, immunocompromising conditions, baseline home oxygen requirement, morbid obesity (BMI ≥ 35), known allergy to HCQ, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Study participants were divided into two groups; those who received the SC and those who received HCQ therapy along with the SC. Per the national ambulatory fever clinic program, the SC included symptomatic therapy with zinc sulphate 60 mg once daily for five days, cetirizine 10 mg once daily for 10 days, and paracetamol on an as-needed basis. Those who received HCQ were prescribed a regimen of 400 mg orally twice a day for the first day, followed by 200 mg twice daily for an additional four days according to the MOH management guideline. No dose adjustment was recommended in cases with renal or hepatic impairment.

Patients who had clinical progression or deterioration at day 3 assessment were referred to a hospital setting for management and continued their participation in the study outcome according to their initial assigned group. Study participants who did not show up for their day 3 assessment were excluded.

Study Outcomes

The primary outcome of interest was hospital admission within 28-days of presentation. The secondary outcome of the study was a composite of ICU admission and/or mortality during the 28-day follow up period.

Data Collection Tools

A research electronic clinical data collection form (CDF) completed at the national fever clinic program and a follow-up telephone questionnaire done at day 28 were used to collect data about the study participants. Trained primary health care physicians filled out the CDF at day 1 and day 3 assessment visits for each patient per the program requirement. The CDF included patient's demographics, chronic medical conditions, presenting symptoms, physical exam findings, laboratory results, procedures, and management done at each visit. Data entry officers at the MOH regional Medical affairs entered the data from the CDFs into an advanced national online database. The day 28 telephone questionnaire was conducted by trained personnel who

contacted the COVID-19 positive patients or their delegated family members and asked about their clinical outcomes. Outcome data of all the PCR-confirmed COVID-19 patients were also verified with reports from the National disease surveillance database (Health Electronic Surveillance Network, HESN) and the MOH national morbidity & mortality registry. All outcome data were additionally shared with regional Medical Affairs and were further verified with local hospitalisation, ICU, and mortality registries.

Statistical Analysis

The data were analysed using SPSS® version 25.0. All the data had categorical characteristics, which was described as frequency and percentages. Chi-square test, Fisher exact test, and Crude odds ratio were used to compare symptomatic patients who received HCQ and SC across Socio-demographic background variables and comorbid conditions. Multivariable Logistic regression model was used to assess for primary and secondary outcomes controlling for age, gender, and major comorbidities. The level of significance was considered at $P<0.05$.

Ethical consideration

The Saudi Arabian MOH central Institutional Review Board (IRB) approved this observational prospective cohort study, log number: 20-129M. Study enrolment was voluntarily, and all study participants signed an informed consent after receiving a detailed explanation of the research study protocol by their treating physicians. As the study design is purely a prospective observational cohort which followed a predefined population rather than an interventional trial, clinical trial registration was exempted by the MOH Central IRB. The process of prescribing HCQ in COVID-19 followed the national guideline of prescribing recommendation in Saudi Arabia.

RESULTS

Among 13,592 patients who presented with symptoms to the ambulatory fever clinics during the study period, 7,892 patients had PCR-confirmed COVID-19 of which 5,541 participants responded to the 28-day telephone questionnaire, and their outcome data could be verified with national registries were included in the final analysis. **Figure.1** summarises patient population selection. Among the study participants, almost 33% (n= 1,817) received HCQ in addition to SC while 67.2% (n= 3,724) received the SC only. **Table.1** summarises the socio-demographic and associated comorbidities distribution between the two groups. Significant differences were noted between the groups at baseline, with more males, ages less than 65 years in the HCQ group. There were no significant differences between both groups in terms of overall comorbid conditions except for chronic lung diseases and hypertension with higher percentages among

the SC group compared to the HCQ group (1.1% and 9.2% versus 0.4% and 7.2% respectively, *p-value* <0.05). In terms of other administered medications, there was no difference between the two groups in receipt of antibiotics at any point during the study period and follow up; however, the SC group had a higher frequency of receiving steroids after hospitalisation compared to the HCQ group (1.6% vs 0.2%, p-value <0.001).

Per the prespecified inclusion criteria, all patients who were included in the analysis have presented with mild to moderate symptoms concerning for possible COVID-19. Almost all the presenting symptoms were seen in higher percentages among the patients who ended up receiving HCQ therapy compared to the SC alone, most notably: fever (83.91% vs 66.27%), headache (49.78% vs 37.41%), cough (44.54% vs 35.41%), and myalgia (43.65% vs 33.94%) (**Figure.2**).

The overall hospitalisation rate from disease progression in the study population was 14.2% (N= 788) with significant fewer hospital admissions in the HCQ group compared to the SC (171 (9.36%) vs 617 (16.6%), *p-value* <0.001). This corresponded to a relative risk reduction in hospital admission of 43% among patients who received HCQ compared to the SC (**Table.2**). The rate of ICU admissions and mortality rate were also lower in the HCQ compared to the SC (0.77 vs 1.5 (*p-value* 0.022), and 0.39 vs 1.45 (*p-value* <0.001), respectively). The primary and secondary outcomes of interest were verified with national mortality data and local hospitalisation and mortality registries for all the COVID-19 symptomatic patients at presentation (N= 7,892), and no outcomes were noted in the population which were lost to follow up.

The multivariate logistic regression model shows a significant decrease in the odds of hospitalisation in mild-moderately symptomatic COVID-19 positive patients who received HCQ compared to SC alone, even after adjusting for potential baseline confounders such as age, gender, and major comorbidities (adjusted OR 0.57 [95% CI 0.47-0.69], *p-value <0.001*) (**Table.3**). The composite outcome of ICU admission and/or death was also lower for the HCQ group compared to the SC group controlling for the same prespecified confounders (adjusted OR 0.55 [95% CI 0.34-0.91], *p-value* 0.019). **Table.4** shows the full multivariable logistic regression model.

DISCUSSION

Our study is a large observational nationwide cohort of PCR-confirmed COVID-19 patients who presented with mild and moderate symptoms to ambulatory fever clinics and were managed according to a national management guideline which included the prescription of

HCQ at an early stage of the disease (25). We describe what happened in real-world clinical practice where the decision to start HCQ therapy was based on the physician risk assessment and the shared decision with the patient which allows assessing the benefit of such intervention if it to be deployed on a population level. Despite the seen differences in the baseline characteristics between the patients who received HCQ and those who received the SC alone, the multivariate logistic regression model that controls for patient-specific prespecified potential confounders shows a lower odds of adverse clinical outcomes, namely, hospitalisation and ICU admission and/or mortality within 28-days of the presentation by 43% and 45% respectively. The decision to start treatment did not differentiate between a specific symptom or combination of symptoms and many patients presented with a group of symptoms thus given the dependent nature of this variable; it was not included in the final multivariable model. As the study protocol did not interfere with the acute care management of the study participants who were hospitalised, it is reasonable to believe that ICU admission criteria would vary between different hospital settings. Nonetheless, there was a trend towards lower ICU admissions in the HCQ group. As the mortality rate in Saudi Arabia is considered low compared to other nations (26, 27), to ensure the stability of the multivariate logistic model, the mortality outcome was looked at as a composite of ICU admissions and/or mortality which reached clinical significance while controlling for the prespecified confounders favouring the effect of early intervention with HCQ.

Per the national ambulatory fever clinic program, at the specified study period, steroid therapy was not advised for the sake of COVID-19 infection per se and was mainly prescribed as indicated, if any. The fact that the receipt of steroid after hospitalisation was significantly higher at the SC group is reassuring that the observed result represents the effect of the early intervention with HCQ rather than the possible confounding effect of early steroid therapy, however, since complete data about steroid prescription at presentation is lacking, this cannot be firmly concluded. Finally, the safety of HCQ therapy in our cohort is described in detail elsewhere, and it was shown to be a tolerable medication with minimum side effects (data submitted for publication by Mohana et al.).

The previously published observational studies which failed to translate the in-vitro mechanistic benefit of HCQ on clinical outcomes mainly introduced the therapy on hospitalised patients (17-21). However, recent large cohort studies showed significantly improved outcomes in patients who received HCQ early during hospitalisation (4,15). This spiked the interest in testing the effect of early administration of HCQ therapy during the initial viral

replication phase prior to the progression to the hyperimmune response phase owing to its variable antiviral properties (28). While an Italian multicentre, open-label, randomised controlled trial did not show benefit of early administration of HCQ therapy to mildly symptomatic young adults (29), other retrospective studies showed a promising benefit of early HCQ treatment in modifying the overall outcome of COVID-19 whether or not it was associated with azithromycin (30,31). Our study further supports these later findings and suggests a possible benefit of this early intervention in preventing adverse clinical outcomes on a population level.

Although our study included a large cohort of symptomatic COVID-19 participants, we acknowledge that it has several limitations. The population represented in the dataset analysed is relatively young with a limited number of patients who were above the age of 65 years based on the cautionary measure taken by the national ambulatory fever clinic program. Although the multivariable model adjusts for this age group, given the small numbers of patients in this stratum, we caution from generalising the results to this age-group. Furthermore, the study took place in all regions of the Kingdom during the pandemic, which imposed some logistic challenges leading to losing the follow up of many patients in both treatment groups. To overcome this anticipated challenge, the study protocol was designed with an additional verification process to ensure capturing all hard outcome data from reliable national registries. As this verification process was non-differential to the initial treatment group allocation, and the fact that the sample size of the cohort is considered large, we believe that the overall results are valid.

CONCLUSION

Although our study population were young and with a relatively low incidence of comorbidities in both treatment groups, early intervention HCQ-based therapy in an ambulatory setting in mild to moderate COVID-19 patients was associated with lower odds of hospitalisation and ICU admission and/or death. Additional large randomised controlled trials are recommended to further support this conclusion, particularly in older populations.

FUNDING

This research was conducted under the umbrella of the Saudi Arabian Ministry of Health and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table.1: Baseline characteristics of mild-moderately symptomatic COVID-19 Positive patients presenting to the national fever clinic program during the study period

Characteristic, n (%)	Total N= 5541 (100%)	Treatment group		*p-value*
		SC N=3724 (67.2%)	HCQ N=1817 (32.8%)	
Male	3951 (71.32)	2595 (69.70)	1356 (74.63)	<0.001
Age (years)				<0.001
< 18	128 (2.32)	106 (2.87)	22 (1.21)	
18 - 30	1766 (32.06)	1198 (32.43)	568 (31.29)	
31 - 40	1775 (32.22)	1114 (30.16)	661 (36.42)	
41 - 50	966 (17.53)	612 (16.57)	354 (19.50)	
51 - 64	710 (12.89)	510 (13.81)	200 (11.02)	
≥ 65	164 (2.98)	154 (4.17)	10 (0.55)	
KSA region*				<0.001
Central	2237 (40.37)	1545 (41.49)	692 (38.08)	
North	315 (5.68)	216 (5.80)	99 (5.45)	
South	598 (10.79)	374 (10.04)	224 (12.33)	
East	1316 (23.75)	705 (18.93)	611 (33.63)	
West	1047 (18.90)	857 (23.01)	190 (10.46)	
Comorbidities				
Heart diseases	248 (4.48)	166 (4.46)	82 (4.51)	0.925
Chronic lung diseases	50 (0.90)	42 (1.13)	8 (.44)	0.011
Hypertension	473 (8.54)	342 (9.18)	131 (7.21)	0.014
Diabetes Mellitus	573 (10.34)	402 (10.79)	171 (9.41)	0.112
Malignancy	23 (0.42)	17 (0.46)	6 (0.33)	0.492
Rheumatological diseases	19 (0.34)	13 (0.35)	6 (0.33)	0.91
Gastrointestinal disease	22 (0.40)	10 (0.27)	12 (0.66)	0.029
Thyroid dysfunction	16 (0.29)	11 (0.30)	5 (0.28)	0.895
Chronic kidney diseases	20 (0.36)	16 (0.43)	4 (0.22)	0.222
Receipt of antibiotics at any point	382 (13.2)	240 (12.5)	142 (14.5)	0.137
Receipt of steroids after hospitalization	63 (1.1)	60 (1.6)	3 (0.2)	<0.001

*Data missing in 28 patients (0.51%)

HCQ: hydroxychloroquine group; SC: supportive care group; KSA: Kingdom of Saudi Arabia.

Table.2: 28-days clinical outcomes of COVID-19 positive patients with mild-moderate symptoms who received hydroxychloroquine at presentation to the national fever clinic program compared to those who only received supportive care.

Characteristic, n (%)	Total N= 5541 (100%)	Treatment Group		*RRR*	*p-value*
		SC N=3724 (67.2%)	HCQ N=1817 (32.8%)		
Hospital admission	788 (14.22)	617 (16.60)	171 (9.40)	43%	<0.001
ICU admission	70 (1.26)	56 (1.50)	14 (0.77)	49%	0.022
Mortality[§]	61 (1.10)	54 (1.45)	7 (0.39)	73%	<0.001
ICU admission and/or Mortality	116 (2.1)	95 (2.6)	21 (1.2)	54%	0.001

HCQ: hydroxychloroquine; SC: supportive care; ICU= intensive care unit; RRR: relative risk reduction.

[§] No deaths in ≥ 65 years in the HCQ group.

Table. 3: Logistic regression model comparing 28-day clinical outcomes of mild-moderate symptomatic COVID-19 positive patients who received hydroxychloroquine as outpatient compared to supportive care

Clinical outcome	Crude OR (95% CI)	Adjusted OR* (95% CI)	*p-value***
Hospital admission	0.52 (0.44 - 0.63)	0.57 (0.47 - 0.69)	<0.001
ICU admission	0.51 (0.28 - 0.92)	0.63 (0.34 - 1.15)	0.133
Mortality[§]	0.26 (0.12 - 0.58)	0.36 (0.16 - 0.8)	0.012
ICU admission and/or Mortality	0.45 (0.28 - 0.72)	0.55 (0.34 - 0.91)	0.019

*adjusted for age (reference = age less than 18), male gender, independent comorbidities: (heart disease, chronic lung disease, hypertension, diabetes and other metabolic disorders, chronic kidney disease, malignancy). ICU= intensive care unit.
** for adjusted OR
[§] No deaths in ≥ 65 years in the HCQ group.

Table.4: Detailed logistic regression model of clinical outcomes of mild-moderate symptomatic COVID-19 positive patients at 28-days who received hydroxychloroquine as outpatient compared to supportive care

Covariate	Adjusted OR (95% CI)	*p-value*
Hospital admission	0.57 (0.47 - 0.69)*	<0.001
ICU admission and/or mortality	0.55 (0.34 - 0.91)*	0.019
Age (years)		
< 18	Ref	
18 - 30	2.22 (1.38 - 3.55)	<0.001
31 - 40	2.77 (1.73 - 4.43)	<0.001
41 - 50	2.74 (1.7 - 4.43)	<0.001
51 - 64	1.91 (1.17 - 3.14)	0.007
≥ 65	0.33 (0.15 - 0.73)	0.011
Gender (male)	1.23 (1.08 - 1.4)	0.002
Comorbidities		
Heart disease	1.12 (0.85 - 1.48)	0.429
Hypertension	1 (0.79 - 1.27)	0.973
Chronic lung disease	0.56 (0.26 - 1.21)	0.141
Diabetes mellitus	1.14 (0.92 - 1.41)	0.244
Chronic kidney disease	0.81 (0.26 - 2.53)	0.715
Malignancy	0.77 (0.3 - 2)	0.594

ICU= intensive care unit.
*The values presented represent the result of independent models which were performed on each outcome separately including the same listed covariates. The adjusted ORs and 95% CI of the age, gender, and comorbidities were the same in both models thus presented once.

Figure. 1: Flow diagram of the cohort selection

Figure 1 Legend: Flow diagram of symptomatic COVID-19 patients assessed at the national ambulatory fever clinics in Saudi Arabia during the period from 5-26 June 2020. Outcome recorded at 28-day follow up.

** The outcome of lost to follow patients were verified with national mortality registry and local hospitalisation and mortality registries and no mortality or hospitalisation were recorded among them.*
HCQ = hydroxychloroquine; SC = standard of care; PCR = polymerase chain reaction.

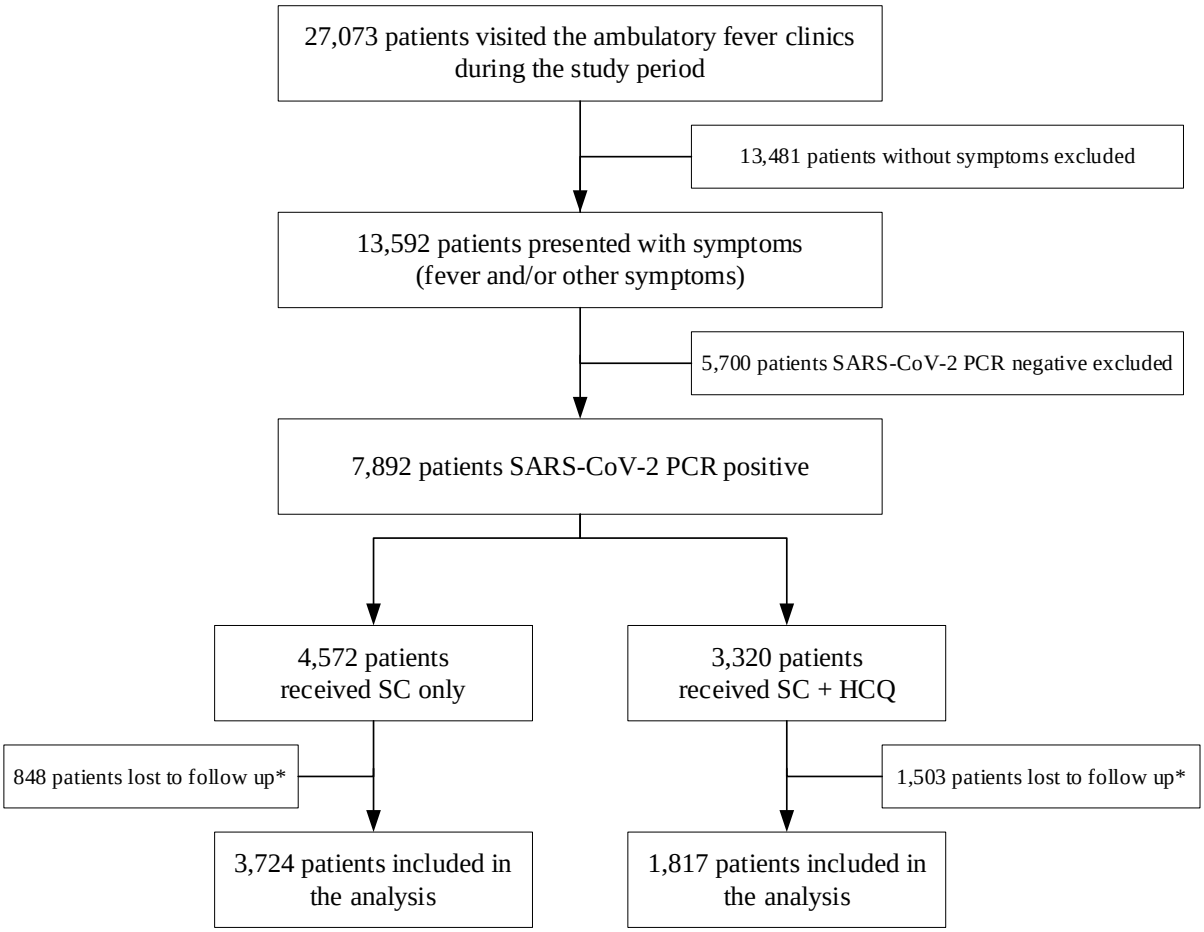
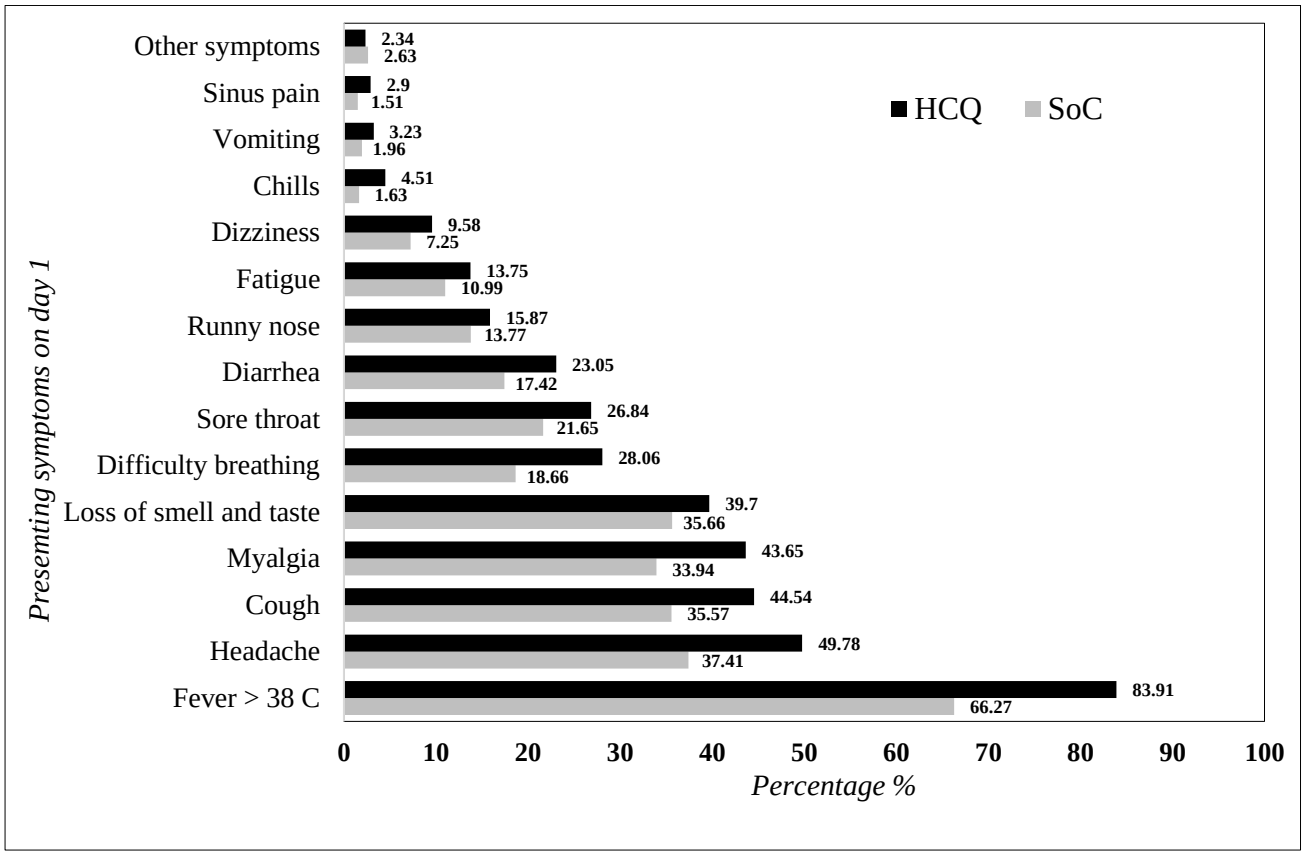
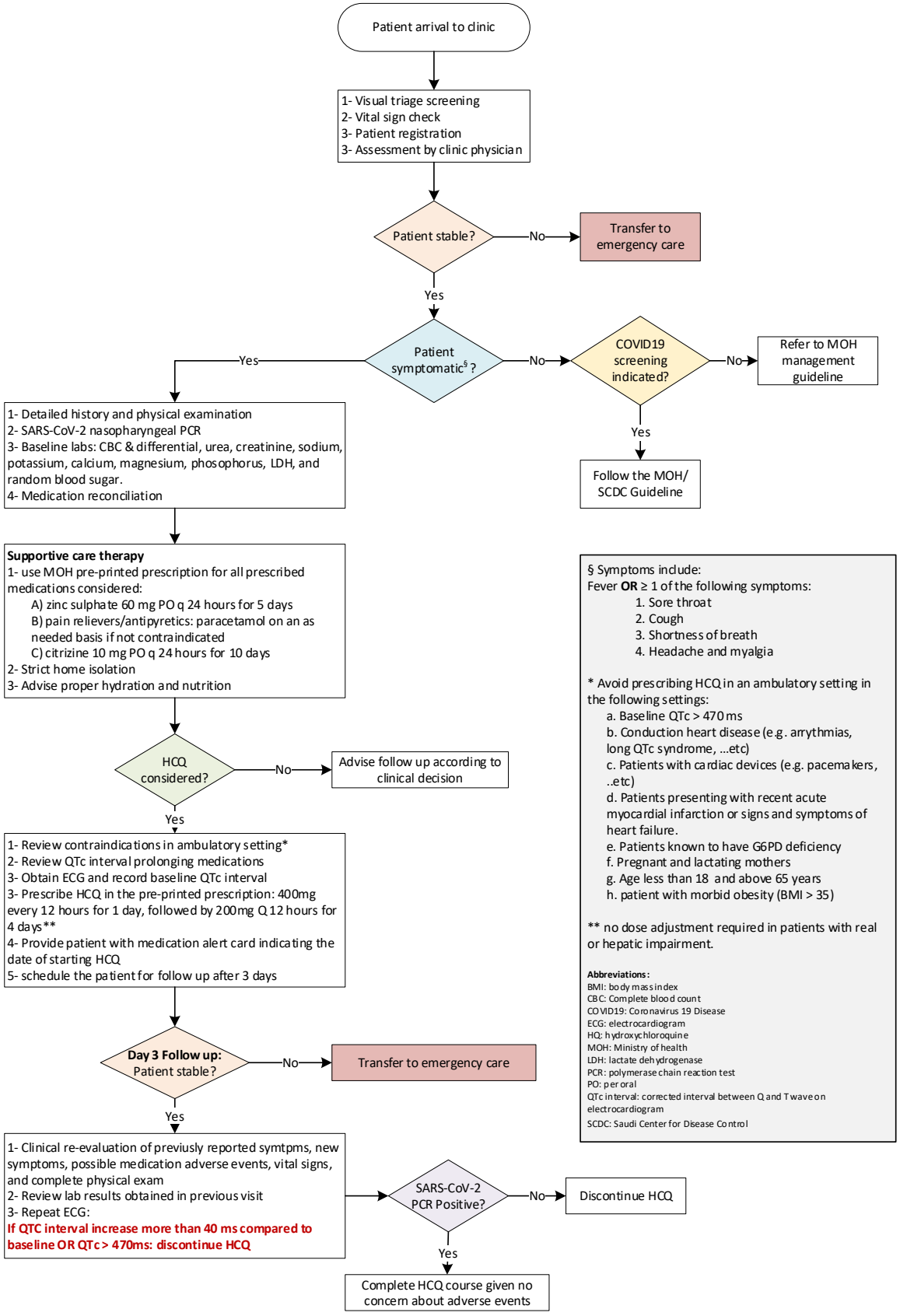


Figure 2: Frequency of COVID-19 symptoms at presentation among patients who received hydroxychloroquine therapy compared to supportive care

Figure 2 Legend: Flow diagram of ambulatory symptomatic COVID-19 patients assessed at the national fever clinics in Saudi Arabia during the period from 5-26 June 2020. Outcome recorded at 28-day follow up. HCQ = hydroxychloroquine; SC = supportive care.



Appendix.1: The Saudi Arabian Ministry of Health ambulatory fever clinic program recommendation for patients presenting with mild to moderate symptoms during the COVID-19 pandemic.



Travel Medicine and Infectious Disease 38 (2020) 101906

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Original article

Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis

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A B S T R A C T

Background: For the past few months, HMOs have faced crowded emergency rooms and insufficient hospital and intensive-care-unit beds, all from the worst pandemic of this century, COVID-19.
Methods: In a large HMO in Brazil, our approach was to allow treating physicians to prescribe antiviral medications immediately at presentation, and prednisone starting on day-6 of symptoms to treat pulmonary inflammation. We implemented this COVID-19 protocol for outpatients and studied 717 consecutive SARS-CoV-2-positive patients age 40 years or older presenting at our emergency rooms.
Results: Use of hydroxychloroquine (HCQ), prednisone or both significantly reduced hospitalization risk by 50–60%. Ivermectin, azithromycin and oseltamivir did not substantially reduce risk further. Hospitalization risk was doubled for people with type-2 diabetes or obesity, increased by two-thirds for people with heart disease, and by 75% for each decade of age over age 40. Similar magnitudes of reduced risk with HCQ and prednisone use were seen for mortality risk, though were not significant because of only 11 deaths among the 717 patients. No cardiac arrhythmias requiring medication termination were observed for any of the medications.
Conclusions: This work adds to the growing literature of studies that have found substantial benefit for use of HCQ combined with other agents in the early outpatient treatment of COVID-19, and adds the possibility of steroid use to enhance treatment efficacy.

1. Introduction

Mankind has been facing one of the greatest challenges of the XXI century: a pandemic [1] caused by a new virus, SARS-CoV-2, thought to be transmitted by airborne particles and droplets and contact with contaminated surfaces or objects [2]. Clinical manifestations of coronavirus disease 2019 (COVID-19) patients range from asymptomatic to mild non-specific signs and symptoms to severe pneumonia with organ function damage and eventual mortality [3,4]. There is a clear need to try to stop disease progression as early in the disease process as possible. Infected patients with comorbidities such as heart failure, type-2 diabetes, asthma or chronic obstructive pulmonary disease and obesity, and patients over sixty years of age are at substantially higher risk to develop severe disease and tend to have higher risks of death [5–7]. Many drugs have been tried in hospitalized patients, with largely discordant results [8–11]. Randomized double-blind controlled trials demonstrating benefit or lack of benefit of drugs in high-risk outpatients will not be available any time soon, as many clinical sites are still recruiting patients [12]. Early outpatient illness is very different than hospitalized severe disease and treatment therefore will differ between these two distinct groups. Relatively little is established about utility of medications in early outpatient treatment. Currently [13,14] it is understood that COVID-19 is at least a four-phase illness: phase 1 is viral replication, followed by pulmonary inflammation in phase 2, “cytokine storm” and acute respiratory distress in phase 3, and disseminated multi-organ involvement in phase 4. For treatment at the beginning of the illness, there are indications that chloroquine and especially hydroxychloroquine (HCQ) may be beneficial [15–18], but no specific antiviral

Abbreviations: ER, Emergency Room; HMO, Health Maintenance Organization; HCQ, Hydroxychloroquine.

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https://doi.org/10.1016/j.tmaid.2020.101906
Received 14 August 2020; Received in revised form 10 September 2020; Accepted 26 October 2020
Available online 31 October 2020

medications have demonstrated proven efficacy as yet [19,20]. Recently, the Brazil Federal Committee for Medicine has approved the prescription of chloroquine and HCQ for clinically suspected COVID-19 patients at the physician's discretion with informed consent [21] and the Health Ministry has also endorsed the use of these medications [22]. Brazil has the highest rate in South America in the ranking of COVID-19 deaths, with more than 4.2 million people infected in the country [23] in circumstances of a large population still to be affected and with economic difficulties resulting in inadequate social distancing. Data over March–May from the Federal Health Ministry [24] show that more than 90% of hospitalized patients with severe respiratory distress who were tested were positive for SARS-CoV-2, with less than 5% detected with influenza. Therefore, we assumed in clinical practice that most patients coming to the emergency room with influenza-like symptoms would have COVID-19. With all that, we developed a protocol for early recognition and treatment of high-risk patients (in our population, age greater than 40 years because of generally poorer health standards, or with comorbidities) who would come to our outpatient network of emergency rooms with influenza-like symptoms: fever, cough, myalgia and headache, among others, and receive early treatment, provided to patients at the first doctor visit, using physician discretion from among HCQ, azithromycin, ivermectin, oseltamivir, zinc sulfate, nitazoxanide and prednisone (the last starting on day-6 of symptoms). We evaluate here risks of subsequent hospitalization based upon outpatient use of these various medications.

2. Methods

Patient data were analyzed from electronic charts of health maintenance organization (HMO) Hapvida Saúde, the largest Brazilian HMO with 6 million members spread over five regions of the country. Data were collected after informed consent and Institutional Ethics Committee (4.087.824 CEP-University Fortaleza UNIFOR) approval for this study. To-date, during the pandemic, more than 300 000 monthly emergency room (ER) consults have occurred. Patients were all seen at the ERs of the widespread country hospital network and admitted if indicated. At the beginning of the pandemic in Brazil, late March–April 2020, the north and northeast cities were more affected, with a great number of ER consults and hospital and intensive-care-unit admissions. A protocol for early treatment of COVID-19 was developed by a team of senior HMO medical staff and started in early May; it included clinical recognition of the commonly described main COVID-19 signs and symptoms, and protocol criteria assessment for hospital admission vs outpatient care. Patients coming with influenza-like symptoms such as fever, sore throat, myalgia, arthralgia or coryza would enter the COVID-19 protocol. Patients presenting with hypoxia, defined as the need of oxygen to maintain an oxygen saturation greater than 92%, respiratory rate of or greater than 24 respirations/minute, hypotension defined as systolic pressure less than 90 mm Hg or diastolic pressure less than 60 mm Hg, or with confusion or extreme lethargy were immediately admitted to the hospital. The remaining patients over age 40 or with comorbidities were defined as high-risk and treated as outpatients. The protocol specifics were chosen by the attending physician, and all of its steps were monitored for quality assurance. The protocol was largely automated through on-screen suggestions and physician choice boxes leading to successive screens, medication prescription choices, etc. After discharge from the ER, patients received paper charts instructing them on isolation, symptoms to expect and medications to use, and QR codes for telemedicine, chat or phone consults. Patients were instructed to return if symptoms of dyspnea, confusion or lethargy occurred. Telemedicine was also always available to HMO patients on the HMO website. For discharged patients, the COVID-19 protocol included (all as oral medications), as chosen by doctors and patients: HCQ as first-line treatment, if used (400 mg bid day 1, 400 mg qd days 2–5), prednisone (1 mg/kg qd x 5 days, maximum 80 mg/day, no taper), azithromycin (500 mg qd x 5 days), ivermectin (12 mg qd x 2 days), plus symptom relievers. Zinc sulfate, oseltamivir and nitazoxanide were also available to be prescribed but were used infrequently. As doctors quickly found that most of the prescribed HCQ was not available at common drugstores, if prescribed it was decided to offer the drug free of charge to all patients who only had to sign informed consent to receive it. Data were collected from the HMO database for consecutive patients registered from May 11th to June 3rd, 2020. We selected all patients 40 years and older who tested positive for SARS-CoV-2 using a real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens [25]. To be clear, while all relevant patients with clinically likely COVID-19 were offered treatment by the HMO, for the present report, we analyzed all those patients whose infections were subsequently confirmed by laboratory assay. The collected data included patient characteristics and comorbidities, age, gender, history of type-2 diabetes, hypertension, cardiac illness, pulmonary disease, other conditions, and facts of hospital admission and death. Collected data were analyzed with multivariate unconditional logistic regression models to determine associations with medication use as well as other risk factors for hospital admission and death. Age (in decades) and presentation delay (days) were treated as continuous covariates whereas all other variables were dichotomous. In addition to the medications, all of the presentation characteristics and comorbidities in Table 1 were examined for statistical significance and for confounding adjustment. Death outcomes were those considered to be due to complications associated with COVID-19. A two-sided p-value less than 0.05 was considered statistically significant.

3. Results

From May to June, 24 927 patients were included in the COVID-19 protocol, 56% from the northeast Brazil states of Ceará, Bahia and Pernambuco. Seven hundred seventy-two patients (3.1%) were admitted to the hospital and 52 died (6.7% of those hospitalized, 0.2% of the whole cohort). Within the cohort of 24 927 patients, because of scarcity of the tests and without selection by disease severity, 3307 had testing for SARS-CoV-2 performed; 1570 were age 40 years or over and 715 (45%) of these patients had positive RT-PCR assays for SARS-CoV-2. We also included 2 patients who had positive SARS-CoV-2 serology (Table 1). Three hundred seventy-two patients were female (52%); the mean age was 50.6 years (range 40–93 years). The average delay from the start of symptoms to ER visit was 4.6 days. Common presenting symptoms included shortness of breath (198, 28%), cough (504, 70%), fever (452, 63%), myalgia (306, 43%) and sore throat (173, 24%); 221 (31%) patients had histories of cardiovascular disease, 123 (17%) had diabetes type 2, 73 (10%) were obese and 25 (3.5%) had chronic pulmonary disease. There were 114 hospital admissions (16%) and of these, 19 (17%) patients required mechanical ventilation and 11 (9.6%) patients died. The median time between start of symptoms and hospital admission was eight days; between hospital admission and death was seven days. One hundred twenty-two of the 717 patients received none of the medications, and 33 (27%) of them required hospitalization.

Associations with fact of eventual hospitalization are given in Table 2. The multivariate logistic regression model presented in the table shows that age, obesity (BMI $>$ 30) and dyspnea were very substantial risk factors for hospital admission. Each additional decade of age over age 40 multiplied the risk of admission by a factor of 1.75. Use of prednisone and use of HCQ were both associated with significantly reduced risk, and both drugs used together seemed to perform slightly better than either one alone. When the analysis was restricted to exclude patients hospitalized within five days, thus not eligible to receive prednisone, the results were essentially unchanged. History of pulmonary disease, presentation delay, or presentations with cough, myalgias, sore throat, headache or diarrhea were not associated with risk of hospitalization. Presentation with fever, however, had OR = 1.93 (95%CI 1.18–3.14), p = .0085, but did not change the associations seen in Table 2, and with consideration for multiple comparisons of the various

Table 1
Characteristics of tested-positive Covid-19 patients treated under the new Hapvida Brazil HMO protocol.

	Given none of the medications (n = 122)	Given neither HCQ nor Prednisone (n = 244)	Given both HCQ and Prednisone (n = 159)	Given HCQ Only (n = 175)	Given Prednisone Only (n = 139)	All Patients (n = 717)
Age (mean, years) (10–90 % iles)	51.3 (41–70)	52.0 (41–71)	50.4 (41–60)	50.3 (41–61)	48.8 (4–59)	50.6 (41–63)
Presentation delay[a] (mean, days) (10–90 %iles)	4.1 (1–8)	4.2 (1–8)	4.5 (1–8)	4.4 (1–9)	5.6 (1–10)	4.6 (1–9)
Sex (% Female)	59.0	54.5	45.9	48.0	59.0	51.9
Hospitalized (%)	27.0	24.2	10.1	14.3	10.1	15.9
Ventilated (%)	4.9	3.3	2.5	1.1	3.6	2.6
Died (%)	3.3	2.9	0.6	0.6	1.4	1.5
Cough (%)	69.7	67.2	73.0	74.9	66.9	70.3
Fever (%)	52.5	59.4	66.7	65.7	61.9	63.0
Myalgia (%)	37.7	37.7	44.7	53.1	36.0	42.7
Sore Throat (%)	17.2	19.3	23.9	29.1	26.6	24.1
Headache (%)	36.1	35.7	41.5	39.4	41.0	38.9
Diarrhea (%)	7.4	7.4	8.2	11.4	11.5	9.3
Shortness of Breath (%)	26.2	30.3	28.9	28.0	20.9	27.6
Type 2 Diabetes Mellitus (%)	14.8	18.4	15.1	21.7	11.5	17.2
Obesity (BMI>30, %)	10.7	7.8	6.9	20.6	5.0	10.2
Heart Disease (%)	21.3	29.9	31.4	41.1	18.8	30.8
Pulmonary Disease (%)	6.6	4.5	1.3	4.0	3.6	3.5
Given Azithromycin (%)	0.0	43.4	50.3	65.7	58.3	53.3
Given Ivermectin (%)	0.0	24.2	77.4	42.9	59.7	47.4
Given Oseltamivir (%)	0.0	9.0	7.5	26.3	7.9	12.7

[a] Number of patients with data on date of start of symptoms, 113, 222, 152, 168, 134 and 676 in the respective columns.

Table 2
Multivariate logistic regression risk factors for hospitalization of tested-positive Covid-19 outpatients at Hapvida HMO, Brazil.

Exposure	Regression Exposure Units	Average of or Number Not Hospitalized (n = 603)	Average of or Number Hospitalized (n = 114)	OR (95% Confidence Interval)	*P*-value
Age at diagnosis (continuous)	Per decade	49.4	57.1	1.75 (1.42–2.16)	$10^{-6.7}$
Gender	Female vs Male	314 vs 289	58 vs 56	0.87 (0.56–1.35)	.52
Dyspnea at diagnosis	Yes vs No	148 vs 455	50 vs 64	2.07 (1.32–3.26)	.0017
Obesity	Yes vs No	55 vs 548	18 vs 96	2.38 (1.24–4.57)	.0090
Diabetes Mellitus Type 2	Yes vs No	83 vs 520	40 vs 74	2.11 (1.26–3.52)	.0045
Heart Disease	Yes vs No	162 vs 441	59 vs 55	1.67 (1.03–2.70)	.037
Prescription of both hydroxychloroquine and prednisone	Both vs not both	143 vs 460	16 vs 98	0.40 (0.21–0.75)	.0042
Prescription of hydroxychloroquine only	Yes vs no	150 vs 453	25 vs 89	0.45 (0.25–0.80)	.0065
Prescription of prednisone only	Yes vs no	125 vs 478	14 vs 100	0.51 (0.26–0.99)	.049

patient characteristics, may not be statistically significant. Based on the model of Table 2, we also examined use of azithromycin, OR = 0.93 (95%CI 0.60–1.45) and use of ivermectin, OR = 1.17 (95%CI 0.72–1.90). Zinc prescription was not given on its own and where prescribed was highly correlated with other medication use and had little independent information for estimation of its own association in the adjusted model. When the model of Table 2 was performed including only individuals who had a history of at least one condition of obesity, diabetes or heart disease (73 hospitalized patients and 232 not hospitalized), the associations with the medications largely remained: for both HCQ + prednisone, OR = 0.33 (95%CI 0.14–0.81), p = .015; for HCQ alone, OR = 0.41 (95%CI 0.20–0.83), p = .013; and for prednisone alone, OR = 0.75 (95%CI 0.29–1.93), p = .55. We also examined the model of Table 2 for the three medication exposures vs receipt of no medications at all. For both HCQ + prednisone, OR = 0.29 (95%CI 0.14–0.58), p = .00053; for HCQ alone, OR = 0.32 (95%CI 0.17–0.63), p = .00081; and for prednisone alone, OR = 0.37 (95%CI 0.18–0.77), p = .0082. Similar magnitudes of association as these were seen for these medications among all 717 subjects for death as the outcome, but the small numbers of deaths precluded statistical significance of these associations. However, the strongest predictors of mortality overall were obesity, OR = 13.0 (95%CI 2.35–72.3), p = .0033, and diabetes, OR = 4.65 (95%CI 1.20–18.1), p = .027. We observed no cardiac arrhythmia events requiring medication termination for any of the medications used in the 717 patients that we analyzed, and no deaths attributable to such arrhythmias.

4. Discussion

SARS-CoV-2 will cause greater mortality than any recent contemporary pandemic; only when the pandemic ends it will be possible to assess the full health, social and economic impact of this global disaster [26–28]. Preliminary data show that in developed countries, the impact will be huge. But in developing countries, where public health systems already face great challenges to provide basic health care to all in need, the impact will be several times greater [26–28]. These problems will not be solved anytime soon. In the midst of the SARS-CoV-2 pandemic, a feasible approach, with inexpensive drugs, relying on syndromic signs and symptoms rather than scarce laboratory tests may help many patients and will be even more important in developing countries. Around the world there are already over 28 million confirmed COVID-19 cases [29]. Brazil has the third-largest number, with 4.2 million cases and 128 000 deaths as of September 9th [29]. If this trend continues, in about six months, Brazil will have the worldwide largest number of deaths of any country.

In March 2020, the World Health Organization recommended the use of medications oseltamivir and antibiotics [30]. On March 28, 2020, the FDA issued an emergency use authorization for remdesivir and HCQ for patients in both clinical trials and with severe hospitalized disease [31]. Since then, pharmacological treatments have been controversial. On June 15 the FDA retracted its earlier authorization and on July 1 posted warnings about its use, leaving HCQ outpatient use not supported [32]. Countries such as China and India have issued guidelines

supporting the use of chloroquine or HCQ in COVID-19 [33,34]. Evidence of the real-world unimportance of arrhythmia and other cardiovascular adverse-event endpoints of HCQ and HCQ + AZ use is given in the large Oxford-based record-linkage study [35] and in a study of 40% of the English population [36]. Understanding the pathophysiology of COVID-19 in the different clinical stages of the disease is important, as treatments will change according to progression of the disease [13]. Our study showed that HCQ alone, prednisone alone, and HCQ plus prednisone did better than standard treatment for early stage COVID-19. It may be that the corticosteroid benefit involves low levels of type I and III interferons juxtaposed to elevated chemokines and high expressions of IL-6. Reduced initial innate antiviral defenses allow the virus to multiply, followed after a few days by relatively excess inflammatory cytokine production, allowing for steroids to reduce the latter in the early features of COVID-19, before appreciable pneumonia has occurred [37]. Hydroxychloroquine has a number of suggested beneficial actions for early COVID-19, not least of which is its non-immunosuppressive immunomodulatory activity [38].

Because all treatments have costs and benefits, treating all high-risk patients early would take a major effort from Brazil's Universal Public System (SUS) and its private HMOs, but would be much less expensive than hospital-based inpatient treatment, which would probably be impossible on the scale needed. Our study showed that about 10% of high-risk outpatients over age 40 treated with prednisone still required hospitalization, which is substantially better than the 24% among untreated patients, thus even this treatment plan could create a large hospital-bed demand. However, we found that even in hospital, these treated patients do better and their mortality is much lower.

In an ideal world, large randomized double-blinded controlled clinical trials establish evidence, but take time to complete and many are not large enough for the randomization to be sufficiently effective in reducing biases. To-date, treatment protocols have proposed drugs with antiviral activity, and with anti-inflammatory responses, such as therapeutic regimens of IFN-α+lopinavir/ritonavir and IFN-α+lopinavir/ritonavir + ribavirin, among others. While cost-effectiveness of these regimens have been challenged, HCQ is generic and has been prescribed for malaria for decades, as it has antiviral and anti-inflammatory properties. On March 27th, 2020 the Brazilian Federal Health Authority issued a note saying that it would treat severely ill patients in the Public System with HCQ [39]. On May 20th, the same authority issued another note that HCQ would be available for physicians to prescribe for outpatients and mild cases, according to symptoms and severity [22]. Prednisone is also generic and inexpensive and has been used for many decades and does not interact adversely with HCQ.

Our results demonstrate a positive benefit of HCQ and prednisone in decreasing hospital admissions in a high-risk population over 40 years of age with RT-PCR-positive SARS-CoV-2 infection when started at first doctor visit. A high-risk outpatient benefit of HCQ use has been summarized elsewhere [35] but to our knowledge this is the first time that efficacy of outpatient prednisone use has been reported. Use of these medications also showed some evidence of reduced mortality in the study group, and larger studies of mortality will be needed to validate this finding. We observed that outpatient hospitalizations of the larger group of suspected COVID-19 ER patients, from the same HMO database before vs after the protocol started, March–April vs May, decreased significantly, 23% vs 9%, and mortality declined from 1.75% to 1.39%. For May, our HMO data also show that the mortality was less than COVID-19 mortality for Brazil as a whole.

Our study has several limitations. This is a retrospective, chart-based study, and even though our initial sample of patients was large, with almost 25 000 patients, few of these patients were tested due to the scarcity of RT-PCR tests. Then, we chose to study only tested-positive SARS-CoV-2 patients to make sure we were dealing with confirmed cases of COVID-19. Limiting analyses to patients greater than 40 years of age further reduced our sample size. Nevertheless, our experience of approaching and treating patients with influenza-like symptoms in this era of pandemic SARS-CoV-2 is useful and more generally applicable. In one State Hospital Network of the cohort this spring, more than 90% of patients admitted to the hospital with appreciable respiratory distress had positive RT-PCR for SARS-CoV-2 [40], so it seems reasonable to infer that it would be similar for patients with influenza-like illness presenting at the emergency room. Also, our study involved a range of treatment medications assigned by HMO physicians using their clinical judgements, rather than mandated by study design. Clinical treatment decisions allow for the possibility that sicker patients get more or more aggressive treatments, creating the potential of confounding by indication. The comorbidity distributions of the various treatments as shown in Table 1 suggest that except for shortness of breath, patients not treated with HCQ or prednisone may have been slightly less symptomatic than treated patients. However, this would if anything have tended to reduce the magnitude of risk lowering that we found for these medications toward the null. A pattern of chronic comorbidity differences is not apparent in the table; nevertheless, our results were adjusted for those comorbidities where associations with risk of hospitalization were observed (Table 2). In spite of the aforementioned, our study was large enough to have observed statistically significant results and was based on actual clinical conditions and data recorded in active clinical charts, to enable reasonable inference about lack of reporting biases in the analyzed data.

Our analyses thus show that it is possible to give HCQ with companion medications in an early stage protocol that proves to be safe, and warnings about cardiac arrhythmia adverse events are unnecessary unless significant contraindications are known. Treatment-failure mortality, while small, is still the major concern of patient management. Our new protocol is continuing in clinical practice in our HMO, and we hope for it to be more generally applied across the rest of Brazil as quickly as possible.

5. Conclusion

We found early outpatient use of HCQ and prednisone, both as individual prescriptions and used together, to lower the risk of hospitalization in symptomatic high-risk COVID-19 patients presenting for primary care at the emergency rooms of our large HMO in Brazil. Other than the small numbers of treatment failure, no potentially life-threatening adverse events were recorded with medication treatment. These medications were found to be safe and beneficial for early high-risk outpatient treatment of COVID-19.

Financial support

None.

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Silvia Nunes Szente Fonseca: Conceptualization, Investigation, Resources, Data curation, Writing - original draft, Project administration. **Anastasio de Queiroz Sousa:** Investigation, Resources, Data curation, Writing - review & editing. **Alexandre Giandoni Wolkoff:** Conceptualization, Investigation, Resources, Data curation, Writing - review & editing, Project administration. **Marcelo Sampaio Moreira:** Investigation, Resources, Data curation, Writing - review & editing. **Bruno Castro Pinto:** Investigation, Resources, Data curation, Writing - review & editing. **Christianne Fernandes Valente Takeda:** Investigation, Resources, Data curation, Writing - review & editing. **Eduardo Rebouças:** Investigation, Resources, Data curation, Writing - review & editing. **Ana Paula Vasconcellos Abdon:** Investigation, Resources, Data curation, Writing - review & editing. **Anderson L.A. Nascimento:** Investigation, Resources, Data curation, Writing - review & editing. **Harvey A. Risch:** Conceptualization, Investigation, Data curation, Formal analysis, Writing - review & editing.

Declaration of competing interest

Dr. Risch acknowledges past advisory consulting work with two of the more than 50 manufacturers of the various medications analyzed herein. This past work was not related to any of these medications and was completed more than two years ago. He has no ongoing, planned or projected relationships with any of these companies, nor any other potential conflicts-of-interest to disclose. None of the other authors have any potential conflicts of interest to disclose.

Acknowledgements

The authors wish to acknowledge the valuable contributions of Ana Briza Campelo Mourão Leopoldo, Caroline de Alencar Santana Monteiro, Jose Amilton Matos Cavalcante Júnior, Rudy Diavila Bingana, Thuliermes Lopes Pamplona, Jamile Nayara da Silva, Fábio Henrique Rodrigues de Souza, José Cristian Brandão Mendes, Iury Handric da Penha Teixeira, Alexmar Matos Queiroz, Bruno Bezerra M. Cavalcante, Francisco Jadson Franco Moreira, Antonio Jefferson Ribeiro Soares, Maria Rejane Maia Pinheiro de Abreu, Alex Jones Flores Cassenote, Tibor Schuster and Alain Benvenuti. Special thanks to Jorge Pinheiro Koren de Lima, MD, and Candido Pinheiro Koren de Lima, MD, for exceptional support and decisive actions for COVID-19 pandemic preparedness.

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Exhibit "F"

This is the Affidavit of

[redacted]

Dr. Harvey Risch

affirmed before me this 12th day of April, 2021.

[redacted]

Commissioner of Oaths

ALBERTO BERNARDEZ
Notary Public, State of Connecticut
My Commission Expires Aug. 31, 2024

Court File No. CV-20-00652216-000

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Applicant/Respondent

AND

ADAMSON BARBECUE LIMITED
AND WILLIAM ADAMSON SKELLY

Respondents/Applicants

ACKNOWLEDGEMENT OF EXPERT'S DUTY

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1. My name is Harvey Risch. I live at Fairfield, in the State of Connecticut, USA.
2. I have been engaged by or on behalf of Respondents to provide evidence in relation to the above-noted court proceeding.
3. I acknowledge that it is my duty to provide evidence in relation to this proceeding as follows:
    a) To provide opinion evidence that is fair, objective and non-partisan;
    b) To provide opinion evidence that is related only to matters that are within my area of expertise; and
    c) To provide such additional assistance as the court may reasonably require, to determine a matter in issue.

4. I acknowledge that the duty referred to above prevails over my obligation which I may owe to any party by whom or on whose behalf I am engaged.

Date: March 30, 2021

[redacted]

Signature

HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO Applicant/Respondent	and	**ADAMSON BARBECUE LIMITED AND WILLIAM ADAMSON SKELLY** Respondents/Applicants	Court File No. CV-20-00652216-0000

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceedings commenced at the City of Toronto

AFFIDAVIT OF EXPERT WITNESS DR. HARVEY A. RISCH

(Sworn on April 12, 2021)

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