THE UNIVERSITY OF BRITISH COLUMBIA

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Date: 25 January 2024

Re: Expert Report – **The efficacy and safety of COVID-19 vaccines and ivermectin**

For the case of Dr. Charles Hoffe represented by Doak Shirreff Lawyers LLP, for a citation issued by the College of Physicians and Surgeons of British Columbia

1. My full name is Steven Daniel Pelech, and I reside at 5640 Musgrave Crescent, in Richmond, British Columbia, Canada. My Ph.D. and post-doctoral training is in the area of biochemistry, and I have been on the faculty of the University of British Columbia as a professor in the Department of Medicine for over 35 years.

2. I have been asked by Mr. Lee Turner of Doak Shirreff Lawyers LLP to provide a letter of opinion regarding the efficacy and safety of COVID-19 genetic vaccines and other treatments such as ivermectin to prevent or treat COVID-19. I was also requested to review the validity of statements made by Dr. Trevor Corneil in his September 26, 2022 letter to Ms. Lisa C. Fong, who is the legal counsel of the College for the citation issued to Dr. Hoffe. Dr. Corneil was sought for his expert opinion, although he retained the services of Dr. Naomi Dove in the preparation of his letter "*for the purposes of research*" (see para. 4 of Dr. Corneil's letter)."

3. In particular, in the letter that was transmitted by e-mail to me by Mr. Turner on December 17, 2023, I was requested to provide the following information:

    1. My name, address, area of expertise and a copy of my *curriculum vitae* (provided as Exhibit A);
    2. My qualifications and employment and educational experience in my area of expertise that pertain to the issues I have been asked to opine on;

3. The instructions that was provided to me in relation to the proceedings of the College of Physicians and Surgeons of British Columbia (CPSBC) verses Dr. Charles Hoffe (as described Mr. Turner's December 17th letter, which is provided as Exhibit B);
4. The nature of the opinion being sought and the issues in the proceeding to which the opinion relates;
5. My opinion respecting those issues; and
6. My reasons for my opinion, including
   (a) a description of the factual assumptions on which my opinion is based,
   (b) a description of any research relied upon that led me to form my opinion, and
   (c) a list of every document relied upon by me in forming my opinion.

4. In addition, I have been asked to certify that:
   1. I am aware of my duty to assist the Disciplinary panel of CPSBC;
   2. I am not an advocate for any party in these proceedings;
   3. I have prepared my report in conformity with my duty; and
   4. I will, if called upon to give oral or written testimony, give that testimony in conformity with my duty.

5. I do certify that I will fulfill my responsibilities to the Disciplinary panel of the CPSBC in full compliance to these obligations and requirements.

6. To address above questions posed by Doak Shirreff Lawyers LLP, this required a broad and comprehensive assessment of the accessible scientific literature with respect to available knowledge about the effectiveness and safety of COVID-19 vaccines as compared to the risks of natural infection with SARS-CoV-2, the virus that causes COVID-19, and the effectiveness of natural immunity. I was also expected to review the available literature with respect to effectiveness of treatments such as ivermectin. With my training and experience, I believe that I am able to provide a qualified expert opinion. While a full copy of my *curriculum vitae* is appended as Exhibit A, my expertise related to the study of the SARS-CoV-2 virus is summarized in **Part 1** of this report.

7. In brief, I have worked with viruses in a research setting ever since I undertook my Ph.D. studies. At that time, I had worked with the Semliki Forest virus in the laboratory of Dr. Dennis Vance to examine its effects on the synthesis of phosphatidylcholine, one of the major lipids inside of cells. This is a positive-sense, singled-stranded RNA virus, like the SARS-CoV-2 virus, and it is known to cause disease in animals and humans. As an undergraduate student at the University of British Columbia, I took second, third and fourth year lecture and laboratory courses in Microbiology and Immunology, including in Virology. Recently, I have been actively involved in COVID-19 research for over 3 and a half years, especially with respect to the replication of the SARS-CoV-2 virus, and the production of antibodies against this virus in people who have been infected by this virus and/or have been vaccinated against this virus. I have been involved in the development of serological tests for SARS-CoV-2 directed antibodies, and the application of these tests to evaluate natural and COVID-19 vaccine-induced immunity in a 4,500-person clinical study that I led.

8. I have read over two thousand publications in the scientific literature, regularly accessed the websites of several Canadian provincial and federal government health agencies as well as those in other countries. I have written several manuscripts related to COVID-19 and SARS-CoV-2 from my original research, and I am an editor and major author of two books on COVID-19 that are presently under review by Skyhorse Publishing. This has informed my opinions about the effectiveness of strategies for prevention and treatment of COVID-19, and the risks and benefits of these interventions. For the purpose of this report, in **Part 2**, I will mainly focus on the science that underlies the specific statements made by Dr. Hoffe that the CSPBC has raised as "misinformation." Throughout this report, I have identified many of the key primary publications in the scientific literature and government websites that addresses these matters and these are cited as footnotes. I recognize that much of what I have written is very technical in nature. However, I have made a concerted effort to permit those not skilled in biochemistry, immunology and virology to comprehend the complexities related to assessing the effectiveness and safety of COVID-19 vaccines and natural immunity control infectious viral pathogens. To assist those that require more introductory background to the nature of genes and proteins, the SARS-CoV-2 virus, the immune system, PCR, rapid antigen and serological testing, vaccine

development, animal and human clinical studies and drug development, and adverse event reporting systems, I have appended Exhibit C. This should serve as a primer on these topics.

9. In **Part 3** of this report, I will focus on mainly the several key issues raised in Dr. Trevor Corneil's September 26, 2022 report with which I disagree. I have not attempted to address every issue, but those that represent, in my view, serious misinterpretations of the available evidence. In view of Dr. Corneil's reference to predictive modeling of the COVID-19 pandemic, I have also attached Exhibit D, which discusses the pitfalls that have plagued work in this area by epidemiologists such as Dr. David Fisman, to whom Dr. Corneil has referred.

Part 1: Qualifications and Acknowledgements as an Expert on COVID-19

10. I am a full Professor in the Department of Medicine and Division of Neurology at the University of British Columbia (UBC), where I have been on faculty since 1988. I was one of the founding senior scientists of The Biomedical Research Centre at UBC in 1987. I hold B.Sc. Honours (1979) and Ph.D. (1982) degrees in Biochemistry from UBC. My post-doctoral training was at the University of Dundee with Sir Philip Cohen, and at the University of Washington in Seattle with Nobel laureate Dr. Edwin Krebs.

11. I have previously completed several courses in microbiology, immunology and virology during my B.Sc. undergraduate training, and I was a founding and senior scientist for six years at The Biomedical Research Centre, which was an immunology-focused institute located at UBC, where I have remained on faculty as a professor in the Department of Medicine for over 35 years. Over a dozen of my scientific research articles have appeared in specialty immunology journals, including the *Journal of Immunology, Blood, Molecular Immunology, Immunology, Infectious Immunology, Cancer Immunology and Immunotherapy*, *International Journal of Vaccine Theory, Practice and Research* and *Vaccines*. These studies document some of my work to understand the molecular mechanisms by which different immune cells, including macrophages, T and B cells become activated. My lectures in formal graduate level courses include teaching in immunology and virology at UBC. I have presented my research at over 100 national and international scientific conferences. My UBC lab and spin-out companies have been engaged in the production and testing of over 1600 antibodies for our internal research programs and for commercial sale for over 30 years. My research as an independent investigator has routinely involved for over 36 years, the use of standard and novel immunological techniques developed in my

lab, such as Western blotting, dot blotting, antibody microarrays, reverse lysate microarrays and epitope mapping for determination of where antibodies specifically bind their targets.

12. I have authored over 270 scientific publications in peer-reviewed journals and book chapters about cell communication systems important for cell survival and function and implicated in the pathology of cancer, diabetes, neurological and immunology-related diseases. My accolades include the 1993 Martin F. Hoffman Award for Research at UBC, and the 1993 Merck Frosst Canada Prize from the Canadian Society of Biochemistry and Molecular Biology. I was the 2001 Distinguished Lecturer for the Faculty of Medicine at UBC for the Basic Sciences. I have served on grant review panels for the US National Institutes of Health, the Canadian Institutes for Health Research, the National Research Council of Canada, the Michael Smith Health Research Foundation, Genome Alberta, Genome Prairie, the Canadian National Cancer Institute, the Canadian Heart and Stroke Foundation and the American Heart Association, and I have acted as an external reviewer for 22 other agencies including the U.S. National Science Foundation and the Israel Science Foundation. I have also been an external reviewer for over 30 different scientific journals, including those that are focused on immunology and vaccines.

13. I was the founder and president of Kinetek Pharmaceuticals Inc. from 1992 to 1998, and the founder, president and chief scientific officer of Kinexus Bioinformatics Corporation from 1999 to the present. Kinetek was engaged in the development of drugs that inhibit protein kinases, primarily for oncology application and diabetes. Kinexus has produced over 1,600 antibody products against cell regulatory proteins, and employs these antibodies in novel, immunology-based, high throughput methods such as antibody microarrays to monitor cell communication systems in biological specimens from over 2000 academic and industrial clients in over 35 countries over the last 22 years. These antibody products include those that specifically recognize parts of the Spike, Nucleocapsid, Membrane and other SARS-CoV-2 proteins encoded by the genome of this virus.

14. My expertise has been sought specifically with respect to understanding the immunological mechanisms by which a natural immune response is elicited by SARS-CoV-2, the causative agent of COVID-19, and the immunity afforded by the lipid nanoparticle Spike RNA- and adenovirus Spike DNA-based COVID-19 vaccines. This has been informed, in part, by clinical studies undertaken in the last three years at my company Kinexus in which we have investigated the nature and production of antibodies against the 28 different proteins that are encoded by the genome in the SARS-CoV-2 virus,

by examination of blood samples from over 4500 participants from across Canada. In this independent ethics review board approved clinical study, I am the lead investigator, and I have been in direct communication with all of the participants. Some of our preliminary findings have already been published in *JCI Insights*, which is the flagship journal of the American Society for Clinical Investigation in 2021.[1] Additional manuscripts that document our SARS-CoV-2 antibody testing study are currently in preparation, and we have recently completed a second antibody testing study to determine the extent of immunity against the Omicron variants and the duration effectiveness of the COVID-19 vaccines.

15. I have also been investigating the use of drugs to inhibit the replication of the SARS-CoV-2 virus in infected host cells. My expertise on enzymes known as protein kinases has permitted me to predict and then verify that compounds that inhibit a protein kinase known as GSK3-beta can block the production of the Spike of the virus, and assembly of SARS-CoV-2 virus particles. A patent based on this work was filed with the University of British Columbia (UBC) and a manuscript that describes this work was published in a peer-review journal.[2] I have also spearheaded the development commercial antibodies against many of the SARS-CoV-2 proteins and verified their utility in another published scientific article in the peer-reviewed journal Microbial Factories.[3]

16. In addition to the direct study of the SARS-CoV-2 and immune responses to this virus in people, I am also a co-founder and vice president of the Canadian Covid Care Alliance (CCCA) and very active within this organization. Recently, the CCCA has been renamed the Canadian Citizens Care Alliance. The CCCA's membership of over 1700 people includes over 600 biomedical scientists, medical doctors and other health practitioners, and the CCCA examines the scientific literature and data from public health authorities to ascertain the threat of COVID-19 and the various strategies available to mitigate its

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1 Majdoubi, A., Michalski, C., O'Connell, S.E., Dada, S., Narpala, S. *et al*. (2021) A majority of uninfected adults show pre-existing antibody reactivity against SARS-CoV-2. JCI Insight. 6(8): e14631. doi:10.1172/jci.insight.146316

2 Shapira, T., Rens, C., Pichler, V., Rees, W., Steiner, T., Jean, F., Winkler, D.F.H., Sarai, I., Pelech, S., Av-Gay, Y. (2022) Inhibition of glycogen synthase kinase-3-beta (GSK3β) blocks nucleocapsid phosphorylation and SARS-CoV-2 replication. Molecular Biomedicine. 3, 43. doi:10.1186/s43556-022-00111-1

3 McGuire, B.E., Mela, J.E., Thompson, V.C., Cucksey, L.R., Stevens, C.E., McWhinnie, R.L., Winkler, D.F.H., Pelech, S., Nano, F.E. (2022) *Escherichia coli* recombinant expression of SARS-CoV-2 protein fragments. Microbial Cell Factories. 21:21. doi:10.1186/s12934-022-01753-0. bioRxiv pre-print. doi:10.1101/2021.06.22.449540v

effects. In my capacity as the co-chair of the Scientific and Medical Advisory Committee (SMAC) of the CCCA, I oversee the activities of a panel of 36 scientists and medical doctors that seeks to provide a scientific evidence-based and balanced, independent, but critical assessment of health care policies related to COVID-19. This Committee has met weekly over the last two years by Zoom, but typically has daily correspondences by e-mails. The fruits of our efforts are published on the CCCA website (www.canadiancovidcarealliance.org) and in peer-reviewed scientific journals. In particular, I was a coauthor on a CCCA report that critiqued the original 6-months clinical study performed by Pfizer/BioNTech on their BNT162b2 RNA vaccine,[4] a published review about COVID-19 vaccines and pregnancy in the peer-reviewed journal *Vaccines*,[5] and another manuscript published in the peer-reviewed journal *International Journal of Vaccine Theory, Practice and Research*.[6] In addition, I am a coauthor on several other publications that have been posted on the CCCA website that relate to the manufacturing and quality issues associated with the BNT162b2 mRNA COVID-19 vaccine,[7] the efficacy and safety of the BNT162b2 mRNA COVID-19 vaccine based on Phase 3 trial results,[8] and the vaccination of children with COVID-19 vaccines.[9] I have been the Senior editor and author of a book

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4 Bridle, B.W., Martins, I., Mallard, B.A., Karrow, N.A., Speicher, D.J., Chaufan, C., Northey, J.G.B., Pelech, S., Shaw, C.A., Halgas, O. (2021) Concerns regarding the efficacy and safety for BNT162b2 mRNA coronavirus disease (COVID-19) vaccine through six months. www.CanadianCovidCareAlliance.org (January 10, 2022) 1-10 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/01/Final-CCCA-Critique-Thomas-COVID-19-Vaccines-6-months-NEJM-Jan-10-22.pdf

5 Karrow, N.A., Shandilya, U.K., Pelech, S., Wagter-Lesperance, L., McLeod, D., Bridle, B, Mallard, B.A. (2021) COVID-19 vaccination and potential impact on fetal and neonatal development. *Vaccines.* 2021, *9*, x. doi:10.3390/xxxxx

6 McLeod, D., Martins, I., Pelech, S., Beck, C., Shaw. C.A. (2022) Dispelling the myth of a pandemic of the unvaccinated. *Int. J. Vaccine Theory Practice Res.* 2(1):267-286.

7 Gutchi, M., Speicher, D. J., Natsheh, S., Oldfield, P., Britz-McKibbon, P., Palmer, M., Karrow, N., Massie, B., Mallard, B., Chan, G. Pelech, S. (2022) An independent analysis of the manufacturing and quality control issues of the BNT162b BioNTech/Pfizer vaccine identified by the European Medicine Agency. www.Canadian Covid Care Alliance.org (October 29, 2022) 1-5 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/11/22OC29_EMA-Analysis-of-BNT162b-Manufacture.pdf

8 Bridle, B.W., Martins, I., Mallard, B.A., Karrow, N.A., Speicher, D.J., Chaufan, C., Northey, J.G.B., Pelech, S., Shaw, C.A., Halgas, O. (2021) Concerns regarding the efficacy and safety for BNT162b2 mRNA coronavirus disease (COVID-19) vaccine through six months. www.CanadianCovidCareAlliance.org (January 10, 2022) 1-10 https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/01/Final-CCCA-Critique-Thomas-COVID-19-Vaccines-6-months-NEJM-Jan-10-22.pdf

9 Payne, E., Rennebohm, R., Bridle, B., Mallard, B., Karrow, N., Massie, B., Northey, K., Shoemaker, C., Pelech, S., Chaufan C., McLeod, D., Hardie, J., Pinto, C., Britz-McKibbin, P., Shaw, C. (2022) Request to halt vaccinations of children. www.CanadianCovidCareAlliance.org (July 14, 2022) 1-28

about the science underlying the SARS-CoV-2 virus, COVID-19, vaccines, therapeutics and masks, which is currently in press.[10] I am also a Senior editor and author of a second book that examines Canada's response to the COVID-19 pandemic.[11] These books have over 1700 primary citations.

17. I believe that my formal training, experience and published research, demonstrates my expertise in immunology, and my recent activities specifically related to SARS-CoV-2 over the last three years, places me in an excellent situation to comment upon related matters. Consequently, I have been sought as an Expert Witness for over two dozen court challenges and college disciplinary hearings with respect to government and private employer mandated vaccination and family disputes over the vaccination of children. In particular, I have been accepted as an expert witness and provided cross-examination in other disciplinary hearings with the British Columbia College of Nurses and Midwives,[12] and the College of Nurses in Ontario.[13] These cases are listed at the end of my *curriculum vitae* in Exhibit A.

Part 2: The Efficacy and Safety of COVID-19 Vaccine Verses Natural Immunity; Ivermectin for COVID-19 Treatment

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https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/07/CCCA-Halt-vaccination-of-children-Officials-Letter-Jul-14-22.pdf

[10] Pelech, S. & Shaw, C.A. (ed.) (2024) Down the COVID-19 rabbit hole: Independent scientists and physicians unmask the pandemic. Skyhorse Publishing. (in press)

[11] Pelech, S. & Shaw, C.A. (ed.) (2024) COVID-19 Pandemonium: A pandemic of ignorance, fear and greed. The capture of our institutions. (in preparation)

[12] Citation issued against Sean Taylor by the BC College of Nurses and Midwives. Disciplinary Hearings in 2023.

[13] Citation issued against Sarah Choujounian-Abulu by the College of Nurses of Ontario. Disciplinary Hearings in 2023.

2.1. Summary Overview

18. Before I discuss the details of the validity of Dr. Charles Hoffe's statements that are in contention, I will offer some opening comments. Overall, I find that I am in agreement with many of his concerns. Whenever dealing with new treatment, it is important to err on the side of caution. The precautionary principle is foundational to the application of interventions in health and the environment. Dr. Jeffrey Aronson in his British Medical Journal article notes:

> *"Many definitions of the Precautionary Principle omit two important ideas: that it applies only when the benefit to harm balance of a proposed intervention is unfavourable or uncertain and that the onus to prove that it is* not *unfavourable is on those who would advocate use of the intervention. The following proposed definition for healthcare interventions incorporates these two ideas: "The principle that if a healthcare intervention, pharmacological or non-pharmacological, may cause harm to the individual, the public, or the environment, the benefit to harm balance being unfavourable or uncertain, precautionary measures should be taken, and the burden of proving that the intervention is* not *harmful falls on those proposing that it be implemented."*[14]

19. The crux of this matter is whether the risks of no intervention and infection with the SARS-CoV-2 and subsequent acquisition of natural immune are greater than the risks posed by taking an experimental vaccine to prevent COVID-19. To answer this question, it is necessary to assess the risks of illness and death from COVID-19, and the efficacy and safety of COVID-19 genetic vaccines. As it turns out, the answer to this question is complicated, because the risks of severe COVID-19 and death are very dependent on age and the presence of co-morbidities as will be presented. The efficacy and safety of

[14] Aaronson, J.K. (2021) When I use a word ….The precautionary principle: a definition. British Medical Journal. 375.:n3111. Doi:10.1136/bmj.n.3111

COVID-19 vaccines is also very dependent on their production and quality control. Consequently, I will consider this as well in my report.

20. I see some parallels with concerns raised by Dr. Hoffe by his early experience with the COVID-19 vaccines in his practice in Lytton and Kamloops area in B.C. with those of Dr. Li Wenliang in the Chinese city of Wuhan.[15] Dr. Wenliang made the original observation that many of his patients were dying from a new virus that induced severe respiratory disease. This doctor was initially reprimanded by the local authorities for raising undue concerns, and he died from COVID-19 as did many others in his community, and ultimately world-wide. Later, Dr. Wenliang was later proclaimed as a hero for raising the alarm about COVID-19.

21. Dr. Hoffe shared his observations and concerns with the BC Ministry of Health in letters and filed vaccine injury reports as a good physician should. He has been an outspoken critic about COVID-19 vaccines and the benefits of ivermectin. This appears to be the main basis of his disciplinary hearing with the College of Physicians and Surgeons of BC. His opinions appear to been informed by his extensive reading of the scientific literature, and a desire to serve his patients as best and honestly as he can.

22. I see my role as an expert witness to serve the College to point out where Dr. Hoffe's concerns may have been on and off the mark. In fairness to Dr. Hoffe, even experts like Dr. Trevor Corneil can be misled by statements in the scientific literature and the bias and views of other "experts." In my learned opinion, the key questions and short answers are:

    a. ***Are COVID-19 vaccine experimental?*** Yes. The underlying technology is novel and new information continued to be reported that documents unexpected issues with efficacy and safety in the scientific literature.

    b. ***Are the COVID-19 genetic vaccines effective in reducing infection and transmission of COVID-19, and reducing the incidence of severe COVID-19 and death?*** These do not, beyond a short period of a few months, prevent infection with SARS-CoV-2, and those vaccinated individuals that get COVID-19 are just as infectious and likely to transmit the virus as non-vaccinated individuals.

[15] (2020) Li Wenliang: Coronavirus death of Wuhan doctor sparks anger. BBC News. Retrieved from https://www.bbc.com/news/world-asia-china-51409801

There are no Phase 3 clinical studies that demonstrate severity and risk of death is lower in vaccinated individuals. This is hard to evaluate, since most people have natural immunity and the virus has evolved through mutation to much more less virulent forms.

c. ***Are there issues with the way COVID-19 genetic vaccines work that would lead to theoretical concerns?*** Yes. There are four facts that together are extremely worrisome. 1) With COVID-19 vaccines, tens of trillions of lipid nanoparticles are injected in the deltoid muscle with each inoculation. 2) Around three-quarters of the lipid nanoparticles leave the site of injection and travel around the body within 2 days. 3) Uptake of the lipid nanoparticles is not directed and they can enter into any cell type. 4) In order to elicit an immune response, it is necessary for immune cells to attack, damage and potentially kill cells that expressed the Spike protein on their surface after they have taken up the Spike RNA in the lipid nanoparticles. These inflammatory attacks may damage and weaken tissues and organs.

d. ***Are there demonstrated adverse reactions to COVID-19 genetic vaccines in clinical studies and following post-marketing approval?*** Yes. The original Phase 3 clinical trials, post-marketing data accumulated by Pfizer, and vaccine injury reports all demonstrate an unprecedented number of vaccine injury reports for COVID-19 vaccines.

e. ***In particular, are there theoretical concerns or demonstrated evidence that COVID-19 vaccines may affect female fertility and the health of a developing fetus?*** The ovaries are amongst the major organs to which the lipid nanoparticles are known to concentrate in. An inflammatory attack against the ovaries might damage oocytes in ovaries, and cause a reduction of their numbers. Changes in menstrual cycles in vaccinated women implicate disruption of the production of female hormones that control menstrual periods, which are produced in part by ovaries. While COVID-19 vaccination during the second and third trimesters of pregnancy do not appear to significantly affect birth weight and basic physiology of newborns, it is impossible to ascertain the long-term effects at this time. The effect of vaccination on fetus viability in the first trimester is also difficult to estimate due to a significant rate of miscarriages that occur independent of vaccination status.

f. ***Are there greater risks of thrombosis, myocarditis and myopericarditis with COVID-19 vaccines than from SARS-CoV-2 infection, and is this serious?*** For particularly males aged 12 to 29 years of age, there is an unacceptable high rate of myocarditis and myopericarditis, which can have persistent symptoms and be lethal. By contrast, in this demographic, the risk of myocarditis and myopericarditis from COVID-19 is 10- to 100-fold lower.

g. ***Do vaccinated people present a health danger to unvaccinated people? Does vaccine shedding exist?*** If COVID-19 vaccination with booster shots leads to immune tolerance, new strains of SARS-CoV-2 may evolve that could infect a person with natural immunity from a previous SARS-CoV-2 infection, as apparently did happen with the Omicron variants. The phenomenon of vaccine shedding remains mysterious, but might arising from shedding of SARS-CoV-2 virus, shedding of vaccine lipid nanoparticles, and/or shedding of exosomes that contain Spike RNA and/or Spike protein. At this time, I do not see this as a major risk for unvaccinated individuals, which are already likely to have effective natural immunity, and new variants of SARS-CoV-2 are relatively benign for the vast majority of people.

h. ***Is ivermectin effective in preventing and treating COVID-19*****?** A large body of independent studies support efficacy for treatment of COVID-19 with this highly safe, and commonly used anti-parasitic drug, which is approved for this particular purpose by Health Canada. However, its use for COVID-19 is neither encouraged or discouraged by Health Canada. It is normally acceptable for a medical doctor to prescribe an off-label drug for the treatment of a new indication if the physician feels from their analysis of the medical literature that this may benefit a patient, especially when there are no clear alternatives.

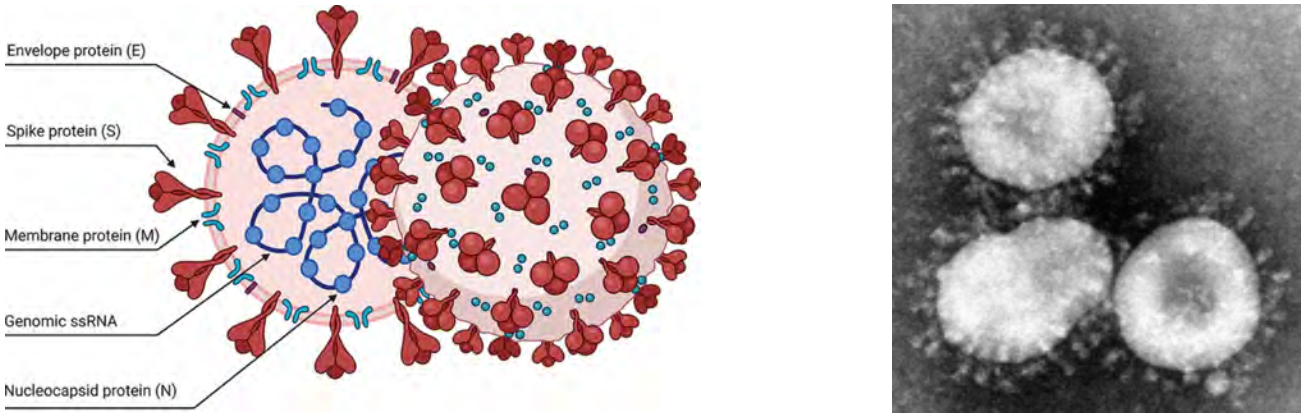
23. In the rest of Part 2, I will provide a sampling of the scientific data that supports my above conclusions. I will commence with a quick review of how natural immunity develops after infection with a virus. Much more information is provided in Exhibit C, which explains in greater detail: how respiratory viruses are transmitted (Chapter 1); how past epidemics have been produced by non-coronaviruses such as influenza and coronaviruses such as SARS-CoV-1 and MERS (Chapter 2); the structures and roles of the various proteins encoded by the SARS-CoV-2 genome (Chapter 2); the various cells of the innate and adaptive immune systems and the nature of different classes of antibodies (Chapter 3); how SARS-CoV-2 infections are tracked by the polymerase chain reaction (PCR), rapid antigen and serological

methods (Chapter 4); and how vaccines are normally test in animal (preclinical), and human phase 1, 2 and 3 clinical trials, and post-marketing reporting of vaccine injuries (Chapter 5).

2.2. *Comparison of Natural and COVID-19 Vaccine-induced Immunity*

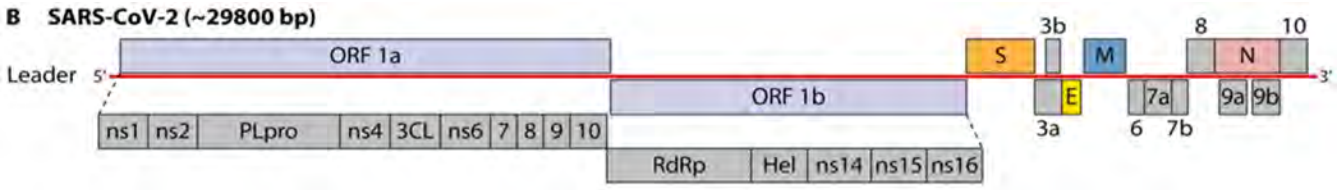
24. In Exhibit C, Chapter 2, I have described the SARS-CoV-2 virus as a small (~0.15 micron-wide) particle that features on its surface the Spike protein complex (a trimer), Membrane and Envelope proteins, and in its interior, Nucleocapid proteins that are bound to a single strand of sense-RNA. This RNA permits the product of all of these four proteins as well as at least 24 other non-structural (NSP) or ancillary proteins, which are required for replication of the virus in infected cells. The basic structure of SARS-CoV-2 virus is very similar to SARS-CoV-1, MERS and other coronaviruses, four of which cause a large portion of common colds. It gains entry into host cells by binding via the Spike protein to host proteins on the surface of cells, most notably angiotensin-converting enzyme 2 (ACE2) and neuropilin. The basic structure of the SARS-CoV-2 virus is shown in Figure 1. Figure 2 illustrates the arrangement of the viral genes in the SARS-CoV-2 virus genome. The Spike protein is the largest protein on the surface of the coronavirus, and accounts for their crown-like appearance in electron microscope-derived images.

Figure 1. Structure of the SARS-CoV-2 virus particle. Adapted from Fig. 1 of Pizzato *et al.* (2022).[16] Right panel shows an electron microscope image of the SARS-CoV-2 virus particle.



[16] Pizzato, M., Baraldi, C., Sopetto, G.B., Finozzi, D., Gentile, C., *et al.* (2022) SARS-CoV-2 and the host cell: A tale of interactions. Front. Virol. 1: 1-29. https://www.frontiersin.org/articles/10.3389/fviro.2021.815388/full

Figure 2. Location of protein-encoding genes in SARS-CoV-2 genome. Of particular relevance are the Spike (S), Membrane (M), Envelope (E) and Nucleocapsid (N) proteins. Adapted from Figure 2 of Tali *et al.* (2021).[17]



25. In Exhibit C, Chapter 3, I have outlined the nature of antibodies that are produced by immune B-cells in response to a natural infection with a respiratory virus like SARS-CoV-2. In particular, the virus enters the body through the mouth and nose (as well as eyes and ears) and infects cells of the nasopharyngeal cavity and lungs. Cells of the innate immune system, such as macrophages, neutrophils and dendritic cells engulf and then digest the virus particles with the production of pieces of the Spike, Membrane, Envelope and Nucleocapsid proteins. In addition, fragments of the other SARS-CoV-2 nonstructural and ancillary proteins may be produced from cells that are successfully infected by the virus, but undergo subsequent attacked by these innate immune cells as well as T-cells of the adaptive immune system. These viral protein fragments become complexed with immune cell proteins called major histocompatibility (MHC) antigens, where they are presented on the surfaces of macrophages, neutrophils and dendritic cells (antigen-presenting immune cells (APC)). When these migrating APC's encounter in the lymph nodes, T- and B-cells that happen to possess a high binding affinity for a fragment of a viral protein presented with an MHC antigen, they are stimulated to grow and divide into expanded colonies of identical cells. In the case of B-cells, they produce antibodies of the IgM and IgA classes primarily in the mouth and airways (see Figure 6 in Exhibit C). Notably, these are secreted antibodies into the mucosa lining the airways. In the case of T-cells, these seeks out and destroy virus-infected cells that produce viral protein fragments that are complexed with MHC antigens. After the viral threat is mitigated, a portion of the B- and T-cells that are specific for recognizing the viral proteins are converted to memory or plasma cells. These adaptive immune cells are quickly reactivated should there be a reinfection at a later date. Memory and plasma B- and T-cells can remain viable for decades. As the natural immune response is directed against almost all of the viral proteins in an infected person,

[17] Tali, S.H.S., LeBlanc, J.J., Sadiq, Z., Oyewunmi, O.D., Camargo, C. *et al.* (2021) Tools and techniques for severe acute respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/COVID-19 detection. Clinical Microbiol. 34 (3): 1-63. doi:10.1128/cmr.00228-20

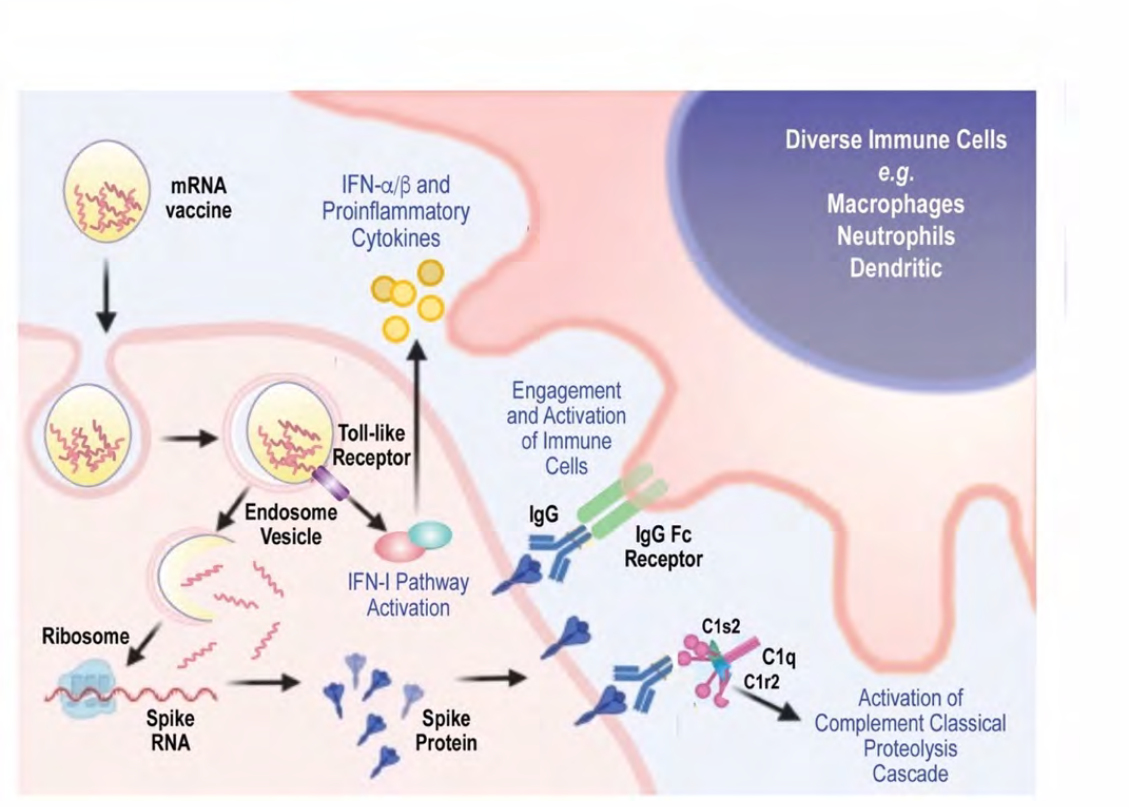
it is able to efficiently deal with the original virus as well as highly related viruses that might be encountered at a later date.

26. The mechanism by which immune protection is conferred by the COVID-19 genetic vaccines is very different from natural immunity, and unfortunately the mechanism is often misunderstood by those not very familiar with immunology. Likewise, the type of immune protection produced from these vaccines is also very different. Dr. Corneil in his letter of September 26, 2023 on page 15 (para. 28) stated: "*When the mRNA vaccine is injected, it is taken up by antigen presenting cells (macrophages and dendritic cells) near the injection site. Inside these cells, the mRNA uses the host cell's ribosomes to produce the SARS-CoV-2 spike protein, which is then expressed on the surface of the cell, stimulating humoral and cellular immune responses. The SARS-CoV-2 mRNA itself does not replicate in the human cell and is rapidly broken down by cellular enzymes*."

27. The COVID-19 vaccines mRNA are specifically for the Spike protein, and due to genetic manipulation, which includes N1-methypseudo-uridine substitution for uridine in the RNA, they are stable for weeks and even months as explained later. However, the main point here is that only a tiny portion of the lipid nanoparticles are directly taken up by antigen presenting cells, and the vast majority of the tens of trillions of lipid nanoparticles enter into other cells. Moreover, the main way the lipid nanoparticles would be taken up by macrophages would be via phagocytosis processes, which would be directed to the lysosomes of these cells, where they and their RNA content would be digested before the Spike mRNA can be translated into making Spike protein. For the small amount of the lipid nanoparticles that are able to deliver their mRNA cargo into the cytoplasm of the cell, it is feasible that the Spike mRNA can be used by the ribosomes to produce Spike protein, but this should be mostly directed into the luminal side of the endoplasmic reticulum. The upshot is this Spike protein is likely to be transported to the outer surface of the intact and remain anchored, but not bound up with MHC antigens. Figure 3 shows the scenario that is likely with any cell that takes up any COVID-19 vaccine lipid nanoparticles with RNA. The important lesson here is that in order to elicit an immune response, the recruited immune cells have to attacked, damage and, to an unclear extent, destroy the cells that present the foreign Spike protein on their surfaces. When small vesicular bits of cells known exosomes are produced during the immune cell attack, these can feature the Spike protein, and when taken up by phagocytosis by antigen-presenting cells, and can be partially digested, so that Spike fragments can be complexed with MHC antigens on their surface.

28. The presence of antibodies against the Spike protein produced from a previous infection of SARS-CoV-2 or related coronavirus will evoke an even stronger immune reaction against the vaccinated cells that took up the lipid nanoparticles and expressed the Spike protein. Those immune cells that were transfected with the lipid nanoparticles and produced Spike protein are more likely to be destroyed by other immune cells, then to be able to act as antigen presenting cells to stimulate specific B- and T-cells for recognition of the Spike protein as an antigen.

Figure 3. Mechanisms of RNA vaccine action. Toll-like receptors (TLR) sense non-natural lipids present in the lipid nanoparticles and induce the release of cytokines that recruit immune cells to the site of the transfected host cell. Existing anti-Spike antibodies may react with the produced Spike protein that is expressed on the surface of the lipid nanoparticle-transfected host cell. Innate immune cells that express a receptor (IgG Fc receptor) that recognize the common portion (Fc) of the IgG class antibodies allows the immune cells to attach and attack the transfected host cell, and generate small pieces of the host cell called exosomes. These exosomes are coated by Spike protein (along with other host cell proteins), and are engulfed and digested by the innate immune cells. Exosomes are a known result of transfection with gene therapy products and are normally assessed for potential excretion into the environment under gene therapy regulations. Fragments of the Spike protein that are generated in the innate immune cells are presented with major histocompatibility antigens (MHCs) by these cells to T-cells and B-cells in lymph nodes and other locations where these adaptive immune cells reside. In addition, antibody-bound Spike proteins on host cells recruit the activation of proteins of the Complement system, leading to formation of holes and destruction of the host cell.



29. As the COVID-19 vaccines are injected into the upper arm into the deltoid muscle, the immune response is mediated in the blood circulation. The primary antibody response is the production of IgG class antibodies, primarily of the IgG1 and IgG3 types, which are very proinflammatory. These are very high affinity and durable antibodies (typically lasting for about 3 weeks) before they are replaced by the production of more antibodies from B-cells if the need persists for more to fight an infection. However, these antibodies (described as bivalent) are not as effective as IgA and IgM secreted antibodies (described as multivalent), which are much more efficient for binding up virus particles (see Exhibit C, Figure 6). Furthermore, unlike IgA and IgM antibodies, the amounts of IgG antibodies are very low in the nasopharyngeal captivity and the upper lungs. With repeated boosting the COVID-19 vaccines, there is also the switching of the IgG antibodies to the IgG2 and IgG4 types, which are much less efficient than the IgG1 and IgG3 antibody types, which facilitates the development of immune tolerance, i.e., the immune system down-regulates its response to a foreign antigen that appears to be a common part of the environment or human body. Finally, because the immune response is directed against only one of the SARS-CoV-2 proteins, which has an appreciable rate of mutation, the antibody and T-cell responses are much more restricted than the natural immunity response to the whole virus.

2.3. Historical Vaccine Development

30. The body has evolved a highly sophisticated and effective immune system that learns to recognize and specifically counteract novel infectious pathogens (see Exhibit C, Chapter 3). In particular, the adaptive immune system relies on the combined actions of B-cells that produce specific antibodies and T-cells that attack pathogen-infected cells. Such recognition depends on the ability of these lymphocytes to target tiny portions of a pathogen called epitopes. Some parts of a pathogen are very immunogenic, *i.e.,* elicit a strong immune response, whereas other portions are ignored by the immune system. Infectious pathogens such as viruses, bacteria, and fungi are constantly evolving, and previous exposure to an earlier version of the pathogen can provide immune protection against future infections, including other highly related pathogens.

31. The development of vaccines goes back over two hundred years ago, when English physician and scientist Edward Jenner developed the first smallpox vaccine from preparations of cowpox in 1796.[18]

[18] (2023) About Edward Jenner. The Jenner Institute. Retrieved from https://www.jenner.ac.uk/about/edward-jenner#

There the introduction of a related or less virulent form of an infectious pathogen became a standard way of conferring resistance to future infections with deadly pathogens. Before there were methods to artificially produce the proteins of these pathogens for direct injection into vaccine recipients, the use of weakened, attenuated strains elicited an immune response with much lower risks of severe disease.

32. Heat or chemical inactivated preparations of a pathogen may be used for such vaccines, but this has the disadvantage that the level of pathogen is restricted to what was injected. With a live pathogen that has retained its ability to multiple, ideally very slowly to give the immune system time to develop counter-defenses before the pathogen can do too much damage, stronger immunity can be achieved. This is why traditional vaccines have typically used inoculants that have from a few dozen copies to thousands of copies of a particular pathogen.

33. With the advent of recombinant DNA technology in the 1970's, it became feasible to isolate the genes that encoded the proteins of pathogens and start to produce them in larger quantities in bacteria like *Escherichia coli* (*E. coli*) and later eukaryotic cells such as the popular Sf9 (*Spodoptera frugiperda*) caterpillar cells, human embryonic kidney cells (*e.g.,* HEK-293 cells), or yeast (*e.g.,* budding yeast *Saccharomyces cerevisiae*). Injection of purified preparations of these recombinantly produced pathogen proteins or short artificial pieces of these proteins created by chemical synthesis in the laboratory, provided for large quantities of antigens that could be injected into animals to induce antibody production against the foreign proteins. However, the immune response would be focused on the specific proteins that were inoculated into the animals and not the whole pathogen, which results in a narrower degree of immune protection. Nevertheless, a polyclonal antibody response would be induced, because a population of different B-cells would be stimulated to produce different antibodies against different parts (*i.e.,* epitopes) of an injected protein or peptide fragment. Incidentally, preparations of monoclonal antibodies can be developed by creation of hybridoma cells where an antibody producing B-cell is fused with a cancer cell, isolated and then repeatedly propagated to give rise to a pure population of identical cells that generate exactly the same antibody specific for a single epitope. Such monoclonal antibodies can be effective therapeutics when they target specific oncoproteins on cancer cells or proteins on the surface of pathogens.

2.4. COVID-19 Vaccine Development

34. Over 200 COVID-19 vaccines have been in development, with over 71 in Phase 3 trials, and at least 38 approved.[194] The Chinese Sinovac (CoronaVac) and Sinopharm vaccines, which use inactivated whole SARS-CoV-2 virus for injection, are essentially traditional vaccines. However, most of the COVID-19 vaccines used in North America and Europe exclusively target the Spike protein of the SARS-CoV-2 virus as the sole antigen to evoke an immune response to achieve immunity. In these latter vaccines, either the inoculation features the Spike protein or it contains messenger-RNA (mRNA) or DNA to instruct infected cells to manufacture the viral protein inside of the cells of the vaccine recipient. The Novavax's Nuvaxovid (also known as Covovax) and Medicago's Corifenz vaccines are protein subunit vaccines that use recombinant purified Spike protein as the antigen. Such preparations of Spike protein may be about 95% pure, as achieved with the histidine-tagged Spike protein in the Novavax product (the other 5% are Sf9 insect proteins). It is possible that the contaminating proteins can also elicit an immune response. All of the aforementioned COVID-19 vaccines have tended to offer poorer initial efficacy for production of anti-Spike protein antibodies than achieved with COVID-19 genetic vaccines.[4] This is likely due to the inability of these vaccines to generate as high levels of the antigens as possible with the lipid nanoparticle (LPN)/mRNA or adenovirus/DNA-based vaccines.

35. The Russian Sputnik V COVID-19 vaccine, AstraZeneca's Vaxzevria, and Janssen's Jcovden (Johnson & Johnson) vaccines, are adenovirus preparations that contain Spike DNA, which provides for Spike messenger-RNA production to then permit biosynthesis of the Spike protein. They use modified adenoviruses to deliver the DNA for the Spike protein into infected cells. Adenoviruses can cause colds and even cancer, but the versions used as delivery vehicles are genetically engineered so as not to replicate and not to cause cancer by removal of viral genes that are necessary for these outcomes.[19] A significant advantage of these adenovirus-based vaccines is that the DNA is fairly stable, and multiple copies of RNA can be produced from each Spike DNA molecule. Multiple copies of each Spike protein can then be generated from a single Spike mRNA molecule. However, the mRNA that is produced is very labile, and the production of Spike protein from that mRNA is presumed to be transient. Moreover, there still remains the chance of integration of the DNA into the host cell genome, which is an

[19] Khoshnood, S., Ghanavati, R., Shirani, M., Ghahramanpour, H., Sholeh, M., *et al.* (2022) Viral vector and nucleic acid vaccines against COVID-19: A narrative review. Front Microbiol. 13:984536. doi:10.3389/fmicb.2022.984536

alternative mechanism by which cells can become cancerous if the integration is near cancer-related genes (known as proto-oncogenes or tumor suppressor protein genes) in the genome. The risk for this may be low, and such cells are likely destroyed by the immune system. Another disadvantage of this type of vaccine is that the immune system also learns to recognize the adenovirus vector with its own viral proteins. Consequently, a different strain of the delivery adenovirus may be required for booster shots, since the immune system can produce antibodies that may inactivate the ability of the adenovirus to enter into cells or facilitate the adenovirus's removal by innate immune cells. This may be alleviated by inoculation of the delivery adenovirus through the mucosal route, either in the airway or by intrarectal administration.

36. Pfizer-BioNTech's BNT162b2 (later named Comirnaty) and Moderna's mRNA-1273 (later named Spikevax) are mRNA-containing vaccines that deliver a genetically modified mRNA (modRNA) gene for production of the Spike protein. These modifications permit high stability of the mRNA through the incorporation of non-natural nucleotides (*i.e.,* N1-methyl pseudouridine for uridine) and an altered nucleic acid sequence, particularly to increase the nucleotide base content in the RNA for more cytidine and guanidine nucleotides. Cytidine and guanidine nucleotides pairs with greater affinity for each other than does adenine and uracil (or N1-methyl pseudouridine) pairs in double-stranded nucleic acids. Higher cytidine and guanidine nucleotides can improve the stability of the RNA. Despite the different RNA sequence from the original Spike gene, the resultant Spike protein should be identical due to the redundancy of the genetic code.

37. The genetic COVID-19 vaccines work to produce an immune response through very different mechanisms of action from traditional vaccines, and while there is overlap in many of the intervening steps, the differences have profound implications for the efficacy and safety of these products. As outlined in Section 2.2, in the case of the traditional COVID-19 vaccines, innate immune cells directly consume and digest the Spike protein, and then present pieces to T-cells and antibody producing B-cells. By contrast, the COVID-19 genetic vaccines penetrate into normal body cells, which produce and then present the Spike proteins on their surfaces. Then the immune cells attack and damage the Spike protein-producing cells. The debris produced from the damaged or destroyed cells, known as exosomes, are then engulfed by immune cells and degraded into pieces of the Spike protein, which are complexed on their surfaces with MHC antigens for presentation to T-cells and B-cells. These immune cells are located in lymph nodes and the spleen. Memory B-cells are also widely distributed in the bone

marrow, Peyers' patches, gingiva (gums), mucosal epithelium of tonsils, the lamina propria of the gastro-intestinal tract, and in the circulation.

38. In the typical descriptions of how the COVID-19 genetic vaccines work, it has been suggested that the lipid nanoparticles or adenovirus in these vaccines are directly taken up by host innate immune cells such as dendritic cells and macrophages. However, as the LPNs used in the Pfizer/BioNTech and Moderna RNA vaccines have no targeting proteins on their surface, they will fuse with any cell membrane that they encounter. Likewise, the adenovirus-based COVID-19 vaccines can bind to a wide variety of different cell surface receptors to gain entry into diverse cell types. Only a very tiny portion of the LPNs or adenoviruses in the COVID-19 vaccines would be expected to end up in immune cells directly. The more likely scenario is presented in Figure 3., where almost any cell could be penetrated by an LPN or adenovirus. It should be appreciated that pre-existing antibodies to the Spike proteins of other coronaviruses or anti-Spike antibodies generated from the first inoculation with a COVID-19 vaccine will elicit a more powerful inflammatory and destructive response with booster injections, unless the mechanisms of immune tolerance are induced.

2.5. COVID-19 Genetic Vaccines Production

39. Large scale production of vaccines comes with major challenges to ensure consistency in the final product to maintain batch stability, efficacy and safety. Since the Pfizer/BioNTech COVID-19 vaccine is the most commonly used vaccine in Canada and the US, the next few subsections provide a summary of the main findings of a more detailed technical assessment concerning the development and manufacturing of BNT162b.[20] A number of deficiencies in the product's development were identified by regulatory agencies and appear to have either been ignored or glossed over. Substantial differences in Pfizer's manufacturing (Process 1 versus Process 2) led to worrisome quality differences between the clinical trials (manufactured with Process 1) and what most people received in the commercial rollout of the Pfizer vaccine (manufactured with Process 2). Vaccine approval for the declared COVID-19 pandemic was given 'fast-track 'conditional approval to address "*a seriously debilitating, rare or life-threatening disease devoid of a viable treatment*" and approval was granted on the condition that

[20] Gutschi, LM. (2022) Quality issues with mRNA Covid vaccine production. Bitchute. Retrieved from https://www.bitchute.com/video/muB0nrznCAC4/

additional information would be forthcoming after the vaccine was rolled out. Much of these data have not been fully provided to date.

40. Data for the following portion of this section was primarily obtained from the European Medicines Agency European Public Assessment Report (EPAR) for the BioNTech/Pfizer vaccine.[21] Additional information was obtained through email leaks from December, 2020 that were released to journalists and to the *British Medical Journal*.[22, 23] It should be appreciated that the information provided to the EMA by Pfizer was very similar to what was provided to other health regulatory agencies, including Health Canada and the US FDA.

41. As mentioned earlier, traditional vaccines contain a known amount of the target antigens found in attenuated or dead versions of pathogens or proteins derived from them to evoke an immune response. They do not require a person's cells to manufacture and present them on their membrane surface at an uncontrolled rate and level. It is this very difference that has been overlooked when assessing the safety, dosage, and pharmacokinetics of BNT162b2 (Pfizer-BioNTech mRNA vaccine) and its by-products, including the mRNA-encoded Spike protein. Therefore, BNT162b2 and the other COVID-19 genetic vaccines are not like any other vaccine that has ever been used successfully in the past as the innate immune response is initially targeted directly against one's own cells rather than against the invading pathogen. Unlike traditional vaccines, in which the formulation contains a known concentration of viral antigen, BNT162b2 does not contain the viral antigen that triggers the immune response. Instead, the mRNA directs the body's cells to manufacture the viral spike protein *in vivo* at levels that may vary over 100-fold or more amongst vaccinees, and it is that very difference that has been overlooked when assessing the safety and pharmacokinetics of BNT162b2 and its components and derivatives. Individuals produce variable amounts of Spike protein due to their genetics, age, hormonal, and nutritional status, which batch of vaccine they receive, and so on. Therefore, since the

[21] (2020) Comirnaty European Public Assessment Report. Dec. 21, 2020. European Medicines Agency. Retrieved from https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

[22] Tinari, S. (2021) The EMA COVID-19 data leak, and what it tells us about mRNA instability. BMJ. 372:n627. doi:10.1136/bmj.n627

[23] (2021) Rappaport Rolling Review Report overview LoQ-COVID-19 mRNA vaccine BioNTec, 2020. COVID Truths. Retrieved from https://www.covidtruths.co.uk/2021/04/ema-leaked-papers/

Spike protein is not part of the BNT162b2 formulation but is in fact the active component of the vaccine, *i.e.*, the actual immunogen, it should have been assessed as a gene therapy product.

2.5.1. Are modRNA Product Vaccines or Gene Therapies?

42. One might have thought *a priori* that mRNA vaccines would be regulated as gene therapy products to which they objectively correspond to. This would require even more testing than traditional vaccines or even drug. When injecting nucleic acids including mRNA, there are potential safety concerns specific to gene therapy products, such as genomic effects or immunological responses that may require additional regulatory assessment of safety risks for these products. However, nucleic acid vaccines have been subject to complex, contradictory and unclear regulatory guidance such that no specific regulatory guidance for these products were available at the time the mRNA vaccines received their Interim Order from the Minister of Health in Canada on December 9, 2020.[24]

43. Of note, BioNTech and Moderna originally expected to see their products regulated as gene therapies. For example, Moderna's statement in their second quarter 2020 Securities and Exchange Commission (SEC) filing *"Currently, mRNA is considered a gene therapy product by the FDA"* is all the more curious given that Moderna had likely already filed an IND (Investigational New Drug) application to FDA to begin clinical trials.[25] The genome sequence for the SARS-CoV-2 virus only become available in mid-January 2020 a few months before.

44. In 2008, the EMA amended its definition of gene therapy products to state, *"Gene therapy medicinal products (GTMPs) shall not include vaccines against infectious diseases."* As a result, the non-clinical requirements and controls as described in the EMA's Guidance for GTMPs would no longer apply, but no rationale was provided for this amendment. These controls include studies on biodistribution, dose response, potential targets of toxicity, identification of the target organ for biological activity, potential of integration into the genome and transmission in the germ line, toxicity related to the expression of

[24] (2020) Media Advisory. Health Canada authorizes first COVID-19 vaccine. Government of Canada. Retrieved from https://www.canada.ca/en/health-canada/news/2020/12/health-canada-authorizes-first-covid-19-vaccine.html

[25] (2020) Moderna. Quarterly Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934. Moderna, Ed.; Securities and Exchange Commission. Retrieved from https://www.sec.gov/Archives/edgar/data/1682852/000168285220000017/mrna-20200630.htm

structurally altered proteins, reproductive toxicity, tumorigenicity, repeated dose toxicity, and excretion into the environment.[26]

45. Similarly, in 2013, the FDA guidance on gene therapy products, without explanation, excluded from its scope vaccines for infectious disease:

> *"This guidance does not apply to therapeutic vaccines for infectious disease indications that are typically reviewed in CBER/Office of Vaccines Research and Review (OVRR)."*[27] [12]

46. This exclusion serves only regulatory purposes. It does not change the US FDA biological definition of gene therapy products which remains as:

> *"Gene therapy products are all products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms."*[28]

47. It is the 2005 WHO Guidelines that grants nucleic acid vaccines, including mRNA vaccines, the status of a vaccine: antigens produced *in vivo* in the vaccinated host following administration of a live vector such as an adenovirus or nucleic acid or antigens produced by chemical synthesis *in vitro* and must comply with this international regulation concerning Good Manufacturing Practices (GMP), including demonstration of the purity and quality of the starting material.[29] The WHO Expert Committee on Biological Standardization provided Guidelines specifically for mRNA vaccines in April 2022, updated

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[26] (2008) Guideline on the non-clinical studies required before first clinical use of gene therapy medicines. CHMP, Ed. European Medicines Agency. Vol. EMEA/CHMP/GTWP/125459/2006. Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-studies-required-first-clinical-use-gene-therapy-medicinal-products_en.pdf

[27] (2013) Preclinical assessment of investigational cellular and gene therapy products. CBER, Ed.; U.S. Federal Drug Administration. Vol. FDA-2012-D-1038. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preclinical-assessment-investigational-cellular-and-gene-therapy-products

[28] (2015) Design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic products. Research, C. f. B. E. a., Ed. US Federal Drug Administration. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-and-analysis-shedding-studies-virus-or-bacteria-based-gene-therapy-and-oncolytic-products

[29] (2005) WHO guidelines on non-clinical evaluation of vaccines TRS No 927. World Health Organization. Vol. Annex 1. Retrieved from https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccines-annex-1-trs-no-927

from the draft guidance document of 2020.[30] These advisory guidelines updated the information and regulatory considerations for modRNA and self-amplifying mRNA vaccine products, addressed development, manufacturing and control of the vaccine, and clarified the requirements for non-clinical evaluation. However, modRNA vaccines remain regulated as vaccine products and not as gene therapy products.

2.5.2. Long-Term Follow-up After Administration of Gene Therapy Products

48. Despite the exclusion of vaccines from gene therapy guidance, the US FDA has active programs in infectious diseases within its Office of Tissues and Advanced Therapies including laboratory research on replication deficient (adenovirus) and replication competent viral vector (measles, vaccinia).[31] these products are regarded as biological drugs as are vaccines.[32] However, the US FDA provides guidance on the long-term follow-up of gene therapy products, such as viral vectors, which requires the manufacturers to systematically record delayed adverse events.[33] Specifically, the emergence of new clinical conditions such as "*a new malignancy, new incidence or exacerbation of a pre-existing neurological disorder, a new incidence or exacerbation of a prior rheumatological or autoimmune disorder, a new incidence of a hematological disorder and new infections especially those potentially product-related*", are to be recorded annually for a minimum of 5 years, followed by up to 10 years of observation. However, these requirements are not imposed on biological or nucleic acid products reviewed under vaccine guidance.

[30] (2022) Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: Regulatory considerations. World Health Organization. Annex 3, TRS No 1039, WHO, Ed. Retrieved from https://www.who.int/publications/m/item/annex-3-mRNA-vaccines-trs-no-1039

[31] Oh, S.S. (2022) Cellular, Tissue, and Gene Therapy Advisory Committee Meeting. Review of Intramural Research Program – Gene Transfer and Immunogenicity Branch, March 10, 2022. US Food and Drug Administration. Retrieved from https://www.fda.gov/media/156771/download

[32] Viswanathan, S., Bubela, T. (2015) Current practices and reform proposals for the regulation of advanced medicinal products in Canada. Regen Med. 10(5):647–663. doi:10.2217/rme.15.28

[33] (2020) Long term follow-up after administration of human gene therapy products: Guidance for industry. Retrieved from https://www.fda.gov/media/113768/download

49. Questions remain regarding the regulatory approval process for mRNA vaccines, specifically those regarding the pharmacological, pharmacodynamic characteristics and safety risks unique to nucleic acid medicinal products, which are further reviewed by Banoun (2023).[34]

2.5.3. Manufacturing and Quality

50. Chemistry, Manufacturing and Control (CMC) are processes to ensure that quality manufacturing standards have been established for the finished product. This is to ensure consistency in identity, safety, quality, stability and strength between the product used in the clinical trials and individual lots produced for commercial purposes. For modRNA commercial vaccines this would include creation of master and working cell banks, test method development and stability testing, process development, qualification and validations as well as quality assurance processes and techniques.[35] However, the modRNA platform was a novel manufacturing platform requiring novel control and analytical technology and thus knowledge from prior platforms for similar products/vaccines were limited and could not be leveraged for quality control.

2.5.4. BNT162b2 modRNA Structure

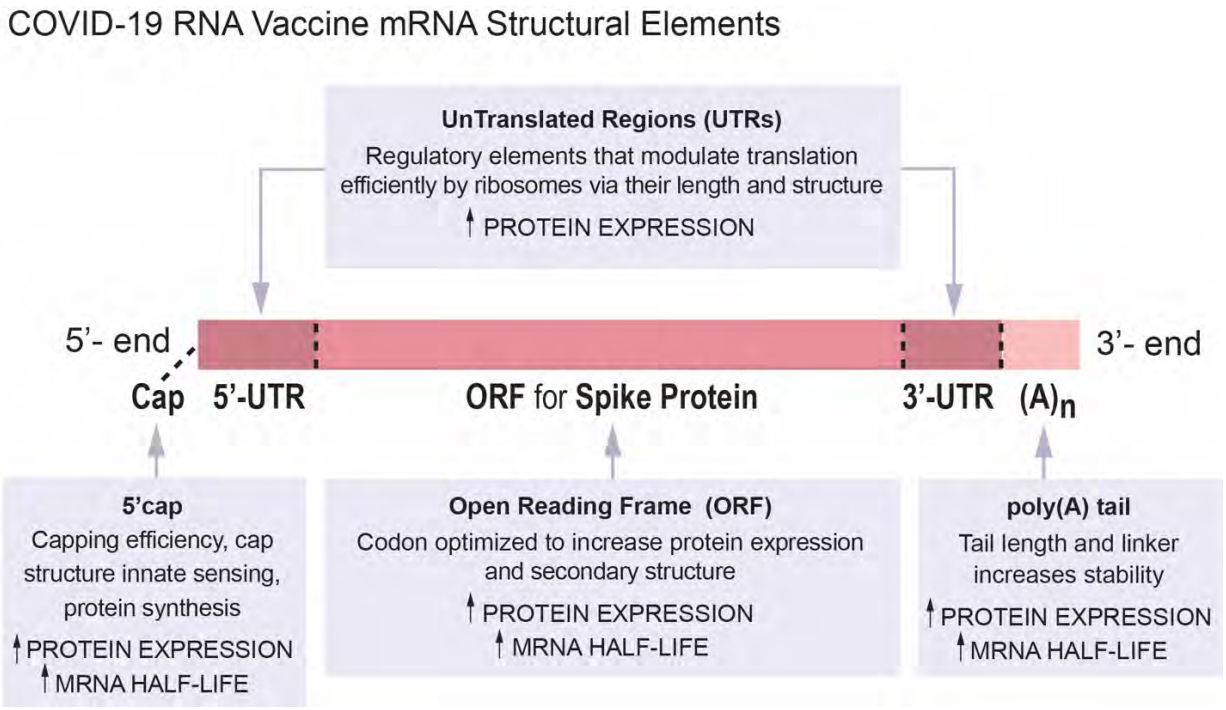
51. In the Pfizer/BioNTech vaccine, the modRNA has been altered from the mRNA sequence of the Spike protein of the SARS-CoV-2 coronavirus by: (a) including mutations to replace two adjacent lysine and valine amino acids with two prolines instead, to ensure an antigenically optimal pre-fusion conformation and reduced the risk of any released Spike protein entering into other cells; (b) replacing all uridine bases with N1-methylpseudouridine to evade defenses against foreign RNA;[35] (c) including human-derived 5' and 3' UTRs (untranslated regions) and a poly-adenine (A) tail with a 30A segment, a linker, and a 70A segment, to enhance translation; and (d) optimizing codon use by selecting synonymous codons that will optimize expression (*i.e.,* replacement of adenine and thymidine nucleotide bases with cytidine and guanidine nucleotide bases in the RNA, while still retaining the final Spike protein amino acid sequence) (Figure 4). The design of the sequence was facilitated by *in silico*

[34] Banoun, H. (2023) mRNA: Vaccine or gene therapy? The safety regulatory issues. Int J Mol Sci. 24(13):10514. doi:10.3390/ijms241310514

[35] Whitley, J., Zwolinski, C., Denis, C., Maughan, M., Hayles, L., *et al.* (2022) Development of mRNA manufacturing for vaccines and therapeutics: mRNA platform requirements and development of a scalable production process to support early phase clinical trials. Transl Res. 242:38-55. doi:10.1016/j.trsl.2021.11.009

methods. Since this mRNA is bioengineered, its non-proprietary name is tozinameran, and Comirnaty is the proprietary name for the Pfizer/BioNTech product. BNT162b2 was the laboratory identifier used to describe the modRNA during its development and testing.

Figure 4. mRNA structural elements that control the structure and stability of mRNA and the protein product.[35] In the cases of the Pfizer/BioNTech and Moderna COVID-19 mRNA vaccines, codon optimization involves use of codon triplicates that favor use of guanidine and cytidine nucleotide bases (but still specify the correct amino acids), replacement of uridine bases with 1-N-methyl-pseudouridine (m1Ψ), and the mutation of Lysine-986 and Valine-987 to Proline-986 and Proline-987, which inhibits the fusion of the resultant Spike protein with membranes following engagement with host cell receptors.



52. In a seminal article written in 2014 by BioNTech founders Drs. Ugur Sahin and Özlem Türeci, along with Dr. Katalin Karikó, they noted that *in vitro* transcribed mRNA represents a new class of drugs to deliver genetic information into cells.[36] The complex pharmacology of mRNA and issues with delivery to achieve sufficient levels of encoded protein and to reach a high number of cells were discussed. Safety considerations of mRNA-mediated activation of immune mechanisms, potential mitochondrial toxicities associated with non-natural nucleotides and prolonged treatment, dosing, and tissue

[36] Sahin, U., Karikó, K., Türeci, Ö. (2014) mRNA-based therapeutics – developing a new class of drugs. Nat Rev Drug Discov. 13(10):759–780. doi:10.1038/nrd4278

targeting were also identified. Many of these issues remain unsolved, which exemplifies their experimental nature even today.

2.5.5. modRNA Effects in Human Cells

53. While this genetic engineering of the viral mRNA results in high levels of Spike protein production, it is now known that this modRNA can persist for days, weeks and possibly months in humans,[37] as can the Spike protein itself.[38]

54. The genetic engineering of the mRNA may result in aberrant protein production. The various modifications made to the mRNA may be prone to errors when translated in cells and this may generate variations in the resulting Spike proteins when compared to the Wuhan Spike protein. For instance, differences in folding of the Spike protein[39] and generation of other antibodies with unknown effects may occur.[40] Abnormal Spike protein and fragments following vaccination have been documented.[41, 42] Interestingly, when the BNT162b2 was used to transfect cells in culture, the resultant Spike protein was observed to be larger than predicted by its amino acid sequence, and this was assumed to be due to the attachment of complex polymers of sugar molecules (*i.e.*, glycosylation) of the protein, but never confirmed experimentally. This was originally flagged by the EMA as one of its initial concerns and assigned as Specific Obligation-1 (SO1) for Pfizer to address.[21] As it stands, it is still unclear if these

[37] Röltgen, K., Nielsen, S., Silva, O., Younes, S.F., Zaslavasky, M., *et al.* (2022) Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. Cell. 185(6):1025–1040.e14. doi:10.1016/j.cell.2022.01.018

[38] Bansal, S., Perincheri, S., Fleming, T., Poulson, C., Tiffany, B., *et al.* (2021) Cutting edge: Circulating exosomes with COVID spike protein are induced by BNT162b2 (Pfizer-BioNTech) vaccination prior to development of antibodies: A novel mechanism for immune activation by mRNA vaccines. J Immunol. 207(10):2405–2410. doi:10.4049/jimmunol.2100637

[39] McKernan, K., Kyriakopoulos, A.M., McCullough, P. (2021) Differences in vaccine and SARS-CoV2 replication derived mRNA. Implications for cell biology and future diseases. OSF Preprints. doi:10.31219/osf.io/bcsa6

[40] Seneff, S., Nigh, G., Kyriakopoulos, A.M., McCullough, P. (2022) Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and microRNAs. Food Chem Toxicol. 164:113008. doi:10.1016/j.fct.2022.113008

[41] Patterson, B.K., Francisco, E.B., Yogendra, R., Long, E., Pise, A., *et al.* (2022) SARS-CoV-2 S1 protein persistence in SARS-CoV-2 negative post-vaccination individuals with Long Covid/PASC-like symptoms. Research Square (Preprint). Retrieved from https://www.researchsquare.com/article/rs-1844677/v1

[42] Magen, E., Mukherjee, S., Bhattacharya, M., Detroja, R., Merzon, E., *et al.* (2022) Clinical and molecular characterization of a rare case of BNT162b2 mRNA COVID-19 vaccine associated myositis. Vaccines (Basel). 10(7):1135. doi:10.3390/vaccines10071135

mutant Spike proteins may be associated with unwanted and adverse events as has been demonstrated with other codon-optimized proteins.

55. The exact features of the Spike protein produced by the synthetic mRNA are unclear, especially with the bivalent Wuhan/Omicron BA.4/5 and the latest monovalent XBB1.5 COVID-19 vaccines. It is not known how the Spike protein translated from the modified mRNA fully compares to the original Wuhan virus version. It is assumed the genetic engineering of the nucleotide sequence as undertaken with the COVID-19 vaccines would not alter the Spike protein amino acid sequence. However, depending where the Spike protein is produced, this alone might give rise to different glycosylation compositions in this highly sugar-coated protein.

56. There is a lack of clarity regarding the Spike protein characterization despite several requests for such data from the EMA. A full comparison of the Spike protein made by the mRNA in the vaccine to the natural virus has not been performed to date. Although the amino acid sequence of the Spike protein produced by the engineered mRNA in the COVID-19 vaccines is currently unknown, thousands of distinct gene sequences for the Spike protein are publicly available from direct gene sequencing of the SARS-CoV-2 virus and its variants. These concerns are further compounded for the 'bivalent' modified mRNA injectable formulations released in the Fall 2022 that encoded two distinct Spike proteins, namely the original ancestral Wuhan strain and a combination of BA.4/BA.5 Omicron sub-variants. This allowed for formation of unnatural trimeric complexes with novel mixes of Spike proteins from both versions of the SARS-CoV-2 virus.

57. On December 6, 2021, at a meeting held by WHO,[43] vaccinologist Professor Florian Kramer anticipated heterotrimer formation with bivalent vaccines, questioning if this could "lead to problems in protein folding?"[44] Presumably this concern was raised because protein folding differences could alter the safety and efficacy profile of the vaccine. However, if heterotrimer formation leads to an improved

[43] (2021) WHO consultation on COVID-19 vaccine research: How can vaccine research further contribute to achieve the control of the pandemic everywhere? World Health Organization. Retrieved from https://www.who.int/news-room/events/detail/2021/12/06/default-calendar/who-consultation-on-covid-19-vaccines-research-how-can-vaccine-research-further-contribute-to-achieve-the-control-of-the-pandemic-everywhere

[44] Krammeer, F. (2021) Challenges to develop and assess variant-specific vaccines. Cdn.who.int. Retrieved from https://cdn.who.int/media/docs/default-source/blue-print/florian-krammer_3_anticipated-challenges_vrconsultation_6.12.2021.pdf

immunological response as Moderna claimed in its submission to the FDA at the CDC meeting on September 1, 2022,[45] it is reasonable to ask if there are also different toxicological or immunological responses that are currently unknown. This issue is less problematic with the more recently released monovalent COVID-19 vaccine with only the XBB.1.5 Omicron subvariant.

2.5.6. modRNA Production: Process 1 vs Process 2

58. The manufacturing process of the modRNA was changed substantially for the commercial scale-up lots (Process 2) from the pilot-scale process used to produce the BNT162b2 vaccine candidate for the clinical trials (Process 1). This had implications for Good Manufacturing Practice (GMP), risked Marketing Authorization, and has implications clinically.

59. The modRNA drug substance in BNT162b2 is produced by *in vitro* transcription from a DNA template. The DNA template defines the sequence of the modRNA, but it is not supposed to be part of the final pro-vaccine product.

60. Process 1 was used to produce modRNA evaluated in the clinical trials. Using a cell free method, linear DNA was amplified using the polymerase chain reaction. This results in a linear template including the open reading frame (ORF) for the S1/S2 protein, and the 3' and 5' UTRs. The 5-prime cap was added enzymatically as was the poly(A) tail.[46] However, this technique does not produce sufficient modRNA for commercialization for billions of doses in the time frame and fidelity required as is possible from a plasmid DNA.[47]

61. Process 2 was used for commercial scale production of BNT162b2 vaccine. Using genetic engineering techniques, DNA containing a Kozak sequence (for direct binding of translated RNA to ribosomes), untranslated regions (UTRs), viral Spike protein sequence, and a poly(A) tail (to protect the translated RNA from degradation and aid in transcription termination), was inserted into a plasmid, which is a circular piece of DNA. In this case, plasmid pST4-1525 was used (Figure 5), which has 7,824 base pairs

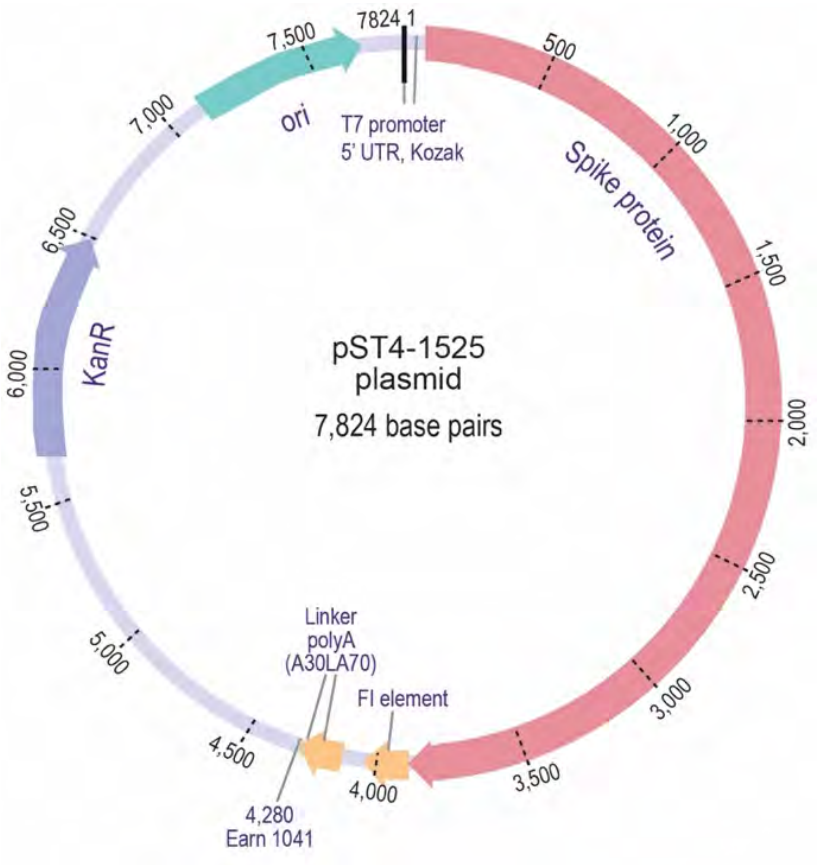
[45] (2022) September 1, 2022 ACIP Meeting – Booster doses of Moderna; Prizer/BioNTech COVID-19 Omicron-modified. YouTube. Retrieved from https://www.youtube.com/watch?v=i34wDDfhRpg&t=2176s

[46] Rosa, S.S., Prazeres, D.M.F., Azevedo, A.M., Marques, M.P.C. (2021) mRNA vaccines manufacturing: Challenges and bottlenecks. Vaccine. 39(16):2190–2200. doi:10.1016/j.vaccine.2021.03.038

[47] Ouranidis, A., Vavilis, T., Mandala, E., Davidopoulou, C., Stamoula, E., *et al.* (2022) mRNA therapeutic modalities design, formulation and manufacturing under Pharma 4.0 Principles. Biomedicines. 10(1):50. doi:10.3390/biomedicines10010050

including a promoter for the T7 RNA polymerase, the recognition sequence for the endonuclease used for linearization of the DNA, a kanamycin resistance gene, and an origin of replication (ORI). The plasmid was taken into *E. coli* bacterial cells. As the *E. coli cells* grow and multiply in the presence of kanamycin (to ensure that only those particular *E. coli* that received the plasmid produce the Spike RNA can survive and proliferate), the plasmid multiplies along with them. *E. coli* is then harvested and chemically lysed to recover the plasmid DNA, which is then further purified. Subsequently, the circular plasmid DNA is linearized by cutting it using a restriction endonuclease enzyme (Eam1104I) and purified by ultrafiltration and Diafiltration (UFDF).[48]

Figure 5. pST4-1525 plasmid map. Adapted from Josephson *et al.* (2020).[49]



[48] (2023) Ultrafiltration and Diafiltration (UF/DF). Unchained Labs. Retrieved from https://www.unchainedlabs.com/ultrafiltration-diafiltration-uf-df/

[49] Josephson, F. (2020) Rapporteur's Rolling Review assessment report. Committee for Medicinal Products for Human Use. EMEA/H/C/005735/RR. Retrieved from https://covidvaccinereactions.com/ema-pfizer-leak/

62. The DNA template in both processes is then used as the starting material for the modRNA production. *In vitro* translation (IVT) transcription is an enzymatic reaction requiring an RNA polymerase, nucleotide triphosphate substrates (substituting N1-methylpseudouridine for uridine), the polymerase cofactor magnesium chloride ($MgCl_2$), and a pH buffer containing polyamide and antioxidants. Like Moderna, Pfizer/BioNTech used the T7 RNA polymerase (derived from the T7 bacteriophage), which binds to a cognate *promoter* sequence likewise derived from T7 that has also been engineered into the DNA plasmid upstream of the gene for the Spike protein. Only a few hours are needed to produce the modRNA and the process can be standardized.[46] The 5-prime cap is also added during the IVT reaction for both processes. Rather than adding the poly(A) tail enzymatically as in Process 1, in Process 2 it is already encoded for in the plasmid.

63. At the completion of IVT using plasmid DNA as used in Process 2, several impurities may be present, notably host cell genomic DNA from *E. coli*, RNA, proteins, endotoxins (bacterial cell wall components from the *E. coli* cells) and isoforms of the plasmid DNA.[49, 50] These were quantified routinely.

64. Manufacturers of biotechnological and biological products including vaccines, often make changes to the manufacturing process including increasing the scale of production, product stability and any changes imposed by regulatory authorities, both during development and post-approval. The manufacturers must demonstrate that the relevant quality attributes do not adversely impact safety or efficacy of these changes. Although there are no specific guidelines for changes in manufacturing processes specific to nucleic acid products, the International Council on Harmonization Q5E[51] did anticipate that: "*The principles outlined in this document might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids*" which would therefore include nucleic acids.

65. In particular, requirements for clinical comparative efficacy and safety studies are dependent on the stage of development and the type of change involved. If changes are made after the confirmatory

[50] Banoun, H. (2022) Current state of knowledge on the excretion of mRNA and spike produced by anti-COVID-19 mRNA vaccines; possibility of contamination of the entourage of those vaccinated by these products. Infect Dis Res. 3(4):22. doi:10.53388/IDR20221125022

[51] (2005) ICH Topic Q 5 E. Comparability of Biotechnological/Biological products. European Medicines Agency. Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-e-comparability-biotechnological/biological-products-step-5_en.pdf

clinical trials, as was done with the Pfizer/BioNTech vaccine, a thorough comparability assessment is generally required including:

> *"…physicochemical and biological in vitro studies, and may include clinical pharmacokinetic and/or pharmacodynamic comparability studies. If this comparability exercise cannot rule out an impact on the efficacy and safety profile of the drug, additional clinical study* (ies) *may have to be performed*."[52]

66. In its rolling review in November 2020, the EMA noted that there was a decrease in the purity of the mRNA. In the clinical trial batches, the intact mRNA was 78-83% pure, which was much higher than in the commercial batches at 60%.[37] Side-to-side comparisons based on analytical testing and biological assays demonstrated significant differences in the purity and amount of intact mRNA with the Process 2 batches. This may indicate notable physical, chemical and biological differences, warranting further comparative clinical studies. Emails from the EMA leak/hack showed that the EMA's Head of Pharmaceutical Quality, Dr. Jekerle Veronika, discussed the "differences in the level of mRNA integrity" between clinical and commercial material. It was hoped than an approval by the end of 2020 could be possible if the mRNA integrity issue (and 2 other major objections) were to be resolved.[53]

67. A protocol amendment to the pivotal trial was therefore added,[54] which required 252 patients receiving Process 2 lots to be compared to patients in the clinical trials receiving Process 1 lots for comparable safety and efficacy. To date, this data is unavailable.[55]

68. Most recently, a Freedom of Information (FOIA) request to the UK Regulator (Medicines and Healthcare Products Regulatory Agency) obtained by the *Daily Skeptic* revealed, *"This exploratory objective was*

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[52] (2007) European Medicines Agency. Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process. Vol. EMEA/CHMP/BMWP/101695/2006. CHMP, Ed. European Medicines Agency. Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-comparability-biotechnology-derived-medicinal-products-after-change-manufacturing-process_en.pdf

[53] Veronika, J. (2020) E-mail dated November 24, 2020, to Dr. Evdokia Korakianiti of the EMA. EMA Leaks\09.png. Retrieved from https://covidvaccinereactions.com/wp-content/uploads/2021/04/EMA-Docs-and-CVR-Edits.zip

[54] Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., *et al.* (2020) C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 383(27):2603–2615. doi:10.1056/NEJMoa2034577

[55] Block, J. (2022) COVID-19: Researchers face wait for patient level data from Pfizer and Moderna vaccine trials. BMJ. 378:o1731. doi:10.1136/bmj.o1731

removed and documented in protocol amendment 20 in September 2022 due to the extensive usage of vaccines manufactured via "Process 2." Thus, this process comparison was not conducted as part of the formal documentation within the protocol amendment." Therefore, clinical comparability between these two manufacturing processes cannot be assumed and thus represents a new biological product, which is not comparable to the product in the clinical trials for safety and efficacy.[56] In essence, the UK regulator used 'real world evidence' to support compatibility of the two processes, in contradiction to the original accepted method of a small, randomized trial.

2.5.7. Impurities Identified in Process 2 Batches

2.5.7.1. Truncated and Fragmented modRNA

69. As discussed above, impurities in Process 2 lots included fragmented mRNA considered a critical quality attribute but it is not yet known what effects these smaller mRNA fragments (impurities) have in the body. These shorter Spike protein fragments may be released more readily into the circulation from vaccine transfected cells. Such truncated fragments may lack the transmembrane domain and attached palmitate fatty acids at the back end of the Spike protein, which would normally anchor them to the cell membrane. At the time of conditional approval, the allowable limits for fragmented mRNA were up to 45% in the final product.[37] Despite alteration of the sequence in the Spike protein with two amino acid residues replaced by two proline residues from mutation of the mRNA sequence, which locks the Spike protein in a prefusion state, the Spike protein should still be able to engage angiotensin-converting enzyme 2 (ACE2) and other Spike receptors that are expressed on cells of the body. ACE2 is important for reducing blood pressure through its ability to degrade the hormone angiotensin 2. The Spike protein binds to ACE2,[57] TMEM16F,[58] and CD42b receptors on platelets, and stimulates their

[56] The Information Commissioner's Office. (2023) Internal review of FOI 23/510. Medicines and Healthcare Products Regulatory Agency. Retrieved from https://dailysceptic.org/wp-content/uploads/2023/09/IR-23-510.pdf

[57] Zhang, S., Liu, Y., Wang, X., Yang, L., Li, H., *et al.* (2020) SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol. 13(1):120. doi:10.1186/s13045-020-00954-7

[58] Cappelletto, A., Allan, H.E., Cresente, M., Schneider, E., Bussani, R., *et al.* (2021) SARS-CoV-2 spike protein activates TMEM16F-mediated platelet pro-coagulant activity. BioRxiv (preprint). doi:10.1101/2021.12.14.472668

activation and aggregation,[59] and contributes to thrombosis (blood clotting) and thrombocytopenia (reduction of production of platelets), which are known risks associated with COVID-19 vaccines.[60]

70. There is also little data on whether these fragmented mRNA pieces result in harmful proteins or peptides (small proteins) or if they induce autoimmunity (cause the body to attack itself). For example, there can be as much as a 30% amino acid similarity between the Spike protein and a human protein called Syncytin-1. Although cross-reactivity of anti-Spike antibodies produced in vaccinated individuals has not yet been reported that is directed towards Syncytin-1,[61, 62, 63] autoimmunity often takes years before its manifests overtly in people.

2.5.7.2. Double-stranded RNA (dsRNA)

71. Other impurities in the BNT162b2 included dsRNA, which occurs secondarily to the *in vitro* transcription process that can generate dsRNA by-products.[64] dsRNA can induce pro-inflammatory cytokines such as type 1 interferon, trigger Toll-like receptor 3 and separately affect expression/translation of Spike protein.[65] Removal of dsRNA is at best, 90%, which indicate that short segments of dsRNA may remain and has been hypothesized to contribute to immune-inflammatory reactions such as myocarditis.[66] When present in LPNs, dsRNA will also be transfected into

[59] Li, T., Yang, Y., Li, Y., Wang, Z., Ma, F., *et al.* (2020) Platelets mediate inflammatory monocyte activation by SARS-CoV-2 spike protein. J Clin Invest. 132(4):e150101. doi:10.1172/JCI150101

[60] Cox, D. (2021) Targeting SARS-CoV-2-platelet interactions in COVID-19 and vaccine-related thrombosis. Front. Pharmacol. 12:708665. doi:10.3389/fphar.2021.708665

[61] Prasad, M., Lin, J.L., Gu, Y., Gupta, R., Macary, P., Schwarz, H. (2021) No crossreactivity of anti-SARS-CoV-2 Spike protein antibodies with Syncytin-1. Cell Mol Immunol. 18(11):2566–2568. doi:10.1038/s41423-021-00773-x

[62] Mattar, C.N.Z., Koh, W., Seow, Y., Hoon, S., Venkatesh, A., *et al.* (2022) BNT162B2 COVID-19 mRNA vaccination did not promote substantial anti-syncytin-1 antibody production nor mRNA transfer to breast milk in an exploratory pilot study. Ann Acad Med Singap. 51(5):309–312. doi:10.47102/annals-acadmedsg.2021447

[63] Pelech, S., Winkler, D. (2023) personal communication.

[64] Baiersdörfer, M., Boros, G., Muramatsu, H., Mahiny, A., Vlatkovic, I., *et al.* (2019) A facile method for the removal of dsRNA contaminant from *in vitro*-transcribed mRNA. Mol Ther Nucleic Acids. 15:26–35. doi:10.1016/j.omtn.2019.02.018

[65] Nelson, J., Sorensen, E.W., Mintri, S., Rabideau, A.E., Zheng, W., *et al.* (2020) Impact of mRNA chemistry and manufacturing process on innate immune activation. Sci Adv. 6(26):eaaz6893. doi:10.1126/sciadv.aaz6893

[66] Milano, G., Gal, J., Creisson, A., Chamorey, E. (2021) Myocarditis and COVID-19 mRNA vaccines: A mechanistic hypothesis involving dsRNA. Future Virol. 10.2217/fvl-2021-0280. doi:10.2217/fvl-2021-0280

macrophages and dendritic cells.[67] Dendritic cells trigger immune responses in lymphoid tissues upon early sensing of infectious pathogens and communicate with immature dendritic cells present in peripheral tissues such as the myocardium which may result in an autoimmune attack and myocarditis.

72. It is worth noting that due to the optimization of a high cytidine and guanidine content from gene-editing of the RNA to make the Spike protein in both the Pfizer/BioNTech and Moderna COVID-19 vaccines, this will produce tighter binding and stability of the dsRNA. This may facilitate more prolonged stimulation of cellular responses to perceived viral infection of cells, since dsRNA is not normally produced in healthy cells.

2.5.7.3. Endotoxin

73. Endotoxin can be introduced into the modRNA drug substance primarily from the *E. coli* used in the DNA template production but also from large volume buffers used in purification and from raw materials used in the manufacturing of the mRNA vaccines.[35] Endotoxin is difficult to remove due to its ubiquity, high heat stability, and hydrophobic properties.[68] Lipopolysaccharides (LPS) from endotoxin can bind both the S1 and S2 subunits of the Spike protein, which may result in enhanced inflammatory responses.[69] Endotoxin is a very potent stimulus of macrophages and monocytes even at picogram levels (a picogram is a trillionth of a gram).[70] Some researchers have suggested Spike protein is not pro-inflammatory on its own in macrophages, except in the presence of endotoxin or lack of glycosylation.[71] LNPs with or without modRNA can induce exacerbated inflammation in the presence of pre-existing

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[67] Kranz, L.M., Diken, M., Haas, H., Kreiter, S., Loquai, C., *et al.* (2016) Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy. Nature. 534(7607):396–401. doi:10.1038/nature18300

[68] Li, Y., Fujita, M., Boraschi, D. (2017) Endotoxin contamination in nanomaterials leads to the misinterpretation of immunosafety results. Front Immunol. 8:472. doi:10.3389/fimmu.2017.00472

[69] Samsudin, F., Raghuvamsi, P., Petruk, G., Puthia, M., Petrlova, J., *et al.* (2023) SARS-CoV-2 spike protein as a bacterial lipopolysaccharide delivery system in an overzealous inflammatory cascade. J Mol Cell Biol. 14(9):mjac058. doi:10.1093/jmcb/mjac058

[70] Munford, R.S. (2016) Endotoxemia-menace, marker, or mistake? J Leukoc Biol. 100 (4):687–698. doi:10.1189/jlb.3RU0316-151R

[71] Cinquegrani, G., Spigoni, V., Iannozzi, N.T., Parello, V., Bonadonna, R.C., Dei Cas, A. (2022) SARS-CoV-2 spike protein is not pro-inflammatory in human primary macrophages: Endotoxin contamination and lack of protein glycosylation as possible confounders. Cell Biol Toxicol. 38(4):667–678. doi:10.1007/s10565-021-09693-y

inflammation due to endotoxin,[72] and concerns have been raised that the unrecognized contamination of nanoparticles with endotoxin may be associated with toxicity.[68] In view of the high level of DNA plasmids in the BNT162b2 vaccine as discussed in the next subsection, it is feasible that endotoxin levels may also exceed current regulatory limits.[73]

2.5.7.4. Plasmid Vector DNA

74. As mentioned above, to produce the mRNA that is encapsulated in LPNs that are used as COVID-19 vaccines, both Pfizer/BioNTech and Moderna utilize DNA copies of the Spike gene that are incorporated into plasmids. These plasmids or vectors were used to transfect *E. coli* bacterial cells for high production of modRNA copies, which were subsequently purified from lysed bacteria. The purification protocols should have removed the plasmid DNA along with bacterial endotoxins and LPS. However, several laboratories have independently confirmed the substantial presence, as much as 35% or more, of the nucleic acid in the COVID-19 mRNA vaccines as DNA.[74, 75, 76, 77, 78] The contamination appears to be higher in the Moderna vaccine than the Pfizer/BioNTech product, but most of the DNA fragments are

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[72] Parhiz, H., Brenner, J.S., Patel, P.N., Papp, T.E., Shahnawaz, H., *et al.* (2022) Added to pre-existing inflammation, mRNA-lipid nanoparticles induce inflammation exacerbation (IE). J Control Release. 344:50–61. doi:10.1016/j.jconrel.2021.12.027

[73] USP-NF. (2023) Analytical procedures for mRNA vaccine quality (Draft Guidelines) – 2nd Edition. United States Pharmacopoeia-National Formular. Retrieved from https://www.uspnf.com/notices/analytical-procedures-mrna-vaccines-20230428

[74] Palmer, M., Gilthorpe, J. (2023) COVID-19 mRNA vaccines contain excessive quantities of bacterial DNA: Evidence and implications. Doctors for COVID Ethics. Retrieved from https://doctors4covidethics.org/covid-19-mrna-vaccines-contain-excessive-quantities-of-bacterial-dna-evidence-and-implications/

[75] McKernan, K., Helbert, Y., Kane, L.T., McLaughlin, S. (2023) Sequencing of bivalent Moderna and Pfizer mRNA vaccines reveals nanogram to microgram quantities of expression vector dsDNA peer dose. ResearchGate. doi:10.31219/osf.io/b9t7m Retrieved from https://www.researchgate.net/publication/369967228_Sequencing_of_bivalent_Moderna_and_Pfizer_mRNA_vaccines_reveals_nanogram_to_microgram_quantities_of_expression_vector_dsDNA_per_dose

[76] Buckhaults, P. (2023) Testimony before South Carolina Senate Medical Affairs Ad-Hoc Committee on DHEC. Retrieved from https://www.youtube.com/watch?v=IEWHhrHiiTY

[77] (2023) Urgent expert hearing on reports of cancer-promoting DNA contamination in C-19 mRNA vaccines. World Council for Health. Retrieved from https://worldcouncilforhealth.org/multimedia/urgent-hearing-dna-contamination-mrna-vaccines/

[78] Speicher, D.J., Rose, J., Gutschi, L.M., Wiseman, D.M., McKernan, K. (2023) DNA fragments detected in monovalent and Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada: Exploratory dose response relationship with serious adverse events. OSF Preprints. Retrieved from https://osf.io/mjc97/

much smaller and less than 200 base pairs in length.

75. A recent preprint by Canadian Citizens Care Alliance scientists and others showed that around 1.9 – 3.7 µg/dose of DNA by fluorometry appears to be typically found in vials of BNT162b2b that are supposed to contain 30 µg of Spike RNA, and 3.3 to 5.1 µg/dose for the Moderna product.[78] This would correspond to around 100 billion or more DNA molecules in each injection and represent contamination levels that exceed 3.33 µg/mg of RNA. However, the DNA contamination in these COVID-19 vaccines meets the European Medicines Agency (EMA) 0.33 µg/mg requirement,[49] and the FDA's 0.010 µg/dose requirements using the qPCR method for quantitation.[79] The large differences in residual DNA levels found between fluorometry and qPCR measurements maybe due to the fact that qPCR cannot quantitate molecules smaller than the size of the amplicon (105-114 base-pairs). Therefore, qPCR underestimates the total DNA in each vaccine and this raises questions of analytical methods recommended by regulatory agencies for modRNA vaccines. Health Canada, the US FDA and the European Medicine Agency have acknowledged the high degree of DNA that contaminated the Pfizer/BioNTech and Moderna vaccines, but have dismissed this and still consider the vaccines to be safe.[78,80, 81, 82, 83] In the recent testing of 27 mRNA Pfizer/BioNTech and Moderna vaccine vials obtained in Canada, "*all vaccines exceeded the guidelines for residual DNA set by the FDA and WHO of* [0.010 µg]/*dose by 188-509-fold*."[78] However, the transfection of these plasmid DNA contaminants using LPNs warrants reconsideration of the current regulatory limits, since these limits are based on injecting naked DNA directed into plasma where it may be rapidly destroyed.

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[79] Sheng-Fowler, L., Lewis, A.M. Jr, Peden, K. (2009) Issues associated with residual cell-substrate DNA in viral vaccines. Biologicals. 37(3):190–195. doi:10.1016/j.biologicals.2009.02.015

[80] Horwood, M., Chartier, N. (2023) Exclusive: Health Canada not concerned about scientists' finding of plasmid DNA contamination in COVID shots. Epoch Times. Retrieved from https://www.theepochtimes.com/world/exclusive-health-canada-not-concerned-about-scientists-finding-of-plasmid-dna-contamination-in-covid-shots-5449394

[81] Phillips, J. (2023) FDA responds to reports of DNA contamination in COVID vaccines. Epoch Times. Retrieved from https://www.theepochtimes.com/article/fda-responds-to-reports-of-dna-contamination-in-covid-vaccines-5496717

[82] Demasi, M. (2023) Exclusive: An interview with Buckhaults about DNA contamination in COVID vaccines…and the FDA responds. MaryAnne Demasi Substack. Retrieved from https://maryannedemasi.substack.com/p/exclusive-an-interview-with-buckhaults

[83] Stieber, Z. (2023) European regulator confirms BioNTech did not highlight DNA sequence in COVID-19 vaccine. Epoch Times. Retrieved from https://www.theepochtimes.com/health/european-regulator-confirms-pfizer-did-not-highlight-dna-sequence-in-covid-19-vaccine-5519668?utm

76. Residual DNA can result in type 1 interferon responses and poses a risk to genomic integration. One of the mechanisms that Pfizer/BioNTech took to reduce the amount of plasmid Spike DNA was to digest it into smaller pieces with enzymes called nucleases. The consequence of this may be to further increase the probability of a piece of the DNA integrating into and disrupting the genomes of cells that take up the LPNs, and this has been explained by South Carolina University professor Dr. Philip Buckhaults when he gave a speech to a South Carolina Senate Medical Affairs Ad-Hoc Committee.[76] This situation can lead to "insertional oncogenesis," which is when foreign DNA gets integrated next to critical growth control genes, known as oncogenes or tumor suppressor genes and interferes with their normal regulation, thereby driving cancer cell proliferation. When DNA is circularized as it is in an intact plasmid, it is less likely to integrate into the genome. However, when it is cut into linear fragments with nucleases, the probability of integration into host cell DNA increases.[84] Even fragments of DNA as little as 7 bp have been shown to disrupt rates of DNA integration or recombination.[85] Some LPNs have been developed to further improve on the delivery of DNA contents into the nucleus of cells, where the genome is normally present.[86]

77. Another problematic aspect of the Pfizer/BioNTech vaccine is that the DNA plasmid includes an SV40 promoter/enhancer/*ori* element, which is the portion of SV40 virus genome that drives the production of flanking genes. This inclusion was not originally disclosed to the EMA, nor to Health Canada, raising questions of adulteration and intention to deceive the regulatory agencies.[81, 87] Health Canada has recently confirmed the presence of the SV40 promoter/enhancer in the Pfizer/BioNTech vaccine after this was brought to their attention, but they have concluded that the risk/benefit profile continues to support the use of the Pfizer/BioNTech vaccine.[88]

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[84] Lim, S., Yocum, R.R., Silver, P.A., Way, J.C. (2023) High spontaneous integration rates of end-modified linear DNAs upon mammalian cell transfection. Sci Rep. 13:6835. doi:10.1038/s41598-023-33862-0

[85] Ledwith, B.J., Manam, S., Troilo, P.J., Barnum, A.B., Pauley, C.J., *et al.* (2000) Plasmid DNA vaccines: Assay for integration into host genomic DNA. Dev Biol (Basel). 104:33–43.

[86] Nie, Y., Fu, G., Leng, Y. (2023) Nuclear delivery of nanoparticle-based drug delivery systems by nuclear localization signals. Cells. 12(12):1637. doi:10.3390/cells12121637

[87] Chartier, N. (2023) Here are the four e-mails from Health Canada which underpin our work on DNA plasmid contamination and the undisclosed presence of Simian Virus 40 enhancer-promoter. X Retrieved from https://twitter.com/nchartieret/status/1716579403243634922?s=46&t=fHNy04S5p-78vK_ah9g3hw

[88] Horwood, M. (2023) Exclusive: Health Canada confirms undisclosed presence of DNA sequence in Pfizer shot. Epoch Times. Retrieved from https://www.theepochtimes.com/world/exclusive-health-canada-confirms-undisclosed-presence-of-dna-sequence-in-pfizer-shot-5513277

78. This SV40 promoter might have been originally included to increase the rate of Spike RNA production from the DNA plasmid during the production phase. However, if portions of the contaminating plasmid integrate into a cell's genome, this could result in increased rates of mRNA production of genes next to the SV40 virus promoter/enhancer elements, which again can potentially contribute to driving oncogenesis. Moreover, the SV40 virus promoter/enhancer features a DNA nuclear targeting sequence.[89] The SV40 virus was a common contaminant in inactivated polio vaccines that were offered from 1955 to 1963, so a substantial portion of the population over 60 years of age may have persistent SV40 infections.[90] The Large T antigen produced from the SV40 virus, which may be present in 10-20% of the population, can bind to SV40 virus promoter/enhancer elements, which could lead to even higher mRNA production of cellular genes at sites of genome integration. However, the risk of this is unclear at this time. The DNA plasmid used to manufacture the RNA in the Moderna COVID-19 vaccine did not include an SV40 promoter.[75]

79. Finally, it should also be appreciated that the RNA in the COVID-19 vaccines may also be converted back into a DNA copy through the action of RNA reverse transcriptases in host cells such as LINE-1.[91] Such a conversion of Spike RNA into stable DNA in the nucleus of a liver cell line by LINE-1 was independently confirmed.[92] Liver is one of the major organs that accumulates the Pfizer/BioNTech vaccine LPNs,[21] and it is feasible that the DNA copy may permit more sustained production of more Spike RNA molecules, and more Spike protein copies.

2.5.8. Lipid Nanoparticles in COVID-19 RNA Vaccines

80. The lipid nanoparticles for use in vaccines are novel for use in humans and have not undergone rigorous safety assessments. The LNPs are semi-spheres made of fat (lipids) that protect the mRNA from

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89 Bai, H., Lester, G.M.S., Petishnok, L.C., Dean, D.A. (2017) Cytoplasmic transport and nuclear import of plasmid DNA. Biosci Rep. 37(6):BSR20160616. doi:10.1042/BSR2016061

90 Institute of Medicine (US) Immunization Safety Review Committee (2002) Immunization Safety Review: SV40 contamination of polio vaccine and cancer. Stratton, K., Almario, D.A., McCormick, M.C., editors. Washington (DC): National Academies Press (US). doi:10.17226/10534

91 Zhang, L., Richards, A., Barrasa, M.I., Hughes, S.H., Young, R.A., Jaenisch, R. (2021) Reverse-transcribed SARS-CoV-2 RNA can integrate into the genome of cultured human cells and can be expressed in patient-derived tissues. Proc Natl Acad Sci USA. 118(21):e2105968118. doi:10.1073/pnas.2105968118

92 Aldén, M., Olofsson Falla, F., Yang, D., Barghouth, M., Luan, C., *et al.* (2022) Intracellular reverse transcription of Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 *in vitro* in human liver cell line. Curr Issues Mol Biol. 2022 Feb 25;44(3):1115–1126. doi:10.3390/cimb44030073

decaying (degrading) and also carry the mRNA into cells. They contain PEGylated lipid (ALC-0159) and the cationic lipid (ALC-0315), *neither of which have been used in humans before*. PEGylation refers to the addition of polyethylene glycol as a component of a lipid or a protein, and in the case of LPNs, it reduces the rate of their clearance from the circulation by certain organs such as the kidneys. ALC-0519 and SM-102, which is found in the Moderna lipid nanoparticles, are not recommended for human use as noted in Safety Data sheets.[92a,92b] Normally, approval for such novel ingredients would require a full independent review for pharmacology and toxicity. These safety studies appear to be incomplete.

81. Cationic (positively-charged) lipids are known to cause inflammation (both with and without mRNA cargo inside them) and can be directly toxic to cells.[93] PEGylated nanoparticles can also cause significant allergic reactions.[94] There is limited data both on the metabolism and distribution of these lipids, and it is not known how much ends up in each organ. There is no formal, controlled clinical data to support the safety of repeated exposures to the LNPs in humans beyond two inoculations.

2.5.9. Analytical Procedures for modRNA Vaccine Quality

82. Due to the rapid development and newness of the mRNA platform compendial standards were lacking. These are official quality standards contained in a pharmaceutical compendium such as the United Stated Pharmacopeia-National Formulary (USP-NF) or the European Pharmacopoeia (Ph Eur). The Ph. Eur standards for the assays used for the pro-vaccines are currently being developed, which will include mRNA-LNP medicinal products as well as the DNA template used for the preparation of the mRNA transcript.[95] The USP-NF developed a second draft of their analytical procedures for modRNA vaccine quality.[73]

[92a] Lt. Colonel Theresa Long (2021) Affidavit of LTC Theresa Long M.D. in support of a motion for a preliminary injunction order. Retrieved from https://www.deepcapture.com/2021/09/affidavit-of-ltc-theresa-long-m-d-in-support-of-a-motion-for-a-preliminary-injunction-order/

[92b] Safety Data Sheets are downloadable from https://sdsmanager.com/ca/search/

[93] Ndeupen, S., Qin, Z., Jacobsen, S., Bouteau, A., Estanbouli, H., Igyártó, B.Z. (2021) The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. iScience. 24(12):103479. doi:10.1016/j.isci.2021.103479

[94] Moghimi, S.M. (2021) Allergic reactions and anaphylaxis to LNP-Based COVID-19 vaccines. Mol Ther. 29(3):898–900. doi:10.1016/j.ymthe.2021.01.030

[95] (2023) Ph. Eur. Commission kicks off elaboration of three general texts on mRNA vaccines and components. Council of Europe. Retrieved from https://www.edqm.eu/en/-/ph.-eur.-commission-kicks-off-elaboration-of-three-general-texts-on-mrna-vaccines-and-components

83. It is important to note that compendial standards define a common set of methods to determine mRNA vaccine quality but do not enforce those standards or determine the acceptance criteria for quality and purity, which is under the purview of regulatory agencies. The updated WHO 2022 guidelines for mRNA vaccines also noted that "*detailed production and control procedures, controls were not yet standardized*" and certain details are not in the public domain and may be considered proprietary and confidential.[30] No specific numerical limit for dsRNA, DNA, plasmid purity and other process related impurities were stated in the WHO 2022 guidelines. The WHO guidelines also stated testing for process or product related impurities "*may be reduced or discontinued once production consistency has been demonstrated*," if the national regulatory agency is in agreement.

84. The United States Pharmacopoeia (USP) Draft Guidelines recommends more sensitive methods for analysis of the modRNA particularly for poly(A) integrity and 5' cap analysis than what was used by the manufacturer for Process 2 lots. Further, more in-depth analysis of purity of the modRNA drug substance such as nucleoside and residual T7 polymerase are additional proposed quality attributes. These are both welcome additions to detect and quantify these impurities since oxidized nucleotides are associated with age-related, especially neurodegenerative diseases.[96]

85. As noted earlier, residual dsRNA is a major contaminant of the modRNA drug substance secondary to the IVT process. dsRNA by-products such as runoff transcripts or an antisense RNA molecule similar in size to the desired mRNA can occur but require various analytical procedures for determining purity and quality. Immunoblot or ELISA analysis used by the manufacturer may not detect these types of dsRNA contamination and are difficult to quantify.[97] Analytical tools such as native and gel electrophoresis were not included to determine these critical quality attributes by the manufacturer or in the draft USP Guidelines.

86. Finally, RNA sequencing for confirming the expected mRNA sequence in addition to RT-PCR, and a full plethora of DNA plasmid testing including sequencing, is also proposed by USP.[73] These proposed compendial standards provide a more sensitive and thorough analysis for purity and safety than were

[96] Li, Z., Malla, S., Shin, B., Li, J.M. (2014) Battle against RNA oxidation: Molecular mechanisms for reducing oxidized RNA to protect cells. Wiley Interdiscip Rev RNA. 5(3):335–346. doi:10.1002/wrna.1214

[97] Jacobsen, E. (2022) Quality control in mRNA vaccine manufacturing – The critical path. Future Lab, Biocompare. Retrieved from https://www.biocompare.com/Editorial-Articles/592381-Quality-Control-in-mRNA-Vaccine-Manufacturing-The-Critical-Path/

used for either Process 1 or Process 2 lots raising questions of safety and purity for the early and current vaccine product. In particular, the sequencing of the DNA starting material which identifies the mRNA sequence performed for Process 1 lots was replaced with qPCR of the RNA for Process 2 lots,[49] a less sensitive method. This raises troubling questions about the fidelity of transcription during IVT and risks for aberrant protein production that were not identified in safety or analytical testing**.**

87. Specifications for quality attributes and testing for the final drug product includes LPNs and their lipid contents, appearance, sterility and selected attributes, which are included in the requirements for final drug product lot testing.

88. Importantly, subdivisible particles were noted in the Process 2 lots but were not described for Process 1 lots. These particles represent impurities and may have toxicological and clinical implications.[98] These impurities may have occurred due to instability of the buffer used in the initial process 2 lots and were likely due to the fact that Process 1 lots had not been previously frozen and were in fact flown to the clinical sites by private jets as needed.[99] On October 29, 2021, the US FDA authorized two presentations representing a manufacturing change from the phosphate-saline/sucrose buffer found in the original purple-topped vials to a Tris/sucrose buffer; the grey topped monovalent adult vaccine and an orange topped vaccine for those aged 6-11 years for increased stability, simpler storage requirements and a ready-to-use formulation.[100] This may be viewed as a tacit admission that the stability of the initial lots of the Process 2 batches were suboptimal with unknown safety and efficacy effects.

2.5.10. Additional Issues

89. A high degree of variability in biodistribution of the COVID-19 vaccines can result from how they are inoculated into the deltoid muscles of recipients. A standard protocol of 'aspiration' during intramuscular injection of COVID-19 vaccines was generally abandoned, since it can slightly increase

[98] Segalla, G. (2023) Chemical-physical criticality and toxicological potential of lipid nanomaterials contained in a COVID-19 mRNA vaccine. Int J Vac Theor Prac Res. 3(1):787–817. doi:10.56098/ijvtpr.v3i1.68

[99] Lewis, L.M., Badkar, A.V., Cirelli, D., Combs, R., Lerch, T.F. (2023) The race to develop the Pfizer-BioNTech COVID-19 vaccine: From the pharmaceutical scientists' perspective. J Pharm Sci. 112(3):640–647. doi:10.1016/j.xphs.2022.09.014

[100] (2021) Emergency Use Authorization (EUA) for an unapproved product review memorandum. U.S. Food and Drug Administration. Retrieved from https://www.fda.gov/media/153947/download

the chances of pain during administration.[101] As a consequence, about 2% or more of the vaccinations would result in delivery of the COVID-19 vaccine LPNs or adenoviruses directly into the bloodstream. This could account in part for why a small portion of vaccines recipients have much more severe adverse effects than most others.[102]

90. No one knows the potency, quantity, or duration of the Spike protein produced in different organs and the endothelium (*i.e.,* lining of blood vessel walls) given widespread biodistribution. There is no control of the amount of Spike protein is produced by transfected cells or duration of production. Tens of trillions of LPNs are injected with each vaccination. It is not known how age, sex, weight or other characteristics affect the potency of the vaccine. It is unknown how much Spike protein is made in each organ in humans that takes up the synthetic mRNA. Evidence appears to indicate that small amounts of LNPs may result in large amounts of Spike protein being produced in particular organs.[103]

91. Mulroney *et al.* (2023)[104] recently noted that N1-methylpseudouridylation of mRNA occasionally causes +1 ribosomal frameshifting in mice and humans with the Pfizer/BioNTech COVID-19 vaccine. This results in production of off-target "Spike" proteins that can feature different amino acid sequences after the frameshift, with the potential for eliciting "off-target" immune responses.[105] The degree to which such novel chimeric proteins are created in COVID-19 RNA vaccinated individuals remains unclear as does the consequences of antibodies that may be produced against the novel sequences and their reactivities with human proteins.

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[101] Rzymski, P., Fal, A. (2022) To aspirate or not to aspirate? Considerations for the COVID-19 vaccines. Pharmacol Rep. 74(6):1223–1227. doi:10.1007/s43440-022-00361-4

[102] Brail, S. (2022) Marc Girardot's unified theory of vaccine injury. Wholistic Substack. Retrieved from https://wholistic.substack.com/p/marc-girardots-unified-theory-of-vaccine-injury

[103] Di, J., Du, Z., Wu, K., Jin, S., Wang, X., *et al.* (2022) Biodistribution and non-linear gene expression of mRNA LNPs affected by delivery route and particle size. Pharm Res. 39(1):105–114. doi:10.1007/s11095-022-03166-5

[104] Mulroney, T.E., Pöyry, T., Yam-Puc, J., Rust, M., Harvey, R.F., *et al.* (2023) (N)1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting. Nature. e-publication December 6, 2023. doi: 10.1038/s41586-023-06800-3

[105] Wiseman, D., Gutschi, L.M., Speicher, D.J., Rose, J., McKernan (2023) Ribosomal frameshifting and misreading of mRNA in COVID-19 vaccines produces "off-target" proteins and immune responses eliciting safety concerns: Comment on UK study by Mulroney *et al*. Retrieved from osf.io/nt8jh. doi:10.31219/osf.io/nt8jh

92. Basic pharmacological data of the optimal dose, its range, and upper toxicity thresholds are lacking. By not performing pharmacokinetic and distribution studies of the encoded Spike protein, which was already known to be toxic and bioactive (off-target effects), the regulatory submissions for the COVID-19 genetic vaccines were incomplete. From the very start, the nonclinical safety studies were designed in order to provide data that would put the manufacturers' products in a "good light." The critical flaw here was that the guidance documents used by Health Canada were only applicable to traditional vaccines, and not vaccines using gene therapy technology.

93. Overall, mRNA vaccine quality has been questionable and variable. There appears to be substantial differences in the mRNA vaccines between batches and even between vials. This may be due to variations in handling, freezing/thawing/dilution requirements, and manufacturing variability. Stainless steel particles seen with the naked eye in some Moderna vials should have forced a larger product review - but this was limited to particular lots.[106] A broad range of limits for purity and quality was permitted in the commercial production of the vaccines. Large manufacturing variability between batches plus patient-to-patient variability likely resulted in different levels of Spike production and response to the vaccine product.[107]

94. There has been significant variability in the severity of adverse events, including lethality, with other COVID-19 vaccines by vaccine maker and batch number. For example, in the UK, a freedom of information request about adverse reactions with COVID-19 vaccines indicated for the ten most reported batches up to April 24, 2022, the number of Yellow Card vaccine injury reports varied from 1-7 reports per 1000 doses; this included 45,320 reports for the AstraZeneca, 32,766 reports for the Pfizer/BioNTech, and 12,550 reports for the Moderna vaccines.[108] Contamination has also been an issue, for example, with the AstraZeneca vaccines (which although manufactured by Emergent

[106] (2021) Moderna COVID-19 vaccine recall investigation report. Takeda Pharmaceuticals. Retrieved from https://www.takeda.com/ja-jp/announcements/statement-regarding-moderna-covid-19-vaccine-recall-investigation-report--october-2021

[107] Schmeling, M., Manniche, V., Hansen, P.R. (2023) Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine. Eur J Clin Invest. 53(8):e13998. doi:10.1111/eci.13998

[108] FOI Team (2022) Freedom of Information request on specific batch numbers on the adverse reactions reported following the COVID-19 vaccinations (FOI release 22/661). Medicines and Health Products Regulatory Agency. Retrieved from https://www.gov.uk/government/publications/freedom-of-information-responses-from-the-mhra-week-commencing-6-june-2022/freedom-of-information-request-on-specific-batch-numbers-on-the-adverse-reactions-reported-following-the-covid-19-vaccinations-foi-22661

Biosolutions in Baltimore, U.S.A., were never approved for use by the FDA, but were exported to Canada and Mexico).[109] More than half of Canada's supply of the AstraZeneca came from the Baltimore plant, until these vaccines were pulled on May 11, 2021 from the Canadian market.[110] Some of the problem involved cross-contamination with Johnston and Johnson COVID-19 adenovirus vaccine. Likewise, there was a major issue with batches of the Moderna COVID-19 vaccines in Japan.[111] Two Japanese men died after receipt of the second dose of the same batch of a Moderna COVID-19 vaccine, and subsequent testing found black substances in a few millimeters in size in 40 of the vials of a different batch of the Moderna COVID-19 vaccine. About half a million people in Japan were inoculated with three batches of the Moderna vaccine before 1.63 million doses were recalled by Moderna Inc, Takeda Pharmaceuticals Co Ltd and the Japanese authorities.

95. Another retrospective study of 66,587 suspected adverse effects (SAE) across 52 specific batches of Pfizer/BioNTech BNT162b2 administered to 4,026,575 people in Denmark between December 27, 2020 and January 11, 2022, revealed large variations in the reported SAE.[107] The SAE rates were lower in the larger vaccine batches, and there were batch-dependent differences in the seriousness of the SAE. Certain smaller batches (representing 4.2% of all the vaccine doses) were associated with 71% of all SAEs, 27.5% of all serious SAEs and 47% of all SAE-related deaths in the Danish study.

2.5.11. WHO Guidelines on Vaccine Evaluation

96. With regard to Health Canada's approval of the Pfizer COVID-19 vaccines. Both Pfizer and Health Canada followed the internationally accepted guidelines from the WHO for vaccine evaluation stating that the "*Pharmacokinetic studies (e.g., determining serum or tissue concentrations of vaccine components) are normally not needed.*"

97. With respect to scope, a WHO 2005 document states: "*For the purposes of this document, vaccines are considered to be a heterogeneous class of medicinal products containing immunogenic substances*

[109] Fenton, N.E. (2023) The scandal of the Astrazeneca vaccine from the Emergent Biosolutions plant in Baltimore. Substack. Retrieved from https://wherearethenumbers.substack.com/p/the-scandal-of-the-astrazeneca-vaccine

[110] Blackwell, T. (2021) More than half Canada's AstraZeneca vaccine came from U.S. plant accused of quality-control problems. National Post. Retrieved from https://nationalpost.com/news/canada/more-than-half-canadas-astrazeneca-vaccine-came-from-u-s-plant-accused-by-fda-of-quality-control-problems

[111] Chooi, W.H., Ng, P.W., Hussain, Z., Ming, L.C., Ibrahim, B., Koh, D. (2022) Vaccine contamination: Causes and control. Vaccine. 40(12):1699–1701. doi:10.1016/j.vaccine.2022.02.034

capable of inducing specific, active and protective host immunity against infectious disease." BNT162b2 does not contain immunogenic substances capable of inducing specific, active, and protective host immunity against infectious disease.[112]

98. The WHO 2014 Annex 2 guidelines states when it comes to scope: "*This document addresses regulatory considerations related to the nonclinical and initial clinical evaluation of adjuvanted vaccines*." BNT162b2 does not contain an adjuvant, although the LPNs do cause inflammation. Essentially, the WHO publications are only applicable to traditional vaccines, and not vaccines using gene therapy technology.[113]

99. In a December 2020 draft document on regulatory evaluation,[112] WHO admitted that detailed information was not available for the production of the COVID-19 mRNA vaccines. The WHO confirmed that controls for safety and efficacy of gene-based mRNA vaccine biologic products were not standardized. Certain details of vaccine components remain proprietary and were not publicly disclosed. In light of these unknowns, the WHO conceded that it was not feasible to develop specific international regulatory guidelines or recommendations, and strict adherence to normal regulatory guidance may not be possible.

100. It appears that there is insufficient evidence that these vaccine products meet the quality required of pharmaceutical products, raising concerns about their safety and efficacy. Regulatory assessment using current vaccine guidance is likely inadequate to determine safety and efficacy for a genetic product.[34] Assessment using a comprehensive gene therapy guidance may have been more appropriate given the nature of transfection with a nucleic acid, but currently is *not required* if the *use* of the product is for prevention of infectious diseases such as a vaccine.[114] Real-world data falsifies the original claim that mRNA-based COVID-19 biologics function as authentic vaccines for preventing viral infection and

[112] (2005) Annex 1 WHO guidelines on nonclinical evaluation of vaccines. World Health Organization. Retrieved from https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1

[113] (2014) Annex 2 Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines. World Health Organization. Retrieved from https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccine-adjuvants-and-adjuvanted-vaccines-annex-2-trs-no-987

[114] (2020) Human therapy for rare diseases. Guidance for industry. Food and Drug Administration Center for Biologics Evaluation and Research. Retrieved from https://www.fda.gov/media/113807/download

transmission rather than short-term gene-based therapeutic agents that might at best alleviate symptom severity.

2.5.12. Concluding Remarks About COVID-19 mRNA Vaccine Production

101. Based on the regulatory assessment of the mRNA vaccines, the following can be reasonably concluded:

a. These products are genetic therapy products that were not fully assessed by regulatory authorities under the guidance and controls required for such products. Although indicated for the prevention of an infectious disease and are used as a vaccine, under new definitions by the CDC and WHO, the mode of action of these products is based on transfection of a nucleic acid containing genetic information, but the appropriate regulatory controls and long-term safety studies were not performed.[34]

b. These products are mislabeled and adulterated. The label does not specify these are bioengineered nucleic acid mRNA, nor include the LNPs which may act as an adjuvant and provide for biodistribution throughout the body. These products are contaminated with small amounts of endotoxin, dsRNA, and significant contamination with plasmid DNA from the template produced by *E. coli.* Residual dsDNA poses particular oncological infectious risks.[79] Furthermore, the frameshifting in the reading of N1-methylpseudouridylated Spike mRNA by ribosomes generates highly mutated forms of the Spike protein that may interfere with the formation of the Spike trimers in cells.

One of the main mechanisms to consider with the dsDNA is insertional mutagenesis, although this is not a prerequisite for limiting dsDNA in medicinal products approved for human use. Firstly, DNA and RNA can enter spermatozoa and be transmitted to the next generation, along with the traits they encode for, without chromosomal integration.[115]

Secondly, a related phenomenon is that of episomal expression, which has been used in the development of gene therapy to achieve genetic modification without altering the chromosomal

[115] Spadafora, C. (2017) Sperm-mediated transgenerational inheritance. Front Microbiol. 8:2401. doi:10.3389/fmicb.2017.02401

DNA. Other aspects of how DNA limits were to be assessed, such as those found in FDA guidelines were not addressed.[116]

c. The US FDA proposed that any DNA contaminants smaller than about 200 bp is unlikely to act as a functional gene sequence, but specific types of contaminating sequences require particular scrutiny, including the SV40 promoter/enhancer sequence containing two 72 bp repeats, as this sequence is a known nuclear localization sequence that can ferry DNA into the nucleus of cells.[117] The commercial product was produced with a sufficiently different manufacturing process (Process 2) requiring verification of clinical comparability for efficacy and safety. This data does not appear to be available. This is a not a theoretical concern since a similar issue arose from the 1976 Swine flu inoculations, where the original influenza vaccine had been field tested but upon the declaration of a pandemic, the updated influenza vaccines were made without any confirmatory comparability testing.[118]

d. Several cases of Guillain-Barré syndrome were associated with this vaccine, and issues with manufacturing such as endotoxin contamination were considered a potential cause.[119]

102. Real-world data falsifies the original claim that mRNA-based COVID-19 biologics function as an authentic vaccine for preventing viral infection and transmission rather than as a short-term gene-based therapeutic agent that might alleviate at best, symptom severity.

2.6. Effectiveness of COVID-19 Vaccines

2.6.1. Approved COVID-19 Vaccines in Canada under Interim Order

[116] (2020) Chemistry, manufacturing, and control (CMC) information for human gene therapy investigational new drug applications (INDs). CBER, Ed.. USFDA. US Department of Health and Human Services. Retrieved from https://www.fda.gov/media/113760/download

[117] Dean, D.A., Dean, B.S., Muller, S., Smith, L.C. (1999) Sequence requirements for plasmid nuclear import. Exp Cell Res. 253(2):713–722. doi:10.1006/excr.1999.4716

[118] Sencer, D., Millar, J.D. (2006) Reflections on the 1976 swine flu vaccination program. Emerg Infect Dis. 12(1):29–33. doi:10.3201/eid1201.051007

[119] Evans, D., Cauchemez, S., Hayden, F.G. (2009) "Prepandemic" immunization for novel influenza viruses, "swine flu" vaccine, Guillain-Barré syndrome, and the detection of rare severe adverse events. J Infect Dis. 200(3):321–328. doi:10.1086/603560

103. Four COVID-19 vaccines, all targeting the Spike protein on the surface of the SARS-CoV-2 virus, were approved for use in Canada in 2021 under Interim Order: Pfizer-BioNTech BNT162b2 (later named Comirnaty) and Moderna mRNA-1273 (later named Spikevax), which are both vaccines that deliver RNA for production of the Spike protein; and AstraZeneca's Vaxzevria and Janssen's Jcovden (Johnson & Johnson (J&J)) vaccines, which are both adenovirus preparations that contain DNA that provide for RNA production to then permit the biosynthesis of the Spike protein. In 2022, Novavax's Nuvaxovid and Medicago's Corifenz were also approved by Health Canada. These latter vaccines used preparations of Spike protein that were purified from genetically engineered caterpillar cells and tobacco leaf cells, respectively, and delivered in a lipid nanoparticle along with a novel adjuvant to stimulate an immune reaction; each Nuvaxovid vaccine dose contained about 5 microgram (µg) of Spike protein, and Corifenz vaccine dose about 3.75 µg of a lipid membrane-encapsulated virus-like particle that is enriched in Spike protein. (1 µg is 1 millionth of a gram)

104. The first two doses for those over 12 years of age of the Moderna vaccine had 100 µg of the RNA for the Spike protein, compared to 30 µg of the RNA for the same protein in the first two adult doses of the Pfizer-BioNTech vaccine. After 6 months, booster shots were recommended for those 12 years of age or older with the Pfizer-BioNTech vaccine (30 µg/dose) and for those over 18 years of age with the Moderna vaccine (50 µg/dose).[120]

105. For the COVID-19 vaccination of children 6 months and older, only the Pfizer-BioNTech and Moderna RNA vaccines have been approved by Health Canada.[120] The Moderna product was approved for 6-month to 5-year-olds with a 2-dose regimen (25 µg/dose one month apart), whereas the Pfizer product was approved with a 3-dose regiment) (3 µg/dose at an interval of three weeks between the first and second doses, with eight weeks between the second and third dose). For 5- to 11-year-olds, the Pfizer-BioNTech vaccine was used at a dosage that was one third of the teen and adult dose (10 µg/dose),[121] whereas the Moderna vaccine was used at half the adult dose (50 µg/dose) for 5- to 11-year-olds,[122]

[120] (2023) Approved COVID-19 vaccines. Health Canada. Retrieved from https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines.html

[121] (2023) Pfizer/BioNTech Comirnaty COVID-19 vaccine. Health Canada. Retrieved from https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/pfizer-biontech.html

[122] (2023) Moderna Spikevax COVID-19 vaccines. Health Canada. Retrieved from https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/moderna.html

and a quarter of the adult dose for 6-months to 4-years old children (25 μg/dose). Therefore, a 5-year-old child received 5-times higher levels of the Spike mRNA with the pediatric dose of the Moderna vaccine when compared to the Pfizer-BioNTech product. A 6-month-old child received an 8-times higher level of the Spike mRNA with the pediatric dose of the Moderna vaccine when compared to the Pfizer-BioNTech product. Normally, a dose of a vaccine would roughly be related to body weight, but it is quite evident that this was largely ignored with the dispensing of the COVID-19 vaccines.

106 Based on the doses of Spike protein mRNA that have been used in these vaccines, it can be estimated that a single 100 μg inoculation may contain over 30 trillion lipid nanoparticles that typically feature around 5 to 10 copies of the Spike protein gene. The whole SARS-CoV-2 RNA is close to 30,000 nucleotides long and is single-stranded, but the Spike gene is only around 4,000 nucleotides long. It is calculated that the human genome, with 2,900,000,000 nucleotides per strand weighs about 0.855 picogram per strand. (A pictogram is a trillionth of a gram) Therefore 4,000 nucleotides would weigh around 0.00000118 picograms or 0.00000000000118 μg per 4,000 nucleotide RNA molecules. With 100 μg of RNA in one vaccine inoculation, this works out to about 85 trillion RNA molecules by this calculation. (As mentioned earlier, there is also some contaminating plasmid DNA with the RNA so the final number of RNA molecules may be slightly less.) From each genetically modified RNA molecule, it is feasible that hundreds of copies of the Spike protein can be produced.

107. Traditional vaccines with attenuated, weakened strains of a pathogenic virus typically range from as low as 50 to a few thousand virus particles in an inoculation, with each virus having only one copy of each viral gene. Consequently, the COVID-19 genetic vaccines permit the generation of Spike proteins in vaccine recipients that are at levels that could never be achieved with previous vaccines or even a natural infection without causing severe disease or death. This incredible capacity of these RNA and adenovirus vaccines to produce such high levels of Spike protein accounts for their ability to elicit strong immune responses, but also their higher potential for vaccine injury.

108. As mentioned above, the four COVID-19 genetic vaccines that were offered in Canada were RNA-based using lipid nanoparticle carriers (*i.e.*, Pfizer-BioNTech and Moderna) or DNA-based using adenovirus carriers (*i.e.*, AstraZeneca and J&J). In each case, these particular vaccines deliver genetic instructions for the production of the Spike protein of the SARS-CoV-2 virus inside of the host cells that take up these vaccines (initially at the site of the injection in the deltoid muscle region of the arm). The Spike

protein is then presented on the surface of these cells to elicit an inflammatory immune response that culminates in the stimulation and proliferation of T-cells and B-cells, the latter producing antibodies that specifically target epitopes on the Spike protein. However, to produce the activation of T- and B-cells, this necessitates the damage and likely destruction of the Spike-presenting transfected cells. This is particularly problematic for neurons and cardiac muscle cells (cardiomyocytes), which do not regenerate in adults.

109. Lipid nanoparticles and adenoviruses have been used previously to deliver drugs and toxins into animals for therapeutic purposes, and even to elicit immune responses.[123] lipid nanoparticles or genetically engineered adenoviruses normally present the antigen of the pathogen on their surfaces. However, the combination of the lipid nanoparticles to get production of a target pathogen's protein on the surface of the body's own cells to elicit an immune response against that target remains experimental, especially since new information continues to accrue about the unexpected consequences of this novel method of antibody production.

110. In a sense, the genetic vaccines are "pro-drugs", which require further processing to produce active ingredients. Unfortunately, the production of the Spike protein is very host cell-dependent, and this processing is influenced by many different factors, including vaccine dose to body size ratio, cell type taking up the vaccine, health, nutritional, hormonal, and pharmacological status.[124] Consequently, the levels of Spike protein could potentially vary by up to two orders of magnitude (*i.e.,* 100-fold) or more. This can lead to marked variations in vaccine efficacy and injury from person to person.

111. Prior to the approvals of these vaccine formulations for human use by the US FDA and Health Canada at the end of 2020, no such lipid nanoparticles or adenoviruses had ever been approved for any RNA- or DNA-based vaccine to produce immunity against a pathogen's proteins by specifying their production within the body's own cells. It should be noted that the European Medicines Agency did approve Zabdeno, an adenovirus-based vaccine for prevention of Ebola virus disease, under Emergency

[123] Dolgin, E. (2021) The tangled history of mRNA vaccines. Nature. 597(7876):318-–324. doi:10.1038/d41586-021-02483-w

[124] Gutchi, L., Speicher, D.J., Natsheh, S., Oldfield, P., Britz-McKibbon, P., *et al.* (2022) An independent analysis of the manufacturing and quality issues of the BNT162b BioNtech/Pfizer quasi-vaccine based on the European Medicines Agency's Public Assessment Report (EPAR). Canadian Covid Care Alliance. Retrieved from https://www.canadiancovidcarealliance.org/wp-content/uploads/2022/11/22OC29_EMA-Analysis-of-BNT162b-Manufacture.pdf

Use Authorization in 2020. However, this vaccine was only about 50% effective in tested animals, and its efficacy in humans still remains to be determined in a formal clinical trial, since ethically it would be wrong to test such vaccines in healthy volunteers with such a high failure rate in animal trials.[125] Zabdeno was not marketed in Canada or the US.

112. To counteract the COVID-19 pandemic crisis, the four COVID-19 genetic vaccines were first released for general use in the Canadian population starting in mid-December 2020 under an Interim Order. In the US, only three of these vaccines (AstraZeneca's adenovirus vaccine was not approved) were authorized for general use through Emergency Use Authorization (EUA). It is noteworthy that EUA approval is normally granted only if there are no alternative treatments for a disease, although technically dexamethasone had already been shown to effectively treat many cases of hospitalized COVID-19 patients that require supplemental oxygen.[126]

113. In Canada, the US and elsewhere, these vaccines were still technically in Phase 3 clinical trials in early 2023. For example, the Pfizer-BioNTech COVID-19 vaccine, which is the most widely used, was in Phase 3 trials that were not scheduled to be completed until July 30, 2023.[127] The approvals provided by Health Canada and the FDA remain contingent on active and passive monitoring of the efficacy and safety of these non-traditional vaccines. Consequently, these COVID-19 vaccines are still regarded by many as highly experimental in nature. The fact that billions of people have been inoculated with these vaccines does not mean that they are not still experimental as their efficacy and safety remain topics of intense biomedical research, which will be evident later starting in Section 2.7.

114. The testing of drugs and vaccines by manufacturers normally requires pre-clinical trials in at least two different animal models to provide initial efficacy and safety data. Phase 1 trials are performed on healthy volunteers to evaluate initial safety concerns. Phase 2 trials are then undertaken with the main

[125] (2020) Summary of product characteristics: Zabdeno suspension for injection. European Medicines Agency. Retrieved from https://www.ema.europa.eu/en/documents/product-information/zabdeno-epar-product-information_en.pdf

[126] RECOVERY Collaborative Group; Horby, P., Lim, W.S., Emberson, J.R., Mafham, M., Bell, J.L., *et al.* (2021) Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 384(8):693–704. doi:10.1056/NEJMoa2021436

[127] (2021) Pfizer-BioNTech COVID-19 BNT162b2 Vaccine effectiveness study – Kaiser Permanente Southern California. U.S. National Library of Medicine. Retrieved from https://clinicaltrials.gov/ct2/show/NCT04848584

targeted participants (*i.e.,* those most vulnerable to a disease) with different concentrations of the drug or vaccine to establish an optimum dose to elicit a desired therapeutic or immune response as appropriate. Phase 3 trials are subsequently conducted on usually thousands of targeted participants in multiple centers to investigate the longer-term efficacy and safety of the tested drug or vaccine at the optimal dose.

115. The importance of continuing Phase 3 studies with COVID-19 vaccines has been prompted by several factors, including an unprecedented shortening of the typical testing period (5 to 10 years) of a vaccine before approval for general release to under a single year with "Operation Warp Speed" in the US. This was achieved by reducing the number of many cell and animal preclinical trials with the vaccines that are normally undertaken over 1 to 3 years down to a couple of months and running them in parallel with Phase 1 and 2 human trials. Of particular concern, many of the safety studies were performed in rats or mice, which is problematic, because these rodents do not feature ACE2 receptors that bind to the original Wuhan SARS-CoV-2 Spike protein. Phase 2 and 3 trials, which instead of being conducted over the usual 3 to 5 years, were combined, and based on just 2 months of testing, were approved for dissemination to the general population with an Interim Order in Canada and an Emergency Use Authorization in the US. For example, the Phase 3 clinical studies with the Pfizer-BioNTech vaccine commenced on July 27th, 2020, and the vaccine was approved for general use for those over 18 years of age by early December of 2020. **Ultimately, these novel genetic vaccines were approved for wide-spread use in about a tenth of the time as compared to traditional vaccines**.

116. It should be appreciated that the RNA- and adenovirus-based genetic vaccines did not satisfy the US CDC's original definition of a "vaccine," which was previously described as "*a product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.*"[128] Later, on September 1, 2021, the definition of vaccine was simplified to "*a preparation that is used to stimulate the body's immune response against diseases*." The new definition of "*immunity*" was also problematic with "*protection from an infectious disease*." The CDC states that "*If you are*

[128] (2018) Vaccines and Immunizations. Immunizations: The basics. Centers for Disease Control and Prevention. Retrieved from http://web.archive.org/web/20200317214611/https://www.cdc.gov/vaccines/vac-gen/imz-basics.htm

immune to a disease, you can be exposed to it without becoming infected."[129] Obviously, this must be false, because the actual infection with the virus still proceeds, but ideally, the immune system is able to eradicate the virus before it can evoke the symptoms of disease. It is amply clear that one can still become infected with SARS-CoV-2 after vaccination, but the claims were later adjusted to suggest that protection is provided to reduce the severity of the illness, but not necessarily to prevent infection. This means that one can still become infected, and still transmit the pathogen after they are vaccinated for COVID-19.

117. The COVID-19 RNA and adenovirus "vaccines" are more like genetic therapy, because they do not contain the actual immunogen to elicit an antibody response but rather provide genetic instructions for the body to produce the immunogen. Normally, the use of genetic therapy products commands a much higher level of testing than traditional drugs or vaccines. It is also noteworthy that vaccines do not carry the same degree of liability to manufacturers for injury from these products in the US compared with other drugs.[130]

118. As mentioned earlier, all COVID-19 vaccines were approved under Interim Order in Canada, and under Emergency Use Authorization in the US. Most people would be surprised to learn that the efficacy and safety requirements for approval of a medication or device under Interim Order are minimal and contrary to popular belief, even amongst health professionals, vaccines and drugs can be approved with little or even no evidence of efficacy and safety under Interim Order, as stipulated in Section 30.1 of the Food and Drugs Act, R.S.C., 1985, c. F-27.[131] This is apparently what happened with Health Canada's approval of the COVID-19 genetic vaccines starting in December 2020. This does not mean that these experimental COVID-19 vaccines were known to be efficacious and safe at the time of their approval. As noted in lawyer Shawn Buckley's discussion publication:[131]

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[129] (2022) Vaccines and Immunizations. Immunizations: The basics. Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/vaccines/vac-gen/imz-basics.htm? Sourced September 10, 2022.

[130] 42 U.S. Code § 300aa-22 – Standards of responsibility. LII Legal Information Institute. Cornell Law School. Retrieved from https://www.law.cornell.edu/uscode/text/42/300aa-22

[131] Buckley, S. (2023) Changes to the drug approval test for COVID-19 vaccines: Permitted vaccines to be approved without objective proof of (1) safety, (2) efficacy, or (3) the benefits outweighing the risks. Natural Health Products Protection Association. Retrieved from https://nhppa.org/wp-content/uploads/2023/03/NHPPA-Discussion-Paper-COVID-19-Vaccine-Test-March-17-2023.pdf

"For COVID-19 vaccines, there were the following major legal changes to deliberately circumvent the normal protections in our drug approval law:

a) The normal drug approval process requires objective proof of:

i. safety;

ii. efficacy; and

iii. benefit outweighing risk.

COVID-19 vaccines were exempted from this normal drug approval process.

COVID-19 vaccines were approved under a subjective test which mandated that approval must be granted if the argument could be made that the benefits outweighed the risk. No actual proof of safety, efficacy or benefit outweighing risk was required.

b) The law was changed so that the approval of a COVID-19 vaccine could not be revoked:

i. due to evidence the vaccine was unsafe or not-effective;

ii. due to assessments the benefits did not outweigh the risks.

These legal changes were in force from September 16, 2020 to:

i. September 15,2021, for the Pfizer and Moderna vaccines;
ii. November 18, 2021, for the AstraZeneca vaccine; and
iii. November 22, 2021 for the Johnson and Johnson vaccine.

c) A classic conflict of interest was created where the Government was allowed to purchase and import unapproved vaccines while the Government waited for itself to approve the vaccines." [131]

2.6.2. Relative and Absolute Risk Reduction with COVID-19 Vaccines

119. Drugs and vaccines are "normally" expected to undergo a rigorous testing process, first in animals and then in people. This is not what happened with the COVID-19 vaccines. Animal trials, when actually performed, were conducted in parallel with human trials, and the Phase 3 human trials were predominantly carried out on healthy people or those who had only one co-morbidity and were mainly working age adults. Normally, Phase 3 trials are carried out on those that would most benefit from a treatment.

120. Before reviewing the Phase 3 clinical trials with COVID-19 vaccines that were used to justify the Interim Order approval in Canada and equivalent approvals by regulatory agencies in other countries, it is instructive to understand the difference between "relative risk reduction" (RRR) and "absolute risk reduction" (ARR) in monitoring the effectiveness of a medical treatment. The ARR is the absolute difference in rates of an event (*e.g.*, infection) between the experimental group and the control group. It is calculated by subtracting the experimental group event rate (ER) from the control group event rate (CR) and is usually expressed as a percentage. In contrast, the relative risk reduction (RRR), or vaccine efficacy (VE), represents the relative decrease in the risk of an adverse event in the experimental group compared to the control group. It is calculated as the relative risk of the rate of the experimental group (ER) minus the rate of the control group (CR) divided by rate of the control group (CR), and, as with the ARR, is usually expressed as a percentage.

121. To illustrate this, consider a trial with 200 participants (100 allocated to the experimental group and 100 allocated to the control group); if one of the experimental participants becomes ill (rate 1/100 = 0.01), compared with two in the control group (rate 2/100 = 0.02) who become ill, the RRR of the vaccine is 50% (=(0.01-0.02)/0.02) x 100%), a potentially attractive reduction likely to persuade users to accept the treatment. In contrast, the ARR is merely 1% (= (0.02 – 0.01) x 100%), which means that most of the individuals who did not take the 'vaccine' are still likely to remain free from the "disease" 98% of the time, as opposed to 99% of the time if they took the vaccine. This may give pause to patients and health professionals when considering the desirability of accepting a new treatment, especially considering the scant safety data.[132] Of note, while the RRR of the first Pfizer-BioNTech Phase 3 trial

[132] Brown, R.B. (2021) Outcome reporting bias in COVID-19 mRNA vaccine clinical trials. Medicina (Mex). 57(3):199. doi:10.3390/medicina57030199

was 95%, the ARR was only 0.8%, which was calculated by independent investigators but not reported in the original peer-reviewed publication (although the raw data was available in the Supplemental section to permit such calculations).[133]

122. Because communicating relative risk can be so misleading, not only to the public but also to health professionals, in a 2011 report entitled "Communicating Risks and Benefits: A User's Guide", the US FDA instructed investigators to "*provide absolute risks, not just relative risks,*" noting (on page 60) that "*Patients are unduly influenced when risk information is presented using a relative risk approach; this can result in suboptimal decisions. Thus, an absolute risk format should be used.*"[134] To put this into perspective, based on the COVID-19 RNA vaccine Phase 3 trial data in a 6-month period (the duration of the clinical study to generate this data), vaccinating everyone in the vaccine group only reduced COVID-19 incidence by less than 1% compared to no vaccination, despite the RRR of 95%.[133] This was because the overall risks of getting symptomatic COVID-19 that was confirmed by PCR testing in the unvaccinated group during the 6-months period was only about 4%.

2.6.3. Distinguishing between the Unvaccinated and Vaccinated in Clinical Studies

123. It should be appreciated that vaccine efficacy estimates that have been published in clinical trial reports of Phase 3 clinical trials with COVID-19 vaccines and highly quoted by public health officials have been RRR and not ARR values. In the Phase 3 clinical trials to ascertain whether the COVID-19 vaccines reduced the actual occurrence of SARS-CoV-2 infection and COVID-19 symptoms, there have been numerous deficiencies in the haste to get these vaccines to market. **These clinical trials did not assess whether the vaccines reduced transmission, severity, hospitalizations, or deaths.** Moreover, they poorly evaluated whether COVID-19 vaccines reduced occurrence of the disease in segments of the population that are at greatest risk, namely the very elderly, obese or those with comorbidities such as diabetes.

[133] Thomas, S.J., Moreira, E.D., Kitchin, N., Absalon, J., Gurtman, A., *et al.* (2021) Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. N Engl J Med. 385:1761–1773. doi:10.1056/NEJMoa2110345

[134] Fischhoff, B., Brewer, N.T., Downs, J.S., eds. (2011) FDA. Communicating risks and benefits: An evidence-based user's guide, 242. Retrieved from https://www.fda.gov/about-fda/reports/communicating-risks-and-benefits-evidence-based-users-guide

124. The preclinical, Phase 1, Phase 2 and Phase 3 trials were all accelerated for these vaccines, and the formal Phase 3 clinical trials never tested end points such as protection from COVID-19-induced death or transmissibility of the virus. Nor were biochemical studies of blood samples performed, such as D-dimer analyses to detect potential blood clotting, C-reactive protein for inflammation, and troponin for heart damage. In the absence of properly matched placebo controls, these deficiencies may not be clear from the post-marketing safety studies of the COVID-19 vaccines following their release to the public. Instead, the post-marketing, Phase 4 studies were relied upon to learn more about the benefits, limitations, and risks of the COVID-19 vaccines, for example, on pregnancy outcomes. For all intents and purposes, these novel RNA and adenovirus vaccines remained "experimental" after their approvals. Ironically, as data accumulate regarding their clinical outcomes, regulations governing their use are constantly being refined. As highlighted in the next few paragraphs, the term "unvaccinated" is very problematic, and can cause significant misrepresentation of the COVID-19 data on public health websites.

125. In consideration of all the epidemiological studies that benchmark the risk reduction of the acquiring COVID-19 with the vaccines relative to "unvaccinated" individuals, irrespective of whether such comparisons are made in the clinical trials or the post-approval release of these vaccines, the following are significant and common issues that must be appreciated:

    a. A higher testing bias by PCR or rapid antigen testing of unvaccinated people occurred, especially since the adoption of vaccine passports, where workplace testing was usually focused, or even restricted to those that were unvaccinated (for example, at the University of British Columbia);

    b. Very frail and elderly people, who are also at greatest risk of requiring hospitalization due to their fragile condition, were often not vaccinated in some places like Quebec for fear of vaccine-induced injury from mounting overly strong immune responses;

    c. The definition of the "vaccinated" included only those who were 2- to 3-weeks after their vaccination (depending on the province in Canada; 3 weeks in British Columbia). Hence, for statistical purposes, patients who were actually vaccinated but developed COVID-19 within the first 2- to 3-weeks post vaccination were categorized as unvaccinated. This is particularly

problematic, because vaccination appeared to initially increase the risk of acquiring COVID-19, especially when this was performed during a wave of COVID-19 cases (see later in para. 127);

d. The over-reporting of hospital cases, intensive care units (ICU) admissions and deaths of individuals with COVID-19 under circumstances where the original hospitalizations were due to other reasons independent of having a SARS-CoV-2 infection, *i.e.,* the individuals had an existing comorbidity or death from other causes but happened to test positive for SARS-CoV-2 at the time of admission or during their stay in hospital. By April, 2022, only 46% of recorded COVID-19 cases in Ontario hospitals had COVID-19 symptoms at the time of admittance. [135] Likewise, in British Columbia by the end of January 2022, only about 40% of all of the COVID-19 cases were symptomatic at admission;[136] and

e. Many of the "vaccinated" and "unvaccinated" cases already had immunity from natural infection with SARS-CoV-2. This was especially evident in children, most of whom were asymptomatic for COVID-19.

126. With respect to Point b above, data from Scotland revealed that at the time of triple vaccination of the elderly, there were increased COVID-19 case numbers in the elderly as shown in a report provide by Public Health Scotland.[137] This was attributed to vaccination "*and the prioritisation of the booster/third dose to the clinically extremely vulnerable at the beginning of the booster programme*." However, as further explained below, due to the extremely high production of Spike protein with each vaccination, the capacity of the highly mobile immune system may be overwhelmed initially with massive appearance of Spike protein on body cells and is unable to also deal with SARS-CoV-2 virus particles that meanwhile enter into the respiratory system. Facing less resistance in the upper airways and lungs by a diverted immune system, these viruses can propagate sufficiently to then produce illness. This is

[135] (2022) Ontario's COVID-19 hospitalizations rise to 1,730, most since mid-February. Canadian Broadcasting Corporation News. Retrieved from https://www.cbc.ca/news/canada/toronto/covid-19-ontario-april-26-2022-hospitalizations-1.6431094

[136] Carrigg, D. (2022) Majority of new COVID-19 hospitalizations in B.C. among people admitted for other reasons. The Vancouver Sun. Retrieved from https://vancouversun.com/news/local-news/majority-of-new-covid-19-hospitalizations-among-people-admitted-for-other-reasons

[137] (2022) Public Health Scotland COVID-19 and Winter Statistical Report. As at 14 February 2020. See Figure 16. Retrieved from https://www.publichealthscotland.scot/media/11916/22-02-16-covid19-winter_publication_report.pdf

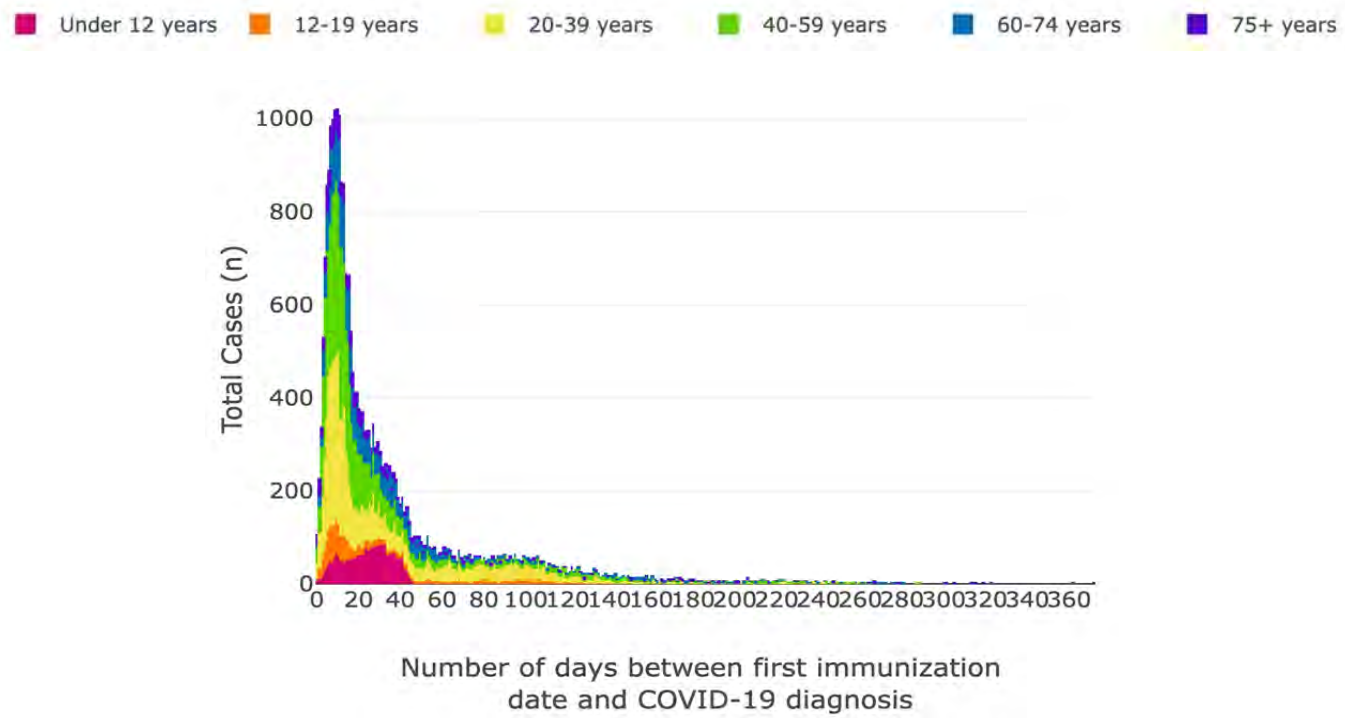
why vaccination during a COVID-19 wave with increased cases is not advised, because it may actually increase the spread of the disease.

127. With respect to Point c above, one of the reasons why the aggregation of COVID-19 cases diagnosed within 2 weeks of injection together with the unvaccinated is very problematic becomes apparent upon the analyses of epidemiological data that was provided by the Alberta Health website.[138] Data in tabular and graphic forms were provided for the occurrence of COVID-19 in vaccinated individuals as a function of time following vaccination that was available between August 11, 2021 and January 11, 2022 on-line. One of these figures (Figure 6 below) showed the timing of COVID-19 infections in people that were vaccinated only once. Note that this data must be recovered using the Way Back Machine website[139] as it was removed on January 11, 2022. This figure revealed a dramatic rise in COVID-19 cases in the first seven days post-inoculation. After about 9 days, the number of COVID-19 cases started to decline. It is clear that vaccination actually increased the chances of getting COVID-19 during the first two weeks. If it did not, then the rate of COVID-19 should have remained unchanged for about a week, and then it should have dropped with the development of immunity. In view of this vaccine-induced increase in COVID-19 cases within the first two weeks of the first vaccination, it is highly inappropriate to include these cases with the unvaccinated cases was routinely done by public health authorities. It renders case counts, hospital admissions, and deaths higher than they should be for the unvaccinated and makes the single vaccinated data look more favorable for vaccine-induced protection from SARS-CoV-2 infection and COVID-19 disease with vaccines. The high levels of Spike production during this initial period places a burden on the immune system that may divert it from an effective response to an actual SARS-CoV-2 infection in the airways. Antibodies and T-cells that could recognize the Spike protein, rather than targeted incoming SARS-CoV-2 virus particles, are instead preoccupied with attacking the vaccinated cells that are actively producing the Spike protein throughout the entire body.

[138] (2022) COVID-19 Alberta statistics. Interactive aggregate data on COVID-19 cases in Alberta. Government of Alberta. Retrieved for January 11, 2022 from https://web.archive.org/web/20220111010547/https://www.alberta.ca/stats/covid-19-alberta-statistics.htm#vaccine-outcomes

[139] (2023) Internet Archive WayBack Machine. The Internet Archive. Retrieved from https://archive.org/web/

Figure 6. Timing of COVID-19 cases in Alberta following first vaccination – January 11, 2022. Reproduced by screenshot from Figure 12 on the Alberta Health website.[138]

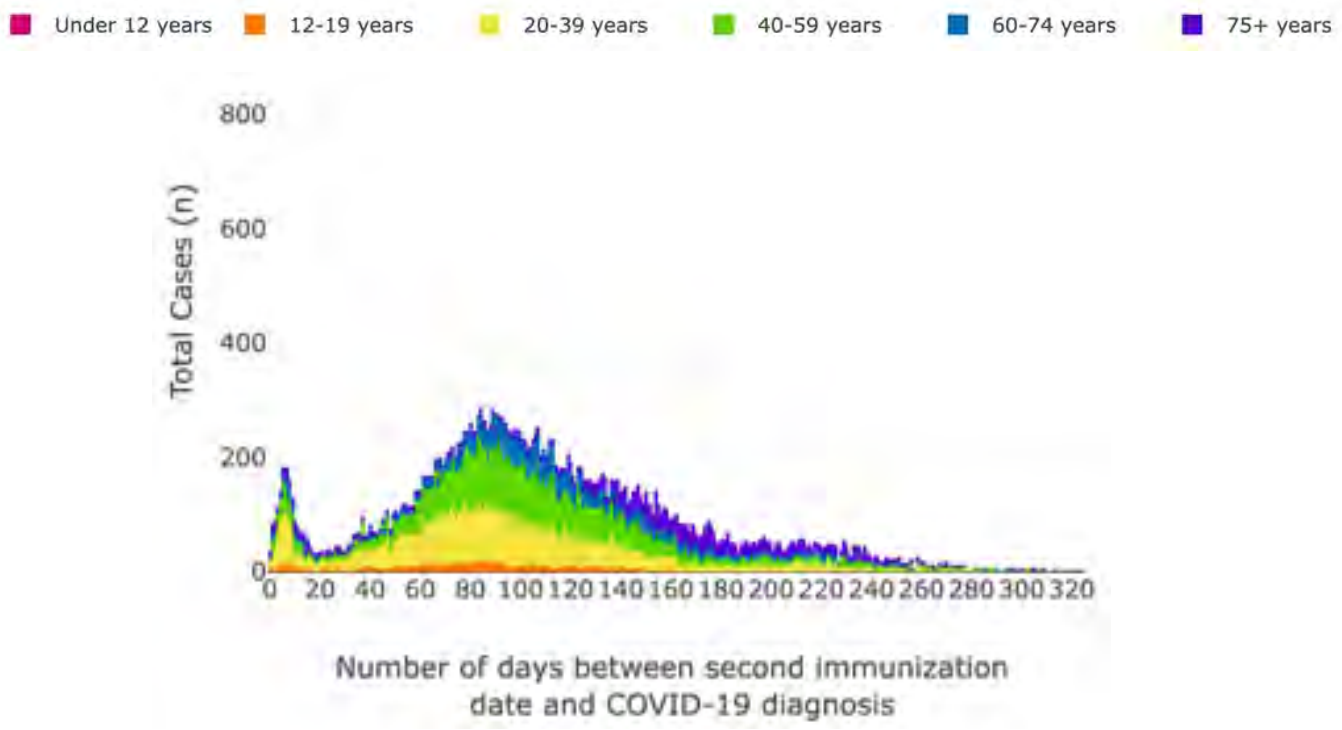


128. An increased risk of getting COVID-19 immediately following a second COVID-19 vaccine inoculation was also evident from the same Alberta Health website (Figure 7).[140] There was also a rise in COVID-19 cases in the first seven days. Considering that these individuals would have been vaccinated typically about 4 weeks to 6 weeks before, and should still have had peak immunity, it was surprising to see an increase in COVID-19 case counts immediately following the second shot. This likely explains why, for some people, the vaccine appeared to increase susceptibility to infection with SARS-CoV-2, which is a phenomenon also consistent with antibody-dependent enhancement (ADE). The data shown on the Alberta Health website indicated that the peak number of the COVID-19 vaccine breakthrough cases up to November 29, 2021 (just prior to the Omicron wave) occurred at around 3 months after the second shot (Figure 7). This indicated that the window of protection offered from COVID-19 by the COVID-19 vaccines for the SARS-CoV-2 Delta variant for many people was only about 3 months rather than the 6 months that was commonly stated by public health authorities. The Alberta Health website

[140] (2022) COVID-19 Alberta statistics. Interactive aggregate data on COVID-19 cases in Alberta. Government of Alberta. Retrieved for November 29, 2021 from https://web.archive.org/web/20211111180117/https://www.alberta.ca/stats/covid-19-alberta-statistics.htm#vaccine-outcomes

was one of the few such public health websites that presented such data, but it was quietly removed in January 2022.

Figure 7. Timing of COVID-19 cases in Alberta following second vaccination – November 29, 2021. Reproduced from Figure 12 on the Alberta Health website.[140] These breakthrough infections correspond to primarily Delta cases and precedes Omicron cases.



2.6.4. The Pfizer-BioNTech BNT162b2 Phase 3 Studies

129. The Pfizer-BioNTech BNT162b2 Phase 3 clinical studies exemplify many of the deficiencies in the general testing of the COVID-19 genetic vaccines. This vaccine was approved under Interim Order in Canada and Emergency Use Authorization in the US after just 2 months of human Phase 3 clinical data had been collected.[141] A 95.1% Relative Risk Reduction amongst the vaccinated cohort (30 µg of Spike RNA in the initial inoculation followed by a second 30 µg of Spike RNA shot 3 weeks later) relative to the unvaccinated participants was reported in the *New England Journal of Medicine (NEJM)*. The clinical trial participants were all 16 years or older, 22% were 65 years or older, but only 4.5% were 75 years

[141] Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., *et al.*; C4591001 Clinical Trial Group. (2020) Safety and efficacy of the BNT162b2 mRNA COVID-19 Vaccine. N Engl J Med. 383(27):2603–2615. doi:10.1056/NEJMoa2034577

or older. Those with more than one co-morbidity were excluded, and only 21% had a co-existing condition. A confirmed COVID-19 diagnosis was based on FDA criteria "*as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was [PCR] positive for SARS-CoV-2...*"[141] There were 8 out of 21,720 vaccinated participants (0.036%) that got symptomatic COVID-19, which was also confirmed by a PCR test, 7 days to 2 months after their vaccination, compared to 162 out of 21,728 unvaccinated participants (0.7456%). This worked out to a ((0.007456-0.00036) x 100% =) 0.71% Absolute Risk Reduction of symptomatic COVID-19 and a Relative Risk Reduction of ((0.007456-0.00036)/0.007456) x 100% =) 95.2%. Following dose 1, but before dose 2, the RRR was 52.4%. In the COVID-19 vaccinated group 1 out of 8 participants (12.5%) had severe COVID-19, compared with 9 out of 162 (5.6%) in the unvaccinated group. The trial did not assess whether the COVID-19 vaccine prevented asymptomatic COVID-19 nor transmission of SARS-CoV-2. In this study, the authors did not observe an increased rate of COVID-19 in the vaccinated group compared to the unvaccinated group in the first 12 days following the first inoculation in October 2020. This contrasts with the Alberta Health data mentioned earlier that was generated from field data that was first posted in August 2021.[138] However, this may have been due to less prevalence of COVID-19 cases in the community during the Pfizer Phase 3 study than what transpired in Alberta nearly a year later.

130. For the 6-months stage of the same clinical Phase 3 study, Thomas *et al.* (2021), updated their clinical findings in *NEJM*, and also included data for 12- to 15-year-olds of age that were vaccinated.[133] There were 81 out of 22,166 vaccinated participants (0.365%) that got symptomatic COVID-19 confirmed by PCR 7 days to 6 months after their vaccination, compared to 873 out of 21,689 unvaccinated participants (4.025%). This worked out to a ((0.04025-0.00365) x 100% =) 3.66% ARR and a 90.7% RRR of symptomatic COVID-19. The incidence of COVID-19 apparently increased in the unvaccinated group from 81 symptomatic cases per month in the first two months of the Phase 3 study to 145.5 cases per month in the next four months of trial. However, in the double-vaccinated group, the number of symptomatic COVID-19 breakthrough cases per month increased from 4 to 20.3 in the first two months compared to the next four months. This indicated a trend toward reduced efficacy of the COVID-19 vaccine over time. Between 4 to 6 months after the second inoculation with the vaccine, the RRR with

the vaccine was reduced to 83.7%. These data indicate that for a portion of the vaccinated participants, there appeared to be an increased risk of getting COVID-19.

131. Some of the issues associated with the Thomas *et al.* (2021) study related to the potentially biased testing of the trial participants, since the study was unblinded to the study subjects and the researchers after 2 months into the Phase 3 trial.[142] This unblinding revealed to both the participants and the researchers who in the trial was actually inoculated and who was not with the BNT162b2 vaccine, which compromised the study and allowed the introduction of bias. The physician researchers in the study decided which participants were to be further tested by PCR to confirm COVID-19 cases. Less than 10% of the trial participants with COVID-19 symptoms were actually tested by PCR. When the suspected and confirmed cases of COVID-19 together were compared in the vaccinated (1,602/22,166 participants) and non-vaccinated (1,978/21,689 participants) populations in the 6-month Pfizer study, the RRR was actually only 19%. One has to wonder what was causing the COVID-19-like symptoms of most of the people in the vaccinated group, since the incidence of RSV and influenza in the general population had plummeted during the same period? Moreover, about 89% of the unvaccinated participants later opted to receive the COVID-19 vaccine, which effectively ended longer term evaluations of safety and efficacy with the experimental vaccines.

132. The 6-months Pfizer-BioNTech clinical study was performed at 153 sites world-wide, with 130 of the testing sites in the US. According to the *British Medical Journal* (*BMJ*), a former regional director Brook Jackson, who worked at one of sites that was operated by the Ventavia Research Group, alleged that "*the company falsified data, unblinded patients, employed inadequately trained vaccinators, and was slow to follow up on adverse events reported in Pfizer's pivotal phase III trial.*"[143] After repeatedly notifying Ventavia of these problems, Ms. Jackson emailed a complaint to the US FDA, and Ventavia fired her later the same day. In August 2021, after granting full approval of the Pfizer-BioNTech vaccine, the FDA reported that it had previously performed inspections at nine of the trial's 153 sites, which

[142] (2021) The Pfizer inoculations for COVID-19: More harm than good. Canadian Covid Care Alliance. https://www.canadiancovidcarealliance.org/wp-content/uploads/2021/12/The-COVID-19-Inoculations-More-Harm-Than-Good-REV-Dec-16-2021.pdf

[143] Thaker, P.D. (2021) COVID-19: Researcher blows the whistle on data integrity issues in Pfizer's vaccine trial. BMJ. 375:n2635. doi:10.1136/bmj.n2635

excluded the three Ventavia sites, but it had not undertaken any new inspections in the 8 months following the FDA's Emergency Use Authorization in December 2020.[143]

133. Following the release of the COVID-19 vaccines to those that were 18 years and older, Pfizer conducted an additional series of Phase 3 studies to permit the marketing of their vaccine to toddlers through to teenagers. This was based on the concept that while these age groups were at extremely low risk of severe COVID-19, they could still acquire SARS-CoV-2 infections and be highly transmissible. These were much smaller sized Phase 3 studies, and their endpoints were primarily to demonstrate that the vaccines successfully boosted anti-Spike antibody levels. Very few of the participants, even in the unvaccinated groups were actually sick with COVID-19. The number of trial participants was clearly insufficient to identify serious safety risks that may have occurred in less than one in a few thousand people.

134. In the first two very small *immune-bridging trials* conducted by Pfizer, fewer than 2,500 participants were enrolled. Each study was designed to establish the presence of effective neutralizing antibody concentrations in the blood of a small subset of 12- to 15-year-olds (n=190) and 5- to 11-year-olds (n=264) children compared to young adults, and provided only preliminary descriptive outcomes for clinical efficacy and safety of the Pfizer-BioNTech vaccine compared to placebo controls.[144, 145] The Phase 2/3 clinical results from testing the Pfizer-BioNTech vaccine in 1,517 children from 5- to 11-year-olds with two vaccine doses (10 µg RNA in each dose) spaced one month apart and followed for 2.3 months was compared to 751 that were treated with a placebo.[145] The mean age of the participants was 8.2 years; 20% of children had coexisting conditions (including 12% with obesity and approximately 8% with asthma), and 9% previously had SARS-CoV-2. The authors reported a RRR of 90.7% for acquiring COVID-19. However, there were only 3 presumed COVID-19 cases in total in the vaccinated group and 16 in the unvaccinated group. None of the COVID-19 cases were severe. The ARR was a mere 2% for both age groups, which were at little to no risk of developing severe COVID-19. Based on this, Health Canada authorized use of Pfizer-BioNTech COVID-19 vaccine in children 12 to 15 years of age on May

[144] Frenck, R.W., Klein, N.P., Kitchin, N., Curtman, A., Absalon, J., *et al.*; C4591001 Clinical Trial Group (2021) Safety, immunogenicity, and efficacy of the BNT162b2 COVID-19 vaccine in adolescents. N Engl J Med. 385(3):239–250. doi:10.1056/NEJMoa2107456

[145] Walter, E.B., Talaat, K.R., Sabharwal, C., Gurtman, A., Lockhart, S., *et al.*; C4591007 Clinical Trial Group (2022) Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med. 386(1):35–46. doi:10.1056/NEJMoa2116298

5, 2021, and this was followed by approval for use of this RNA vaccine (at a third of the adult dosage) for 5- to 11-year-olds on November 19, 2021.[146] Thereafter, Health Canada approved on March 17, 2022, the Moderna Spikevax COVID-19 vaccine (two doses, 50 µg RNA in each dose, four weeks apart) for 6- to 11-year-olds.[147] It should be appreciated that the amount of Spike RNA in Moderna COVID-19 vaccine for this age group of children was 67% higher than the adult dose of Spike RNA in the Pfizer-BioNTech vaccine.

135. On June 15, 2022, the US Food Drug Administration authorized the Pfizer-BioNTech for children 6 months or older,[148] and then similarly authorized the Moderna vaccine on July 14, 2022. In Canada, the Pfizer-BioNTech vaccine for this age group was approved on September 9, 2022, following a review by the National Advisory Committee on Immunization (NACI).[149, 150] Like the earlier Pfizer COVID-19 mRNA vaccination trials in children 5- to 11-year-olds and 12- to 15-year-olds, the studies with 2- to 4-year-olds, and 6- to 23-month-olds were also very small immuno-bridging trials, enrolling fewer than 3,000 participants in each cohort. They were "***not designed to establish the superiority of vaccination compared to naturally acquired immunity,***" but only the non-inferiority of "neutralizing" antibody concentrations in the blood of a small number of 2- to 4-year-olds (*n*=143), and 6- to 23-month-olds (*n*=82) participants compared to children that were 5- to 11-year-olds (*n*=264). Because antibody titers in the blood are not a clinically validated measure of efficacy for mucosal infections of the respiratory tract, any study claims regarding efficacy are actually speculative. Moreover, in these studies,

[146] (2021) Health Canada authorizes use of Comirnaty (the Pfizer-BioNTech COVID-19 vaccine) in children 5 to 11 years of age. Health Canada. Retrieved from https://www.canada.ca/en/health-canada/news/2021/11/health-canada-authorizes-use-of-comirnaty-the-pfizer-biontech-covid-19-vaccine-in-children-5-to-11-years-of-age.html

[147] (2022) Health Canada authorizes use of Moderna Spikevax (50 mcg) COVID-19 vaccine in children 6 to 11 years of age. Health Canada. Retrieved from https://www.canada.ca/en/health-canada/news/2022/03/health-canada-authorizes-use-of-the-moderna-spikevax-50-mcg-covid-19-vaccine-in-children-6-to-11-years-of-age.html

[148] (2022) Vaccines and Related Biological Products Advisory Committee June 14–15, 2022 Meeting Announcement – 06/14/2022. FDA. Retrieved from https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-14-15-2022-meeting-announcement

[149] (2022) National Advisory Committee on Immunization (NACI): Meetings. June 17, 2022. Public Health Agency of Canada. Retrieved from https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/meetings.html

[150] (2023) Drug and vaccine authorizations for COVID-19: List of authorized drugs, vaccines and expanded indications. Health Canada. Retrieved from https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/list-drugs.html#wb-auto-4

assessment of "neutralizing" antibodies only focused on those antibodies that block the binding of the original Wuhan strain of SARS-CoV-2 to the ACE2 protein and entry into test cells. Many of the mutations in the first Omicron variants occurred within the receptor binding domain of the Spike protein (see Exhibit C, Figure 4). Furthermore, over 95% of antibody responses to the SARS-CoV-2 Spike protein in both vaccinated and SARS-CoV-2-infected individuals are directed toward other regions of the Spike protein, and most of the immune protective responses are not captured by "neutralizing" antibody tests (see Exhibit C, Figure 7).

136. From 7 days to 3 months post-vaccination for those under 5 years of age, the aforementioned studies provided descriptive RRR values in symptomatic cases of COVID-19 of 82%, and 76%, respectively, for children aged 2- to 4-years-old and 6- to 23-months-old. Moreover, when outcomes were analyzed to reflect the net benefit of the vaccinations in these groups, the ARR in mild symptomatic COVID-19 was a mere 2% or lower for all groups following COVID-19 vaccination. In addition, the vaccines did not demonstrate an ability to reduce severe COVID-19 or halt transmission, rendering any claims regarding protection in the majority of children dubious. The trial was originally planned to investigate the vaccinal efficacy of two doses. Of great concern, however, were findings in the 2- to 4-year-olds cohort that showed that following the first dose, the vaccine was associated with a 199% relative risk increase in severe COVID-19 and a 149% relative risk increase in multiple COVID-19 infections compared to the placebo control subjects.[151] Astonishingly, the 76% RRR noted for 6- to 23-month-old infants was based on just three participants in this age group who tested positive for SARS-CoV-2 (1 vaccinated versus 2 placebo), and the 82% RRR based on just seven participants in the older 2–to 4-year-olds (2 vaccinated versus 5 placebo) and was only after triple vaccination of these children.

137. The pivotal child vaccination studies were much too short (*i.e.,* 3 months) to establish vaccinal efficacy and did not control for natural immunity. Natural immunity was only assessed by the detection of antibodies against the Nucleocapsid protein of SARS-CoV-2, which often fails to be measurable in people that have recovered from COVID-19. Moreover, the child vaccine trials were designed to test vaccines developed against the original Wuhan strain of SARS-CoV-2, which had not been in circulation for over 2 years. While this probably did not make much difference with respect to the overall immune

[151] Muñoz, F.M., Sher, L.D., Sabharwal, C., Gurtman, A., Xu, X., *et al.*; C4591007 Clinical Trial Group. (2023) Evaluation of BNT162b2 COVID-19 vaccine in children younger than 5 years of age. N Engl J Med. 2023 Feb 16;388(7):621–634. doi:10.1056/NEJMoa2211031

response to Omicron variants, this does make a difference if the serological tests narrowly rely on detection of antibodies that are "neutralizing" and just targeted the ACE2 receptor binding domain of the Spike protein.

138. Pregnant women were originally excluded from the earlier Pfizer-BioNTech clinical trials for their monovalent COVID-19 vaccine based on the Wuhan Spike RNA sequence. On February 18th, 2021, Pfizer-BioNTech commenced a 4,000-person Phase 2/3 study to evaluate the efficacy and safety of their vaccine on pregnant women.[152] As of December 2023, there have been no published reports from this specific trial.

2.6.5. Post-Marketing Performance of COVID-19 Vaccines

139. With the rollout of COVID-19 vaccines starting in December 2020, in Canada, the initial priority was to vaccinate hospital workers and those at high risk, in particular the very elderly in nursing homes, indigenous people living on reservations and those with comorbidities. A shortage of COVID-19 vaccine supply in Canada meant that most people had to wait several months after their initial vaccination to receive their second shot. This was much longer than the manufacturers' recommended 3- to 4-week interval, which was used in the Phase 3 clinical studies.

140. The NACI and the Canadian federal government felt that people in Indigenous communities were particularly at risk from COVID-19 and should be prioritized. This had nothing to do with any genetic differences between Indigenous and non-Indigenous people, but was because these communities had fared more poorly in past pandemics and diseases. This decision was largely political.[153] Consequently, Indigenous adults as young as 18 years old were prioritized for vaccination before non-Indigenous 70-year-old people in Canadian provinces like Ontario and British Columbia. A cynical observer might wonder why the First Nations communities would be amongst the first to receive experimental, poorly

[152] (2021) Pfizer and BioNTech commence global clinical trial to evaluate COVID-19 vaccine in pregnant women. Pfizer. Press release retrieved from https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate

[153] DeRoy-Olson, I. (2021) Why Indigenous communities are prioritized for the COVID-19 vaccine. Canadian Broadcasting Corporation Kids News. Retrieved from https://www.cbc.ca/kidsnews/post/watch-why-indigenous-communities-were-prioritized-for-the-covid-19-vaccine

tested vaccines considering the historical experimentation on these populations in North America in the past for much less altruistic reasons.

141. Despite the availability of COVID-19 vaccines for everyone by the summer of 2021, Canada continued to experience successive waves of COVID-19, in part from the emergence of new, more infectious variants of SARS-CoV-2. Much ado was initially expressed from health officials that it was primarily unvaccinated people who were filling the hospitals, ICU's and dying from COVID-19. Often in the late summer of 2021, provincial public health officials would state that "*since the vaccination program began in December 2020, the vast majority of hospital cases and deaths were unvaccinated*." Even US president Joseph Biden famously claimed during a town hall in Cincinnati, Ohio on July 21, 2021 that "*Ten thousand people have recently died; 9,950 of them, thereabouts, are people who hadn't been vaccinated.*"[154] President Biden's comment was based on a July 1, 2021, statement by Dr. Rochelle Walensky, then the director of the US Centers for Disease Control and Prevention, that during the prior six months, 99.5% of COVID-19 deaths occurred in the unvaccinated.[155] The problem with such comments is that the vast majority of COVID-19 deaths in the previous 6 months occurred in the first couple of months of 2021 when most people were unvaccinated. One of the largest waves of COVID-19 deaths spiked in January 2021, with a smaller peak of deaths in April and May of 2021.[156] By April 3, 2021, only 13.3% of Canadians were COVID-19 vaccinated once and 1.9% vaccinated twice. By July 31, 2021, 59.2% of Canadians had been doubly vaccinated and 10.9% vaccinated only once.[157] In July 2021, with the fifth major wave of COVID-19, the number of cases and deaths slowly began to increase rather than decrease as anticipated with vaccination.

142. With the initial COVID-19 vaccinations applied so close to the resurgence of COVID-19 cases in the late Summer and Fall of 2021, these vaccinations were likely very effective temporarily in reducing the

[154] (2021) Joe Biden town hall in Cincinnati: Here's the full CNN transcript. The Enquirer. Retrieved from https://www.cincinnati.com/story/news/politics/2021/07/21/joe-biden-cnn-town-hall-transcript/8051311002/

[155] (2021) Press briefing by White House COVID-19 Response Team and public health officials. The White House. Retrieved from https://www.whitehouse.gov/briefing-room/press-briefings/2021/07/01/press-briefing-by-white-house-covid-19-response-team-and-public-health-officials-43/

[156] (2023) Canada COVID-19 Situation. World Health Organization. Retrieved from https://covid19.who.int/region/amro/country/ca

[157] (2023) COVID-19 vaccination: Vaccination coverage. Government of Canada Health Infobase. Retrieved from https://health-infobase.canada.ca/covid-19/vaccination-coverage/

incidence of COVID-19 hospitalization and deaths during a limited period of 3 to 6 months. However, it soon became apparent that high rates of COVID-19 vaccination in Canada, the US and elsewhere did not prevent an individual from getting COVID-19 or transmitting SARS-CoV-2 if they did become infected. Eventually, real world, in-the-field data started to reveal that these COVID-19 vaccines had limited effectiveness. At a time when vaccination should have reduced the incidence of hospitalizations and deaths from COVID-19, these actually increased in Canada and the US when compared to the pre-vaccination period in 2020.

143. The RNA and adenovirus COVID-19 vaccines appeared to be initially effective at inducing a strong immune response and protection from infection by SARS-CoV-2 within the first few months following an initial inoculation and a booster shot a month later. However, they clearly had waning efficacy to lower than 50% relative risk reduction by 6 months after double vaccination. This period of protection continued to decline with further boosting and started to produce negative efficacy in preventing COVID-19.

144. This trend was even evident in 2021. For example, one of the largest studies indicating that the relative effectiveness of COVID-19-injections wanes over time was conducted on more than 780,225 of the US Veteran Health Administration (VA) patients.[158] The study indicated that in a time span of around 9 months from February 1 to October 1, 2021, the ability of COVID-19 vaccines to protect from infection declined - from 86.9% to 43.3% for the Pfizer/BioNTech product, from 89.2% to 58% for the Moderna product, and from 86.4% to 13.1% for the Janssen product. For those aged 65 years and older, the relative risk reduction of COVID-19 vaccines to protect from death was 70.1% for the Pfizer/BioNTech product, 75.5% for the Moderna product, and 52.2% for the Janssen product.[158] It should be appreciated that this was a passive reporting study, and included an elderly population with a high risk of death, and US veterans that have a higher rate of lifetime injury (following combat duty) and co-morbidities than the general population. The poorer performance of these vaccines in the elderly was not surprising. In the original Pfizer/BioNTech 6-month Phase 3 trial with the BNT162b2 mRNA COVID-19 vaccine, only 4% of the trial participants were 75 years of age or older, although 58% of the people at risk from death from COVID-19 were in this age group.[133]

[158] Cohn, B.A., Cirillo, P.M., Murphy, C.C., Krigbaum, N., Wallace, A.W. (2022) SARS-CoV-2 vaccine protection and deaths among US veterans during 2021. Science. 375(6578):331–336. doi:10.1126/science.abm0620

145. With respect to the ability of the COVID-19 vaccines to reduce the acquisition and spread of COVID-19, these vaccines have clearly failed. Early on, one study in Dane County, Wisconsin, with among the highest vaccination rates in the US at the time, indicated equally high viral loads in the vaccinated (84%) and the unvaccinated (83%) – in other words, an equal capacity of both to spread infection.[159] It is now widely accepted that COVID-19 double-vaccinated individuals can still become infected with SARS-CoV-2, develop sickness and can transmit the virus with equal viral loads as unvaccinated individuals.[160] This has been clearly expressed by Dr. Anthony Fauci, who was until the end of 2022, the Director of the US NIH National Institute for Allergy and Infectious Diseases (NIAID).[161]

146. One study also showed that COVID-19 vaccine boosted individuals were more likely to transmit SARS-CoV-2.[162] In this study, one-third of boosted people still carried live, culturable virus at 10 days after the beginning of the infection. This contrasted with unvaccinated people with COVID-19, of whom only 6% of the persons were still contagious at Day 10 of the same study.

147. British Columbia was one of the few provinces in Canada that provided breakdowns for the incidence of COVID-19 hospitalization, ICU admissions and deaths, which was regularly posted on the British Columbia Centre for Disease Control (BCCDC) website. From April to June, 2022, hospitalizations and critical care cases per 100,000 persons were at best 2-fold higher for unvaccinated as compared to double- or triple-vaccinated individuals (Figure 8).[163] Moreover, during this period, the rates of COVID-19-related deaths were fairly comparable in the vaccinated versus the unvaccinated group. This is despite the fact that deaths included all individuals with a COVID-19-positive laboratory result who had died from any cause (COVID-19 or non-COVID-19, as recorded in Vital Statistic, BC Ministry of Health,

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[159] Riemersma, K.K., Haddock, L.A. 3rd, Wilson, N.A., Minor, N., Eickhoff, J., *et al.* (2022) Shedding of infectious SARS-CoV-2 despite vaccination. PLOS Pathog. 18(9):e1010876. doi:10.1371/journal.ppat.1010876

[160] Franco-Paredes, C. (2022) Transmissibility of SARS-CoV-2 among fully vaccinated individuals. Lancet Infect Dis. 22(1):16. doi:10.1016/S1473-3099(21)00768-4

[161] (2021) Dr. Fauci on COVID-19 spread: Vaccinated people who have an ... infection are capable of transmitting. Retrieved from https://www.youtube.com/watch?v=mP9iHyj1uiU

[162] Boucau, J., Marino, C., Regan, J., Uddin, R., Choudhary, M.C., *et al.* (2022) Duration of shedding of culturable virus in SARS-CoV-2 Omicron (BA.1) infection. New Engl. J. Med. 387:275-277. doi:10.1056/NEJMc2202092

[163] (2022) BCCDC COVID-19 Regional Surveillance Dashboard – Archived. BC Centre for Disease Control. Retrieved on April 28, 2022 from http://www.bccdc.ca/health-professionals/data-reports/covid-19-surveillance-dashboard

within 30 days of their first laboratory positive result date). In considering such data, it is important to also recognize the caveats presented earlier (Section 2.6.3). Such comparative data was no longer provided on the BCCDC website after June 23, 2022, likely because such data no longer supported the public health agency narrative. As shown in Figure 9, the data from Quebec was even worse for elderly patients that were hospitalized with a third dose of COVID-19 vaccines.[163a]

Figure 8. Age-standardized hospitalization, critical care and death rates in BC from March 27 to April 23, 2022.[163] Vaccinated persons account for 86 percent of combined Cases, Hospitalizations and Critical Care.

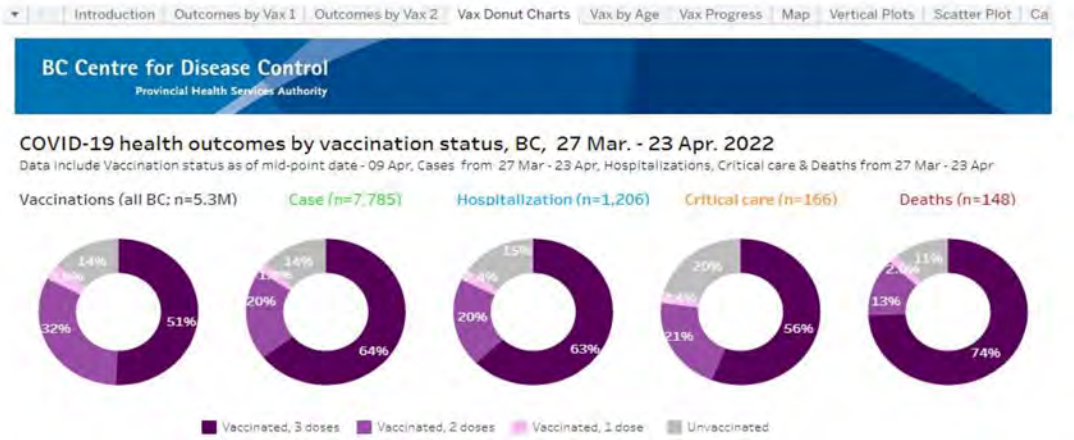
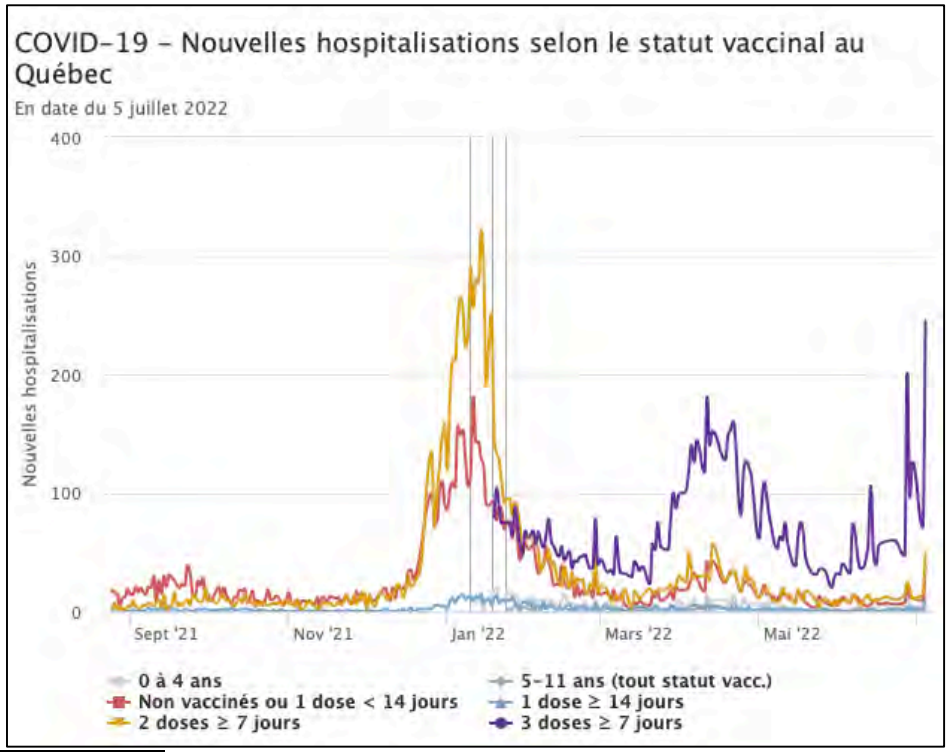


Figure 9. Quebec hospitalization data, showing a higher frequency of hospitalization in boosted patients to July 5, 2022. Retrieved from VaccinTrackerQC.[163a]



[163a] (2022) COVID-19 – Nouvelles hospitalisations selon le statut vaccinal au Quebec. July 5, 2022. Retrieved from https://vaccintrackerqc.ca/cas_et_hospitalisations/#selon-le-statut-vaccinal

148. The phenomena of increased rates of COVID-19 cases numbers, hospitalizations and deaths in vaccinated compared to unvaccinated persons in other countries also become quite apparent in 2022 as different Omicron variants successively predominated over each other. For example, in the March 27, 2022, report of the UK Health Security Agency, using data from the Office of National Statistics, as presented in Table 13 of the report for the period of February 20 to March 13, 2022, the incidence rates of COVID-19 cases were typically 3-fold or greater for those who were at least triple vaccinated than those who were unvaccinated per 100,000 persons.[164] For those who were hospitalized or died with COVID-19, the rates between the at least triple vaccinated and unvaccinated groups for those under 50 years of age was very similar. For those over 50 years of age, there appeared to be a reduction in hospitalizations and deaths of up to 3-fold with 3 or more vaccinations, but it was likely that these individuals were just recently vaccinated and did experience some temporary protection. Interestingly, no data was provided on the COVID-19 cases numbers, hospitalizations or deaths for those who had only one or two doses of a COVID-19 vaccine in Table 13 of the same report. It can be calculated based on the data presented in the earlier Tables 10, 11 and 12 in the same report. In these tables, the numbers of COVID-19 cases, hospitalization and deaths were either higher or comparable in the population over 18 years of age who received only two vaccine doses compared to those that were not vaccinated. A footnote was added to Table 14 of the report that stated "*Comparing case rates among vaccinated and unvaccinated populations should not be used to estimate vaccine effectiveness against COVID-19 infection*."[165] However, such data was quick to be used when it appeared to support COVID-19 vaccination earlier on. The surveillance reports stopped providing this information after March 2022. Collection of such information after April 1, 2022, became limited as free COVID-19 testing was suspended by the UK government. It would seem that the epidemiology data no longer supported the UK Health Security Agency narrative of COVID-19 vaccine efficacy and was no longer presented.

[164] (2022) COVID-19 vaccine surveillance report. Week 11. UK Health Security Agency. https://assets.publishing.service.gov.uk/media/623310c88fa8f504a316aa21/Vaccine_surveillance_report_-_week_11.pdf

[165] (2023) UKHSA vaccine efficacy data stopped after new footnote added. Jikkyleaks on Twitter. Retrieved from https://twitter.com/Jikkyleaks/status/1675005411014107136

149. Careful analysis of studies claiming vaccine efficacy against hospitalization and death from COVID-19 have indicated that they are systemically flawed and biased.[166] Responses to FOIs requesting hospitalization rated by vaccination status data inevitably reveal disproportionately higher rates among the vaccinated. For example, Public Health Wales confirmed that in the first two weeks of October 2021, 2.5% of hospitalized patients aged 60+ were unvaccinated compared with 96% that were double vaccinated.[167] This would be during the period in which the delta variant of SARS-CoV-2 predominated, prior to prevalence of Omicron variants. Consequently, reduced immune recognition of Omicron variants does not explain why so many COVID-19 vaccinated people were hospitalized.

150. Large scale studies of COVID-19 vaccination in children have shown extremely poor efficacy for the RNA vaccines. In one study of 74,208 children and adolescents aged 5 to 11 years at 6,897 sites across the US, the estimated vaccine effectiveness (VE) to reduce COVID-19 incidence was only 60.1% one month after the second dose and 28.9% after two months.[168]

151. In another study conducted in New York State with 365,502 fully vaccinated children 5- to 11-years-old after the emergence of Omicron BA.1, VE was only 12% after 5 weeks after inoculation.[169]

2.6.6. Keeping up with "Variants of Concern"

152. It has been commonly suggested that inoculation with COVID-19 vaccines based on the structure of the original Wuhan strain of SARS-CoV-2 renders the antibodies that are produced much less effective against the Omicron variants. This appears to be incorrect based on several points:

    a. The overall difference in amino acid structure between the Spike proteins of the Wuhan and Omicron strains is only 3% (*i.e.,* ~34 mutated amino acids out of 1273 amino acids in the whole

[166] Fenton, N.E. and Neil, M. (2023) Claims the unvaccinated were at higher risk of hospitalisation and death were based on deliberately murky record keeping. 2023. Substack. Retrieved from https://wherearethenumbers.substack.com/p/claims-the-unvaccinated-were-at-higher

[167] (2022) COVID hospitalisation rates. Public Health Wales. Retrieved from https://www.gov.wales/atisn16308

[168] Fleming-Dutra, K.E., Britton, A., Shang, N., Derado, G., Link-Gelles, R., *et al.* (2022) Association of prior BNT162b2 COVID-19 vaccination with symptomatic SARS-CoV-2 infection in children and adolescents during Omicron predominance. JAMA. 327(22):2210–2219. doi:10.1001/jama.2022.7493

[169] Dorabawila, V., Hoefer, D., Bauer, U.E., Bassett, M.T., Lutterloh, E., Rosenberg, E.S. (2022) Effectiveness of the BNT162b2 vaccine among children 5–11 and 12–17 years in New York after the emergence of the Omicron variant. medRxiv (preprint). doi:10.1101/2022.02.25.22271454

protein). Recovered COVID-19 survivors each generate antibodies against scores of different parts of the Spike protein (see Exhibit C, Figure 7);

b. The actual regions that most people tend to make antibodies against the Spike protein are largely distinct from where the Omicron mutations occur (see Exhibit C, Figure 7);

c. The vaccines that are produced with the Wuhan Spike protein RNA are still effective, at least initially for reducing Omicron infections in vaccinated people, so the antibodies that are produced must still recognize the Omicron variants;

d. RNA vaccines that are based on the Omicron Spike protein, when tested in monkeys and other animals, gave no better immune protection against COVID-19 than RNA vaccines based on the Wuhan Spike protein amino acid sequence.[170, 171, 172 , 173] Note that some studies observed a decline in "neutralizing" antibodies that specifically target the ACE2 receptor binding domain of the Spike protein.[53, 54] However, most protective antibodies can still permit the tagging of viruses and bacteria for their efficient recognition by immune cells and the complement system, which leads to their destruction; and

e. The fact that previously infected people get milder symptoms with Omicron variants and are able to more quickly recover from these variants clearly shows the capacity of the immune system of these individuals to recognize and neutralize the Omicron variants.

[170] Gagne, M., Moliva, J.I., Foulds, K.E., Andrew, S.F., Flynn, B.J., *et al.* (2022) mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits comparable B cell expansion, neutralizing antibodies and protection against Omicron. bioRxiv (preprint). doi:10.1101/2022.02.03.479037

[171] Ying, B., Scheaffer, S.M., Whitener, B., Liang, C-Y., Dymtrenko, O., *et al.* (2022) Boosting with Omicron-matched or historical mRNA vaccines increases neutralizing antibody responses and protection against B.1.1.529 infection in mice. bioRxiv (preprint). doi:10.1101/2022.02.07.479419

[172] Hawman, D.W., Meade-White, K., Clancy, C., Archer, J., Hinkley, T., *et al.* (2022) Replicating RNA platform enables rapid response to the SARS-CoV-2 Omicron variant and elicits enhanced protection in naïve hamsters compared to ancestral vaccine. bioRxiv (preprint). doi:10.1101/2022.01.31.478520

[173] Lee, I.-J., Sun, C.-P., Wu, P.-Y., Lan, Y.-H., Wang, I.-H., *et al.* (2022) Omicron-specific mRNA vaccine induced potent neutralizing antibody against Omicron but not other SARS-CoV-2 variants. bioRxiv (preprint). doi:10.1101/2022.01.31.478406

153. In a large study with the Moderna mRNA-1273 COVID-19 vaccine, the relative risk reduction (*i.e.,* VE) of booster shots against Omicron variants was assessed.[174] The study included 30,809 SARS-CoV-2-positive and 92,427 SARS-CoV-2-negative individuals aged 18-years and older, tested during the January 1 to June 30, 2022 period. While three-dose VE against BA.1 infection was high and waned slowly, VE against BA.2, BA.2.12.1, BA.4, and BA.5 infection was initially moderate to high (61.0%-90.6% 14-30 days post third dose) and waned rapidly. The four-dose VE's against infection with BA.2, BA.2.12.1, and BA.4 ranged between 64.3%-75.7%, was low (30.8%) against BA.5 14-30 days post fourth dose, and was lost beyond 90-days for all subvariants. The three-dose VE's against hospitalization for BA.1, BA.2, and BA.4/BA.5 was 97.5%, 82.0%, and 72.4%, respectively; four-dose VE against hospitalization for BA.4/BA.5 was 88.5%. In analyses of three-dose VE (versus unvaccinated) against infection with Omicron subvariants by time since vaccination, the three-dose VE's against BA.1 ranged from 85.8% in the 14–30 days after the third dose to 54.9% greater than 150 days after the third dose. VE's for these two different time intervals, respectively, were 61.0% and −24.9% for BA.2, 82.7% and −26.8% for BA.2.12.1; 72.6% and −16.4% for BA.4; and 90.6% and −17.9% for BA.5. Thus, there was a clear trend to negative efficacy by 5 months after the third dose for the various Omicron variants that followed BA.1.

154. With the predominance of Omicron variants of SARS-CoV-2 in late 2021, there was a large number of breakthrough cases of COVID-19 in those who were double-vaccinated, which exceeded the total numbers of unvaccinated persons with COVID-19. To offset the relative loss of efficacy of the original COVID-19 vaccines with the Omicron variants, new bivalent COVID-19 vaccines were tested in clinical studies that use a combination of mRNA for the original Wuhan Spike protein and the Omicron BA.1 variant Spike protein.[175] This was despite the fact that the Wuhan SARS-CoV-2 virus and even the Omicron BA.1 variant were already supplanted by the Omicron BA.4 and BA.5 variants. On August 31, 2022, bivalent COVID-19 vaccines from Moderna and Pfizer/BioNTech that include mRNA for the Wuhan Spike protein and a variant that features the mutations in the BA.4 and BA.5 lineages of Omicron were

[174] Tseng, H.F., Ackerson, B.K., Bruxvoort, K.J., Sy, L.S., Tubert, J.E., *et al.* (2023) Effectiveness of mRNA-1273 vaccination against SARS-CoV-2 omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, and BA.5. Nat Commun. 14(1):189. doi:10.1038/s41467-023-35815-7

[175] Chalkias, S., Harper, C., Vrbicky, K., Walsh, S.R., Essink, B., *et al.* (2022) A bivalent omicron-containing booster vaccine against COVID-19. New Eng. J. Med. 387(14):1279–1291. doi:10.1056/NEJMoa2208343

approved by the FDA based only on pre-clinical studies in mice.[176] At the same time, monovalent vaccines based on the original Wuhan Spike protein were no longer authorized as booster doses for individuals 12 years or age and older. It is noteworthy that the Pfizer bivalent COVID-19 vaccine was approved based on studies with only 8 mice for their efficacy in producing "neutralizing" antibodies that blocked Omicron BA.4 and BA.5 Spike protein binding to ACE2.[177] From a safety standpoint, the Wuhan SARS-CoV-2 Spike protein is not capable of binding to mouse or rat ACE2, so evaluation of Spike protein toxicity was highly compromised in these animal models.[178] Data from no other animal model or humans was presented to the FDA by these manufactures for these particular bivalent vaccines prior to their approval.[177]

155. More recent studies have continued to reveal negative efficacy associated with the booster vaccines. From COVID-19 surveillance data from January to July 2023 across 33 California state prisons, primarily a male population of 96,201 individuals, the incidence rate of new COVID-19 infections among COVID-19-bivalent-vaccinated and entirely unvaccinated groups (those not having received either the bivalent or monovalent vaccine) was compared.[179] The authors noted the infection rates in the bivalent-vaccinated and entirely unvaccinated groups were 3.24% and 2.72%, respectively, with an absolute risk difference of only 0.52%. Among those aged 65 years and above, the infection rates were 6.45% and 4.5%, respectively, with an absolute risk difference of 1.95%. The bivalent-vaccinated group had a slightly but statistically significantly higher infection rate than the unvaccinated group in the statewide category and for those aged 50 years and above.[179]

156. One of the most devastating studies that challenged the wisdom of booster COVID-19 vaccines for reducing COVID-19 was performed on 51,017 employees of the Cleveland Clinic who were tracked for

[176] (2022) Coronavirus (COVID-19) update: FDA authorizes Moderna, Pfizer-BioNTech bivalent COVID-19 vaccines for use as booster dose. US Food and Drug Administration. Retrieved from https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-pfizer-biontech-bivalent-covid-19-vaccines-use

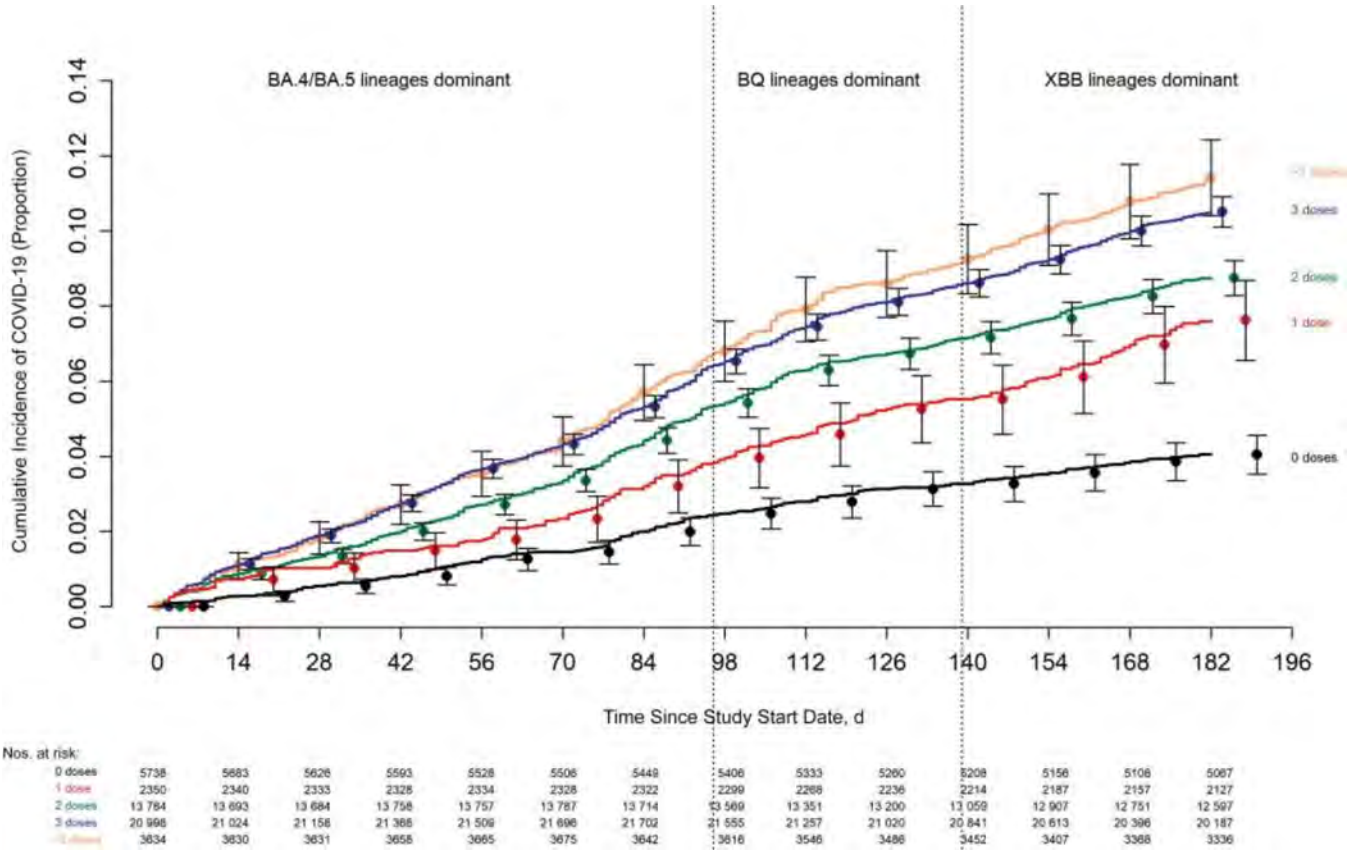
[177] Vogel, G. (2022) Omicron booster shots are coming – with lots of questions. Science. 377(6610):1029–1030. doi:10.1126/science.ade6580

[178] Rawle, D.J., Le, T.T., Dumenil, T., Yan, K., Tang, B., *et al.* (2022) ACE2-lentiviral transduction enables mouse SARS-CoV-2 infection and mapping of receptor interactions. PLOS Pathog. 17(7):e1009723. doi:10.1371/journal.ppat.1009723

[179] Ko, L., Malet, G., Chang, L.L., Nguyen, H., Mayes, R. (2023) COVID-19 infection rates in vaccinated and unvaccinated inmates: A retrospective cohort study. Cureus. 15(9):e44684. doi:10.7759/cureus.44684

VE of the bivalent COVID-19 vaccines over a 6-months period that started September 12, 2022.[180] The bivalent-vaccines were associated with a VE of 29% of COVID-19 during the BA.4/5-dominant phase, a VE of 20% in the BQ-dominant phase, and a VE of 4% during the XBB-dominant phase. What was particularly striking from the study was that the risk of getting COVID-19 increased successively with each vaccination up to four COVID-19 vaccine doses, with the lowest risk for COVID-19 by far in the unvaccinated employees (Figure 10).

Figure 10. Cumulative incidence of COVID-19 cases for Cleveland Clinic study participants stratified by the number of COVID-19 vaccine doses previously received. Day 0 was September 12, 2022, the date the bivalent vaccine was first offered to Cleveland Clinic employees. Point estimates and 95% confidence intervals are jittered along the x-axis to improve visibility. Reproduced from Figure 2 of Shreshtha *et al.* (2023).[180]



[180] Shrestha, N.K., Burke, P.C., Nowacki, A.S., Simon J.F., Hagen, A., Gordon, S.M. (2023) Effectiveness of the coronavirus disease 2019 bivalent vaccine. Open Forum Infect Dis. 10(6):ofad209. doi:10.1093/ofid/ofad209

157. On June 15th, 2023, the US FDA's Vaccines and Related Biological Products Advisory Committee met to discuss their recommendations for the next COVID-19 booster vaccine for Fall of 2023.[181] Presentations from Pfizer, Moderna, Novavax, the NIH and the FDA all documented that the bivalent Wuhan/BA.4/5 vaccines failed to produce neutralizing antibodies that would block the binding of the Spike protein of Omicron XBB variants to ACE2. Ultimately, the Committee recommended that these companies should focus on development of a monovalent vaccine that targeted the Spike protein of the XXB.1.5 variant. The XXB.1.5 variant was largely supplanted by newer variants such as EG.5 by the time the XXB.1.5 Spike protein-based COVID-19 vaccines were launched in September, 2023. With the focus on neutralizing antibodies against the Spike protein by industry and government agencies for assessing the effectiveness of vaccines, this undervalues the actual effectiveness of natural immunity and older COVID-19 vaccines against the earlier SARS-CoV-2 strains to prevent COVID-19 and reduce illness.

158. Collectively, all of these findings seriously call into question the wisdom of vaccination of youth and most working adults considering that they are already at such low risk of hospitalization and death from COVID-19, especially in view of the poor and even negative efficacy of these COVID-19 genetic vaccines, and their potential for vaccine injury in the short and long term. In fact, from a Freedom of Information request in Israel, with a population of 9.4 million, it was determined that only 356 people between ages 18 to 49 died with COVID-19 during the COVID-19 pandemic up to May 29, 2023.[182] Of the 27 people for which full data was available, none of them died from COVID-19, but instead from other comorbidities.

2.6.7. Age Demographic of COVID-19 Cases, Hospital Admissions, ICU Admissions and Deaths in Canada

159. Despite the risk of potentially serious symptoms and complications of COVID-19 including death, many Canadians remained completely asymptomatic following infection with SARS-CoV-2. According to Statistics Canada, by August 2022, 98% of Canadians had antibodies against the SARS-CoV-2 and 54%

[181] (2023) 182nd meeting of Vaccines and Related Biological Products Advisory Committee. June 15, 20123. US Food and Drug Administration. Retrieved from https://www.youtube.com/watch?v=gBOyPREXGh8

[182] Monk, E. (2023) Is it really true that no healthy under 50s died from COVID-19 in Israel? West Country Voices. Retrieved from https://www.westcountryvoices.com/is-it-really-true-that-no-healthy-under-50s-died-from-covid-19-in-israel/

had clear serological evidence of a natural infection with the virus.[183] Moreover, about 41% of adult Canadians and most children following infection developed immunity without any symptoms of COVID-19, *i.e*., they were asymptomatic. Clearly, those in the lower age groups are at much lower risk of hospitalization, ICU admissions and deaths than the elderly. Table 1 provides an assessment of the risks by Health Canada. The actual risks are at least an order of magnitude (*i.e.,* 10-times) lower than these estimates, because Health Canada numbers are based on less than 10% of Canadians recorded as having had COVID-19, whereas, serological testing indicates 50 to 90% of the population have antibodies that support prior infection with SARS-CoV-2. Furthermore, as much as half of recorded hospitalizations, ICU admissions and deaths were from individuals that came to hospital initially for reasons distinct from COVID-19[184, 185] Another issue is that there are 4.2-times fewer ICU admissions than recorded deaths with COVID-19 for those over age 80 years in Table 1. On top of this, the current Omicron variants of SARS-CoV-2 induce less severe clinical disease and are accompanied by lower rates of hospitalizations, ICU admissions and deaths from COVID-19 than seen with the earlier variants.[186] Overall, considering that close to 90% of around 40 million Canadians have had COVID-19 at least once, and 35,079 deaths have been attributed to this disease, its average rate of lethality is close to 1 in 1000, with it being closer to 1 in 100,000 for those from 0 to 25 years of age, and 1 in 200 for those over 65 years of age. This is a far cry from the average lethality estimates of COVID-19 that ranged from 1% to 4% from more commonly cited estimates.[187]

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[183] (2023) Between April and August 2022, 98% of Canadians had antibodies against COVID-19 and 54% had antibodies from a previous infection. Statistics Canada. Retrieved from https://www150.statcan.gc.ca/n1/daily-quotidien/230327/dq230327b-eng.htm

[184] Klann, J.G., Strasser, Z.H., Hutch, M.R., Kennedy, C.J., Marwaha, J.S., *et al*.; Consortium for Clinical Characterization of COVID-19 by EHR (4CE). (2022) Distinguishing admissions specifically for COVID-19 from incidental SARS-CoV-2 admissions: National retrospective electronic health record study. J Med Internet Res. 24(5):e37931. doi:10.2196/37931

[185] Carrigg, D. (2022) Majority of new COVID-19 hospitalizations in B.C. among people admitted for other reasons. The Vancouver Sun. Retrieved from https://vancouversun.com/news/local-news/majority-of-new-covid-19-hospitalizations-among-people-admitted-for-other-reasons

[186] Lewnard, J.A., Hong, V.X., Patel, M.M., Kahn, R., Lipsitch, M. Tartof, S.Y. (2022) Clinical outcomes associated with SARS-CoV-2 Omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in southern California. Nat Med. 28(9):1933–1943. doi:10.1038/s41591-022-01887-z

[187] (2023) Mortality Analysis. John Hopkins University of Medicine Coronavirus Resource Center. Retrieved from https://coronavirus.jhu.edu/data/mortality

Table 1. Cumulative risks of COVID-19 cases, hospitalizations, ICU admissions and deaths by age in Canada since the start of the COVID-19 pandemic to September 6, 2023.[188]

Age Group (Years)	Cases	Hospitali-zations	Hospitali-zations %	ICU Admissions	ICU Admissions %	Deaths	Deaths %
0-11	420,604	7,358	1.75	759	0.18	47	0.011
12-19	329,710	2,733	0.83	310	0.09	18	0.005
20-29	750,597	9,923	1.32	1,071	0.14	125	0.017
30-39	724,796	14,763	2.04	2,025	0.28	308	0.042
40-49	637,143	15,742	2.47	3,244	0.51	664	0.104
50-59	553,316	25,445	4.6	6,086	1.1	1,744	0.315
60-69	370,316	39,211	10.59	8,905	2.4	4,144	1.119
70-79	258,163	53,823	20.85	8,630	3.34	7,776	3.012
80+	347,257	80,501	23.18	4,860	1.4	20,253	5.832
All groups	4,391,902	249,499	5.68	35,890	0.82	35,079	0.799

2.6.8. Development of Tolerance

160. The apparent reduction in immune recognition following repeated large exposures to an immunogen is a classic response known as development of tolerance. It is the way in which the immune system learns to recognize self and common benign substances in the environment from new and potentially dangerous ones. Repeated booster injections over several years of large amounts of Spike mRNA, for what is essentially a protein that is 97% identical, is a recipe for immune tolerance and can account for the waning efficacy of the COVID-19 vaccines. This likely explains why highly vaccinated individuals can still suffer frequent re-infections. They have essentially damaged their natural immunity against the SARS-CoV-2 virus and potentially other coronaviruses.

161. With initial COVID-19 vaccinations, the primary response is the production of antibodies of the proinflammatory IgG1 and IgG3 classes, which provide immune protection against the SARS-CoV-2 virus. However, especially with more than two COVID-19 inoculations, there is a shift to the production

[188] (2023) COVID-19 epidemiology update: Summary. Health Infobase. Public Health Agency of Canada. Retrieved from https://health-infobase.canada.ca/src/data/Covidlive/epidemiological-summary-of-Covid-19-cases-in-Canada-Canada.ca.pdf

of IgG2 and IgG4 class antibodies, which confer immune tolerance.[189, 190, 191] IgG4 antibody class switching can be induced by excessive antigen concentration and prolonged exposure to an antigen, repeated vaccination, and the type of vaccine used. Elevated IgG4 levels appear to have a protective role through prevention of immune over-activation. IgG4 has a more non-inflammatory character than IgG1 and IgG3, with reduced affinity to most FcγRs and C1q (Figure 3), and much reduced potential for antibody-dependent cellular cytotoxicity (ADCC) and C1q complement-mediated killing of cells that have antigen-antibody complexes on their surfaces. IgG4 antibodies also uniquely undergoes structural changes that render them to be functionally monovalent and unable to form immune complexes. Immunosuppressive drugs been shown to have a minor inhibitory effect on the production of IgG4 antibodies after a third COVID-19 mRNA vaccine inoculation, and the production of interleukins 4 and 13 as well as tumor necrosis factor-alpha were implicated to have roles in IgG4 class switching.[192]

162. The development of tolerance is even more problematic when one considered that most people in B.C., more than a year into the COVID-19 pandemic already had antibodies that could recognize SARS-CoV-2 Spike and its other proteins. When 1600 participants in the Kinexus Bioinformatics COVID-19 Antibody Clinical Study, all of which had COVID-19-like symptoms and tested positive for SARS-CoV-2-directed antibodies, were asked when they first experienced these symptoms, about three-quarters of them reported having them between November 2019 and March 2020 (see Figure 11). This high rate of infection of British Columbians with SARS-CoV-2 very early in the COVID-19 pandemic was also indicated in a peer-reviewed study that was published in the flagship journal of the American Society for Clinical Investigation *JCI Insights*.[1] In this study performed in collaboration with the BC Children's Hospital Research Centre, we reported that in May of 2020, 90% of 276 healthy tested adults had antibodies that recognized the SARS-CoV-2 antibodies using the Kinexus tests as well as an

[189] Uversky, V.N., Redwan, E.M., Makis, W., Rubio-Casillas, A. (2023) IgG4 antibodies induced by repeated vaccination may generate immune tolerance to the SARS-CoV-2 spike protein. Vaccines (Basel). 11(5):991. doi:10.3390/vaccines11050991

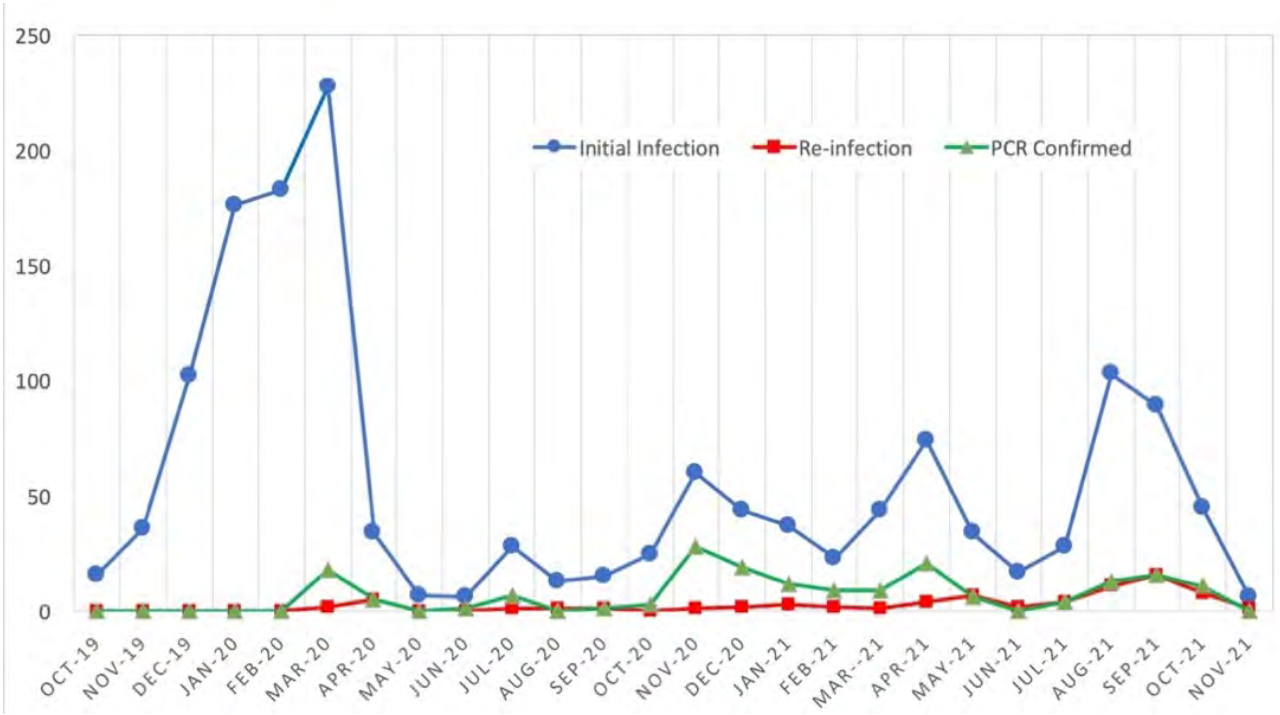
[190] Irrgang, P., Gerling, J., Kocher, K., Lapuente, D., Steininger, P., *et al.* (2023) Class switch toward noninflammatory, spike-specific IgG4 antibodies after repeated SARS-CoV-2 mRNA vaccination. Sci Immunol. 8(79):eade2798. doi:10.1126/sciimmunol.ade2798

[191] Kiszel, P., Sík, P., Miklós, J., Kajdácsi, E., Sinkovits, G., *et al.* (2023) Class switch towards spike protein-specific IgG4 antibodies after SARS-CoV-2 mRNA vaccination depends on prior infection history. Sci Rep. 13(1):13166. doi:10.1038/s41598-023

[192] Valk, A.M., Keijer, J.B.D., van Dam, K.P.J., Stalman, E.W., Wieske, L., *et al.* (2023) Suppressed IgG4 class switching in dupilumab- and TNF inhibitor-treated patients after repeated SARS-CoV-2 mRNA vaccination. medRxiv (preprint). doi:10.1101/2023.09.29.23296354

independent test developed by MesoScale Devices for SARS-CoV-2 antibodies against the Spike and Nucleocapsid proteins.[1] Interestingly, while the British Columbia and other provincial health authorities discounted natural immunity in the issuing of vaccine passports, the BC COVID Therapeutics Committee in their "Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19" stated that "*previous infection alone is equivalent to 2-dose vaccination*."[193] Thus, for most people, when they received their first dose of a COVID-19 vaccine, it was already like a booster dose for the Spike protein antibodies. The original COVID-19 vaccine clinical trials never tested for the effects of the vaccine on people who had already recovered from COVID-19, nor was the efficacy of the vaccine compared to natural immunity in Phase 3 trials.

Figure 11. Number of monthly symptomatic COVID-19 cases reports in the Kinexus SARS-CoV-2 antibody testing study from October 2019 to November 2021. The number of first cases with COVID-19 symptoms each month are shown (circles), including those that were confirmed by PCR (triangles) and apparently with a second bout of COVID-19 (squares).



[193] http://www.bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/ClinicalPracticeGuide_Therapeutics_MildModerateCOVID.pdf

163. The accumulating evidence has shown that the COVID-19 genetic vaccines had limited efficacy, and when used repeatedly, may actually damage the immune response towards negative efficacy. On this basis alone, the continued use of these genetic products must be called into question. In the next section, the safety of these vaccines is further investigated and found to be problematic too. This skews the benefit versus risk ratio for most people with respect to COVID-19 vaccines.

2.7. Safety Studies for COVID-19 Vaccines

164. Ultimately, the decision to approve a drug or vaccine for general use is based on the level of the severity of the disease, and on the safety and effectiveness of the treatment. COVID-19 was a potentially life-threatening disease for especially the elderly and those with multi-comorbidities. As presented in Section 2.5, the production of COVID-19 genetic vaccines had major issues, and in Section 2.6, these products were shown to have fleeting and even negative efficacy. In the following sections, the issue of the safety of these vaccines is given closer scrutiny. The Spike protein produced by the COVID-19 vaccines or SARS-CoV-2 is now well recognized to be pathogenic on its own.[194] Thus, high levels of Spike production in the human body with the vaccines might be expected to have negative consequences *a priori*.

2.7.1. Pre-clinical Safety Studies

165. With COVID-19 mRNA or DNA vaccinations, the genetic information to manufacture the Spike protein of SARS-CoV-2 is initially injected into the deltoid muscle area. From there, the lipid nanoparticle or adenovirus carriers do not remain localized, but instead disseminate throughout the body and may result in Spike production by various tissues and organs. Previous animal studies have highlighted the potential of lipid nanoparticle carriers to widely spread throughout the body, particularly as shown in earlier mice and rat studies with their accumulation in the ovaries.[195] While biodistribution data is lacking for the actual COVID-19 mRNA vaccines in animal and human studies, Pfizer did submit data to regulatory agencies in their bid for approval of their COVID-19 mRNA vaccine BNT162b2. This

[194] Parry, P.I., Lefringhausen, A., Turni, C., Neil, C.J., Cosford, R., *et al.* (2023) "Spikeopathy": COVID-19 spike protein is athogenic, from both virus and vaccine mRNA. Biomedicines11(8):2287. doi:10.3390/biomedicines11082287

[195] Schädlich, A., Hoffmann, S., Mueller, T., Caysa, H., Rose, C., *et al.* (2012) Accumulation of nanocarriers in the ovary: A neglected toxicity risk? J Control Release. 160(1):105–112. doi:10.1016/j.jconrel.2012.02.012

information first came to the attention of the public from translated documents recovered from the Japanese government regulatory bodies through the efforts of Dr. Byram Bridle of the Canadian Citizens Care Alliance.[196] The same data were later evident from Pfizer submissions to the European Medicines Agency (see page 47 of the EMA Assessment report for Comirnaty),[197] and most likely were available to the US FDA and Health Canada. These biodistribution studies (undertaken by the Canadian developer of the lipid nanoparticles Acuitas Therapeutics) performed in rats using lipid nanoparticles with a similar formulation to those used in the Pfizer/BioNTech vaccine demonstrated that they travel practically throughout the entire body, with accumulation in many tissues and organs, especially the liver, spleen, adrenals and ovaries, over the 48-hour study window, after which the experiments were terminated. These lipid nanoparticles also traversed the blood brain barrier.[196]

166. By not performing pharmacokinetic, and distribution studies of the encoded Spike protein, which was already known to be toxic and bioactive (off-target effects), the regulatory submissions of the mRNA vaccines were incomplete. It is also problematic that the rodent studies conducted to evaluate the toxicity of the Spike protein, when it was produced, were compromised by the fact that the Spike protein was based on the structure of Wuhan version, and the receptor binding domain of the original strain of the SARS-CoV-2 poorly interacts with the ACE2 protein in laboratory rats and mice, although later variants of SARS-CoV-2 virus developed the ability to infect these rodents.[198, 199] The Wuhan version of SARS-CoV-2 more readily infects Syrian golden hamsters, so this animal model would have been better suited for earlier testing for toxic effects of Spike protein production from the COVID-19 vaccines.[200]

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[196] (2021) SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048) 2.6.4 薬物動態試験の概要文 (translation: "Summary of pharmacokinetic study"). Retrieved from https://pandemictimeline.com/wp-content/uploads/2021/07/Pfizer-report_Japanese-government.pdf

[197] (2021) Assessment report: Cromirnaty. European Medicines Agency. Retrieved from https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

[198] Yao, W., Ma, D., Wang, H., Tang, X., Du, C., *et al.* (2021) Effect of SARS-CoV-2 spike mutations on animal ACE2 usage and *in vitro* neutralization sensitivity. bioRxiv (preprint). 2021.01.27.428353. doi:10.1101/2021.01.27.428353

[199] Zhang, C., Cui, H., Li, E., Guo, Z., Wang, T., *et al.* (2022) The SARS-CoV-2 B.1.351 variant can transmit in rats but not in mice. Front Immunol. 13:869809. doi:10.3389/fimmu.2022.869809

[200] Rosenke, K., Meade-White, K., Letko, M., Clancy, C., Hansen, F., *et al.* (2020) Defining the Syrian hamster as a highly susceptible preclinical model for SARS-CoV-2 infection. Emerg Microbes Infect. 9(1):2673–2684. doi:10.1080/22221751.2020.1858177

167. It would seem from the very start that the preclinical safety studies were designed to provide data that would put the mRNA COVID-19 vaccines in a "good light." Another critical flaw was that the guidance documents used by Health Canada were only applicable to traditional vaccines, and not vaccines using gene therapy technology.

2.7.2. Clinical Safety Studies

168. For efficiency, the pre-clinical studies on the COVID-19 genetic vaccines were often performed in parallel with human clinical trials. As the Pfizer/BioNTech COVID-19 RNA vaccine was the most widely used of the COVID-19 vaccines in North America and Europe, this section will tend to focus on the BNT162b2 (Comirnaty) product. These initial clinical studies were all undertaken with more purified preparations of this vaccine developed with their Process 1 manufacturing method (see Section 2.5.6). The Phase 3 clinical study with BNT162b2 has been more fully described with respect to efficacy in Section 2.7.4. The initial results after 2 months were published in the *New England Journal of Medicine* (*NEJM*),[201] and this was used to justify the efficacy and safety concerns to the US FDA, Health Canada and other regulatory agencies in countries around the world to permit its conditional approval for those 18 years and older. There were 21,720 people aged 16 years of age or older in the vaccinated cohort, who received two doses of BNT162b2 a month apart, and 21,728 matched participants who were unvaccinated. In the *NEJM* publication, the authors reported that "*the safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.*"[201]

169. For the 6-months stage of the same clinical Phase 3 study, Thomas *et al.* (2021) updated their clinical findings in *NEJM*, which also included data for 12- to 15-year-olds who were vaccinated.[202] The vaccinated participants had 300% more total adverse events and 75% more severe adverse events than observed with the placebo-injected, control participants (considered unvaccinated). The authors noted, '*new adverse events attributable to BNT162b2 that were not previously identified in earlier*

[201] Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., *et al.*; C4591001 Clinical Trial Group. (2020) Safety and efficacy of the BNT162b2 mRNA COVID-19 Vaccine. N Engl J Med. 383(27):2603–2615. doi:10.1056/NEJMoa2034577

[202] Thomas, S.J., Moreira, E.D. Jr, Kitchin, N., Absalon, J., Gurtman, A., *et al.*; C4591001 Clinical Trial Group. (2021) Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. N Engl J Med. 385(19):1761–1773. doi:10.1056/NEJMoa2110345

reports included decreased appetite, lethargy, asthenia [abnormal physical weakness or lack of energy]*, malaise, night sweats, and hyperhidrosis* [excessive sweating not related to heat or exercise]." Around 5% of vaccinated recipients experienced severe adverse events from the inoculations. Moreover, there were more deaths in the vaccinated than in the unvaccinated, control group (21 versus 17 deaths; and 2 of these deaths in the vaccinated group were previously unvaccinated but opted after 2 months to get vaccinated after unblinding of the trial). The vaccine-associated deaths had higher rates of cardiovascular disease including arteriosclerosis, cardiac arrest, congestive heart failure and hypertensive heart disease.[203]

170. A re-analysis of the Pfizer 6-month clinical study with BNT162b2 with respect to the 38 deaths in vaccinated and unvaccinated participants was later performed by an independent group of researchers associated with the *Daily Clout*.[204] In their analysis, they noted:

> *"Surprisingly, a comparison of the number of subject deaths per week during the 33 weeks of this study found no significant difference between the number of deaths in the vaccinated versus placebo arms for the first 20 weeks of the trial, the placebo-controlled portion of the trial. After Week 20, as subjects in the Placebo were unblinded and vaccinated, deaths among this still unvaccinated cohort of this group slowed and eventually plateaued. Deaths in the BNT162b2 vaccinated subjects continued at the same rate. Our analysis revealed inconsistencies between the subject data listed in the 6-Month Interim Report and publications authored by Pfizer/BioNTech trial site administrators. Most importantly, we found evidence of an over 3.7-fold increase in number of deaths due to cardiovascular events in BNT162b2 vaccinated subjects compared to Placebo controls. This significant adverse event signal was not reported by Pfizer/BioNTech."* [204]

[203] Supplement to: Thomas, S.J., Moreira, E.D. Jr, Kitchin, N., Absalon, J., Gurtman, A., *et al.*; C4591001 Clinical Trial Group. (2021) Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. N Engl J Med. 385(19):1761–1773. doi:10.1056/NEJMoa2110345. Retrieved from https://www.nejm.org/doi/suppl/10.1056/NEJMoa2110345/suppl_file/nejmoa2110345_appendix.pdf

[204] Michels, C., Perrier, D., Kunadhasan, J., Clark, E., Gehrett, J., *et al.* (2023) Forensic analysis of the 38 subject deaths in the 6-Month Interim Report of the Pfizer/BioNTech BNT162b2 mRNA Vaccine Clinical Trial. (2023). Int J Vacc Theor Prac Res. 3(1):973–1008. doi:10.56098/ijvtpr.v3i1.85

171. Likewise, in a substack, Drs. Tore Gulbrandsen, Martin Neil and Norman Fenton described anomalous behavior of the mortality data associated with the Pfizer 6-month clinical study with BNT162b.[205] They concluded that *"the only explanation compatible with all the non-random patterns is that the records of vaccine recipients suffering adverse events and death were changed, moving them to the placebo arm after the event."*

172. In another secondary analysis of the 6-month, placebo-controlled, Phase 3 randomized clinical trials of the Pfizer/BioNTech and Moderna mRNA COVID-19 vaccines in adults (NCT04368728 and NCT04470427), the authors calculated an excess risk of serious adverse events (AE) with vaccination of 1 in 990, and 1 in 662 over placebo baselines, respectively.[206] These AE were defined as an adverse event that results in any of the following conditions: death; life-threatening at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; a congenital anomaly/birth defect; or a medically important event, based on medical judgment.

173. In further clinical studies with younger age BNT162b2-vaccinated participants in smaller trials, the studies were too underpowered to pick up adverse events that would occur in less than a thousand participants. However, it is noteworthy that one 13-year-old participant in the 12-15-year-olds BNT162b2 trial conducted at the Cincinnati Children's Hospital, Maddie de Garay, within 24 hours of her second dose of the vaccine experienced severe adverse reactions. As described in an FDA submission by her parents:

> *"She received her first dose on 12/30/2*[0] *and had the expected side effects which were no cause for concern. She got her second dose on 1/20/21 and less than 12 hours later she experienced severe abdominal pain, painful electric shocks on her spine and neck, swollen extremities, ice-cold hands and feet, chest pain, tachycardia, pins and needles in her feet that eventually led to the loss of feeling from her waist down. She had blood in her urine from 7 tests over 3 months, mysterious*

[205] Gulbrandsen, T., Martin, N., Fenton, N. (2023) Anomalous patterns of mortality and morbidity in Pfizer's COVID-19 vaccine trial. Substack. Retrieved from https://wherearethenumbers.substack.com/p/anomalous-patterns-of-mortality-and

[206] Fraiman, J., Erviti, J., Jones, M., Greenland, S., Whelan, P., *et al.* (2022) Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. Vaccine, ISSN 0264-410X. doi:10.1016/j.vaccine.2022.08.036

rashes, peeling feet, reflux, gastroparesis, vomiting, and eventually the inability to swallow liquids or food, dizziness, passing out, convulsions, the inability to sweat, swollen lymph nodes in her armpits, urinary retention, heavy periods with clots of blood, decreased vision, tinnitus, memory loss, mixing up words, extreme fatigue, and sadly more. She spent 64 days in the hospital, had 3 hospital stays, and 9 trips to the ER. We are 9 months into this, we have no real answers."[207]

174. Maddie de Garay was referred to hospital for a full assessment and a doctor diagnosed her with a "functional disorder."[208] As described by Dr. Maryanne Demasi in her substack, "*this doctor decided she had a pre-disposition to hysteria, and she was referred to a mental health facility. Professor and psychiatrist David Healy subsequently conducted a thorough review of her medical records, including an interview with her family, and found no such history of pre-existing conditions or mental illness."* While Maddie de Garay was acknowledged as a participant in a Pfizer Phase 3 study with an adverse event with BNT162b2, her condition was described in an official Pfizer report as merely abdominal pain. However, her case was not mentioned in the *NEJM* publication that published the results of this clinical study.[209]

175. A glaring deficiency in all of the COVID-19 genetic vaccine Phase 3 trials has been the reluctance to perform biochemical tests to actively monitor potential injury from vaccination in all trial participants. For example, there were apparently no blood tests performed such as D-dimer analyses to detect for potential blood clotting, C-reactive protein for inflammation, and troponin for heart damage.

176. On page 27 in section 2.5.3 of Pfizer's Overview of Clinical Overview document, it states: "*Pharmacokinetic studies are not usually required for vaccines. Measurement of the plasma concentration of the vaccine over time is not feasible*."[210] At the time that Pfizer's Nonclinical Overview

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[207] (2021) Docket No. FDA-2021-N-1088 for "Vaccines and Related Biological Products; Notice of Meeting." Retrieved from https://www.regulations.gov/comment/FDA-2021-N-1088-129763

[208] Demasi, M. (2021) Are adverse events in COVID-19 vaccine trials under-reported? Substack. Retrieved from https://maryannedemasi.com/publications/f/are-adverse-events-in-covid-19-vaccine-trials-under-reported

[209] Frenck R.W. Jr, Klein N.P., Kitchin N., Gurtman A., Absalon J., *et al.*; C4591001 Clinical Trial Group. (2021) Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med. 385(3):239–250. doi:10.1056/NEJMoa2107456

[210] (2021) Pfizer, Inc. BLA Submission for BNT162b2 Module 2.4. Clinical Overview. Public Health and Medical Professionals for Transparency Documents. [Online] April 30, 2021. Retrieved from https://phmpt.org/wp-content/uploads/2022/06/STN-125742-0-0-Section-2.5-Clinical-Overview-reissue.pdf

was approved the definition of a vaccine was: "*A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.*" As this product did not meet the definition of a traditional vaccine, the pharmacokinetics of the encoded Spike protein (*i.e.,* the viral antigen) should really have been determined in an ascending dose Phase 1 clinical trial along with the appropriate biomarkers (as mentioned in the previous paragraph) associated with possible vaccine adverse effects. The other advantages for having a full pharmacokinetic profile would be to estimate the variability in levels of Spike protein production between individuals, which so far had not been established, its persistence in the circulation, and its distribution out of the circulation and into tissues, as well as the efficiency of translation from mRNA. Also, adverse effects could then be collated with the Spike protein concentration in the blood. These studies appear to have never been performed.

2.7.3 Post-marketing Safety Studies

177. Further concerns regarding the safety of the Pfizer/BioNTech vaccine were raised by the first release of the Pfizer's originally confidential post marketing pharmacovigilance report to the FDA.[211] On November 17, 2021, the FDA released the first batch of what was predicted to be at least 451,000 pages of documents that they were ordered by a court to provide. This was to satisfy a Freedom of Information request by a group called Public Health and Medical Professionals for Transparency, who wanted access to the data used by the FDA to approve Pfizer/BioNTech's COVID-19 inoculations. The FDA originally asked in court to have 55 years to release the documents, and then calculated it would take 75 years. It makes one wonder how the FDA was originally able to review the vaccine information within a couple of months to provide its continuing approval. With the first release that covered the period of up to February 28, 2021, there were 42,086 cases of adverse events, of which 11,361 (27%) had not recovered and 1,223 deaths recorded (Table 2).[211] In the 9 pages of the appendix of this report, there were over 1,236 different diseases that were potentially linked with the Pfizer/BioNTech COVID-

[211] (2021) 5.3.6 Cumulative analysis of post-authorization adverse event reports of PF-07302048 (BNT162B2) received through 28-FEB-2021. World-wide Safety. Pfizer. Retrieved from https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf

19 vaccine. As of June 18, 2022, Pfizer had records with an accumulation of 4,964,106 total adverse events across 1,485,027 total cases.[212]

Table 2. General overview: Selected characteristics of all cases received during the reporting interval. (From Table 1 of original Pfizer report.[211])

Characteristics		Relevant cases (N=42086)
Gender:	Female	29914
	Male	9182
	No Data	2990
Age range (years): 0.01 -107 years Mean = 50.9 years n = 34952	≤ 17 18-30 31-50 51-64 65-74 ≥ 75 Unknown	175[a] 4953 13886 7884 3098 5214 6876
Case outcome:	Recovered/Recovering	19582
	Recovered with sequelae	520
	Not recovered at the time of report	11361
	Fatal	1223
	Unknown	9400

a. in 46 cases reported age was <16-year-old and in 34 cases <12-year-old.

178. Since late 2022, Dr. Naomi Woolf and her War Room/*DailyClout* research team of over 3000 volunteers have pored through 1,875 Pfizer clinical trial documents (for ages 16 years and older) and have published regular reports on *the Daily Clout* with their findings. Some 89 reports on the Pfizer Reports have been issued on the *Daily Clout* website as of October 16, 2023.[213] Their work has revealed numerous vaccine AE and cover-ups by Pfizer to minimize the extent of these vaccine injuries. The team expects to be reviewing another 101 Pfizer adolescent (ages 12-15 years) clinical trial documents and 46 Moderna clinical trial documents throughout 2024 and 2025 (estimated to be about 4 million pages of documents).

2.7.4. Vaccine Adverse Event Reporting Databases

179. Several government agencies have established public reporting sites for recording adverse events related to specific drugs and vaccines post approval of these products. These websites warn that reports of injury from drugs or vaccines do not necessary infer a causal relationship, as many of the same illnesses can arise from other causes in the general population. Reports of AE and especially death

[212] (2022) Appendix 2.2: Cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources: BNT162B2. Page 1. Retrieved from https://lawyerlisa.substack.com/p/pfizer-data-attached-393-pages-of

[213] (2023) Pfizer reports. Daily Clout. Retrieved from https://dailyclout.io/category/pfizer-reports/

from COVID-19 vaccines are typically described by public health officials '*as very rare, and when such deaths are reported, they do not necessarily mean that the vaccine caused the death*.' However, it is notable that there are more reports of severe injury and deaths from the four COVID-19 vaccines in the last three years in the US FDA Vaccine Adverse Effects Reporting System (VAERS) than in the previous 33 years for all other vaccines combined since VAERS was established in 1990.[214] As of October 27, 2023, there were 2,543,974 AE reports posted on VAERS since its inception, and 1,605,764 (63%) were related to COVID-19 vaccines. Of the total of 46,581 deaths associated with all vaccines in VAERS since its inception, 36,501 (78%) were specifically linked to COVID-19 vaccines. Of the COVID-19-related deaths, 92% occurred between December 2019 and December 2022, and only 8% in the subsequent 9 months, in parallel with the large decline in COVID-19 vaccination in 2023.

180. It should be appreciated that most VAERS reports are made by doctors and other health professionals, and the system is closely monitored for the quality of the reports. Table 3 shows the number of reports filed on VAERS following the release of the COVID-19 vaccines to the public around mid-December 2020.[214] Moreover, these numbers underreport the true extent of AE after injection of the COVID-19 vaccines by an underreporting factor (URF) from 10-times[215] to 41-times.[216] If the number of deaths reported in the US up to November 3, 2023 in VAERS is multiplied by the most conservative URF, this would approximate to over 180,000 deaths in the US from the COVID-19 vaccines. About half of the 1,148,691 deaths with COVID-19 in the US up to October 14, 2023 are thought to actually be from co-morbidities, in part due to Federal government offered strong financial incentives in the US to attribute any death to COVID-19.[217] This really calls into question the benefits of lives saved by COVID-19 vaccination versus injury and deaths from the administration of COVID-19 vaccines.

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[214] (2023) VAERS COVID vaccine adverse events report. Open VAERS. Retrieved from https://www.openvaers.com/covid-data

[215] Lazarus, R., Klompas, M. (2011) Harvard Pilgrim Study – Lazarus Final Report 2011. Adverse Effect. Grant Final Report ID R18 HS 017045. Retrieved from https://www.scribd.com/document/434088983/Lazarus-Final-Report-2011

[216] Kirsch, S., Rose, J., Crawford, M. (2021) Estimating the number of COVID vaccine deaths in America. October 8, 2021 update. Trialsite News. 57. Retrieved from https://www.datascienceassn.org/content/estimating-number-covid-vaccine-deaths-america-updated-october-8-2021

[217] (2023) COVID data tracker. Centers for Disease Control and Prevention. Retrieved from https://covid.cdc.gov/covid-data-tracker/#datatracker-home

181. Several other post-hoc passive surveillance systems also track COVID-19 vaccine injury, including the Canada Adverse Events Following Immunization Surveillance System (CAEFISS), the United Kingdom Yellow Card Scheme, the WHO VigiAccess website, and the European Medicines Agency EudraVigilance website. The data in these systems can be difficult to interpret. AE are widely underreported, and those that are filed are vetted with strict criteria.[218] Nevertheless, numerous AE have been attributed to the current COVID-19 vaccines in all of these databases. As of October 30, 2023, reported AE worldwide with COVID-19 vaccines had surpassed 5.2 million in the WHO reporting system VigiAccess.[219] Table 4 shows how vaccine injury reports with the COVID-19 genetic vaccines compare with the other most commonly applied vaccines. It is evident that the COVID-19 vaccines have 63-times more reports of vaccine AE since the release of the COVID-19 vaccines than seen for influenza vaccines during the same period, which are also widely used. This clearly shows that the COVID-19 genetic vaccines incur more adverse vaccine injuries than reported from any of the traditional vaccines in the past.

Table 3. Number of files reports in VAERS related to COVID-19 vaccinations world-wide and in the US from December 2020 to November 3, 2023. Data was recovered from Open VAERS.[214]

	Mar. 5, 2021	Dec. 31, 2021	Dec. 30, 2022	Nov. 3, 2023		Nov. 3, 2023; US only
Adverse Reports	31,079	1,016,999	1,494,382	1,615,020		997,917
Hospitalizations	3,477	113,303	188,270	212,294		88,472
Urgent Care	5,806	110,785	143,153	153,281		117,818
Deaths	1,524	21,382	33,469	36,726		18,382
Anaphylaxis	292	8,765	10,315	10,706		2,471
Bell's Palsy	367	12,765	16,572	17,575		6,294
Thrombocytopenia /Low Platelet	103	5,102	8,386	9,008		3,612
Heart Attacks	332	10,863	18,115	21,155		9,171
Myocarditis/ Myopericarditis	NA	23,713	26,096	27,832		5,095
Severe Allergic Reaction	1,917	36,955	41,955	46,529		36,380
Miscarriages	66	3,511	4,643	5,071		2,045
Life Threatening	NA	24,344	35,788	38,959		14,834
Permanently Disabled	NA	36,758	61,764	68,819		17,647

[218] Di Pasquale. A., Bonanni, P., Garçon, N., Stanberry, L.R., El-Hodhod, M., Tavares Da Silva, F. (2016) Vaccine safety evaluation: Practical aspects in assessing benefits and risks. Vaccine. 34(52):6672–6680. doi:10.1016/j.vaccine.2016.10.039

[219] (2022) VigiAccess – WHO collaborating center for international drug monitoring. World Health Organization. Retrieved from http://vigiaccess.org/

Table 4. VigiAccess listing of vaccine adverse events (AE) associated with the most commonly used vaccines. Sourced on October 30, 2023 and search with "Comirnaty" for COVID-19 and other terms shown in the first column.[219]

Disease Targeted	Number of Total Adverse Events	Since First Year of Reporting	Number of Adverse Events since 2021	Rate Compared to Diphtheria since 2021
COVID-19	5,202,729	2021	5,202,729	32,929X
Influenza	314,501	1968	82,007	519X
Polio	136,363	1882	25,881	164X
Hepatitis B	111,791	1985	11,406	72X
BCG for TB	40,179	1973	6,675	42X
Tetanus	16,513	1968	2,316	15X
Measles	7,973	1968	2,351	15X
Diphtheria	1,965	1979	158	1X

182. Despite the high levels of COVID-19 vaccine injuries that have been reported with the VAERS, VigiAccess, EudraVigilance and the UK YellowCard vaccine injury reporting systems, relatively few adverse events reports are posted for the COVID-19 vaccines in Canada's CAEFISS.[220] This is likely due to the long time it takes (over 20 minutes) for a doctor or nurse to file a vaccine injury report to local public health units, the strict criteria applied to local acceptance of an injury report with significant rejection rates, and the further scrutiny subsequently applied at the level of the Public Health Agency of Canada, which manages the CAEFISS Database. Only recently have patients been able to report their own injuries. In addition to Dr. Hoffe, physicians have been reprimanded by professional colleges for filing COVID-19 vaccine injury reports, such as exemplified in disciplinary proceedings that were taken by the Ontario College of Physicians and Surgeons against Dr. Patrick Phillips.[221] Dr. Phillips submitted 6 COVID-19 vaccine injury reports to CAEFISS, and all but one were rejected, with his patients being advised to get further vaccinations for COVID-19.

[220] (2023) Reported side effects following COVID-19 vaccination in Canada. Public Health Canada. Retrieved from https://health-infobase.canada.ca/covid-19/vaccine-safety/

[221] (2023) College of Physicians and Surgeons of Ontario v. Phillips, 2023 ONPSDT 16. Tribunal File No.: 21-023. Ontario Physicians and Surgeons Discipline Tribunal. Retrieved from https://doctors.cpso.on.ca/cpso/getdocument.aspx?flash=check&pdfid=nfDo8bWUK0M%3d&id=109364&doctype=PastFinding

183. About 72.5% of all AE reports to CAEFISS were from women, which is also a phenomenon observed in VAERS, YellowCard and VigiAccess.[222] This has been attributed to differences in health care seeking behavior as well as biological differences between females and males.[220]

184. As of September 10, 2023, there were 57,436 Canadians that reported adverse events on CAEFISS following administration of 99 million COVID-19 vaccine doses, which corresponds to about 6 out of 10,000 people that were vaccinated.[220] Of all of the reports, 11,231 were deemed to be serious. For 9,611,886 bivalent COVID-19 vaccines given to Canadians, there were 975 AE, of which 255 AE were considered serious (3 out of 100,000 vaccinations). Of 455 reports of death associated with the COVID-19 vaccines in Canada, only 4 were deemed to be causally associated with the vaccinations, although there were 166 deaths that were unclassifiable due to insufficient information.[220] It seems that when adjusted for population size, there were nearly double the number of adverse events per capita with COVID-19 vaccines reported in Americans in VAERS than Canadians in CAEFISS, and 4.5-times more deaths per capita.

185. Anaphylaxis was evident in about 1 report for every 100,000 COVID-19 vaccine doses administered in CAEFISS. The two safety signals for COVID-19 vaccines that were acknowledged as confirmed on CAEFISS were thrombosis (blood clotting) with thrombocytopenia syndrome (low platelet count in blood) and myocarditis/myopericarditis.

2.8. COVID-19 Vaccine Effects on Blood

2.8.1. Thrombosis and Thrombocytopenia

186. An increased risk of thrombosis was one of the earlier risks associated with COVID-19 vaccines. This concern was raised when Dr. Charles Hoffe, as a family physician in Lytton, British Columbia found that about 62% of his recently Moderna COVID-19-vaccinated patients had evidence of elevated D-dimer levels, and reported this in an open letter on April 5, 2021, to Dr. Bonnie Henry, the Chief Medical Officer in BC.[223] D-dimer is a breakdown product of blood clots, and Dr. Hoffe thought that these might

[222] Dutta, S., Kaur, R.J., Bhardwaj, P., Sharma, P., Ambwani, S., *et al.* (2021) Adverse events reported from the COVID-19 vaccines: A descriptive study based on the WHO database (VigiBase®). J Appl Pharm Sci. 11(08):001–009. doi:10.7324/JAPS.2021.110801

[223] Shilhavy, B. (2021) Canadian doctor defies gag order and tells the public how Moderna COVID injections killed and permanently disabled indigenous people in his community. Health Impact News. Retrieved

be arising from microclots induced by the COVID-19 vaccines. He also noted that there had been numerous allergic reactions, including two cases of anaphylaxis, three cases of people with "ongoing and disabling" neurological deficits, and what appeared to be a vaccine-related death amongst his practice of about 900 patients of primarily Indigenous background. Elevation of D-dimer levels have since been confirmed in COVID-19 vaccinated individuals (in 9 of 20 published reports), along with thrombosis, thrombocytopenia, elevated anti-platelet factor 4 antibodies, and myocardial infarctions (heart attacks) in a systematic literature review.[224] Thus, Dr. Hoffe's initial concerns of elevated D-dimer levels have been well substantiated in the literature.

187. Due to issues of blood clotting and vaccine-induced immune thrombotic thrombocytopenia (VIIT) following injection with the AstraZeneca COVID-19 adenovirus vaccine Vaxzevria/COVISHIELD, the National Advisory Committee on Immunization (NACI) in Canada recommended a pause for using this vaccine in people under 55 years of age.[225] Ontario Public Health suspended offering the AstraZeneca vaccine on May 11, 2021 out of caution due to the increased risk of blood clots of 1 in 55,000 that were vaccinated,[226] although it continued to be offered in other provinces such as British Columbia. Health Canada never approved AstraZeneca's COVID-19 vaccine for those under 18 years of age, based on continuing increased safety concerns for this age group.[227] Ultimately, Vaxzevria/COVISHIELD along with the Jcovden COVID-19 vaccine (Ad26.COV2.S) from Janssen Inc. were withdrawn from the market in Canada.

188. It should be appreciated that the COVID-19 RNA vaccines have also been linked with elevated D-dimer and VITT as exemplified in cases studies of individuals that were vaccinated with either the

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from https://vaccineimpact.com/2021/canadian-doctor-defies-gag-order-and-tells-the-public-how-the-moderna-covid-injections-killed-and-permanently-disabled-indigenous-people-in-his-community/

[224] Mani, A., Ojha, V. (2022) Thromboembolism after COVID-19 vaccination: A systematic review of such events in 286 patients. Ann Vasc Surg. 84:12–20.e1. doi:10.1016/j.avsg.2022.05.001

[225] Cochrane, D., Tasker, P. (2021) Suspend AstraZeneca use for people under 55, vaccine committee recommends. Canada Broadcasting Corporation News. Retrieved from https://www.cbc.ca/news/politics/astrazeneca-under-55-1.5968128

[226] Draaisma, M. (2021) Ontario will no longer give AstraZeneca COVID-19 vaccine as 1st dose due to blood clot risk. Canada Broadcasting Corporation News. Retrieved from https://www.cbc.ca/news/canada/toronto/ontario-update-astrazeneca-vaccine-1.6022545

[227] (2023) COVID-19 vaccines: Canada immunization guide. Public Health Agency of Canada. Retrieved from https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html

Pfizer/BioNTech or Moderna vaccines for COVID-19.[228, 229] In a systematic review of the literature,[230] Tan *et al.* (2023) reported:

> *"Studies included in this review included 10 cohort studies and 57 case report or case series. A total of over 24,000 thrombotic events have been reported, the majority of which have been associated with adenoviral vector-based vaccine, particularly AstraZeneca (5 in 100,000 up to 6 in 1000), followed by Janssen (8–30 in 1,000,000 doses), Pfizer (6 in 1,000,000 up to 1 in 1000 doses) and Moderna (4 in 10,000,000)."* [230]

2.8.2 Post-mortem Blood Clots

189. With the introduction of the COVID-19 vaccines, there have been a number of morticians that have noted an increased frequency of blood clots during the embalming of cadavers, and in particular white, fibrous, calamari-like clots that are shaped like blood vessels. The Canadian Covid Citizens Alliance interviewed UK funeral director John O'Looney and US embalmer Richard Hirschman about these abnormal blood clots that they commonly found during the embalming process of the deceased.[231] Hirschman presented images of abnormal clots retrieved from deceased individuals. Other embalmers as well as US pathologist Dr. Ryan Cole have also reported a rise in these irregular, hardened blood clots.[232, 233] Their findings have been confirmed in a survey that was prepared by Tom Haviland and Laura Kasner, which was sent to 30 state funeral director/embalmer associations and 800 funeral

[228] Kaimori, R., Nishida, H., Uchida, T., Tamura, M., Kuroki, K., *et al.* (2022) Histopathologically TMA-like distribution of multiple organ thromboses following the initial dose of the BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech): An autopsy case report. Thromb J. 20(1):61. doi:10.1186/s12959-022-00418-7

[229] Bekal, S., Husari, G., Okura, M., Huang, C.A., Bukari, M.S. (2023) Thrombosis development after mRNA COVID-19 vaccine administration: A case series. Cureus15(7):e41371. doi:10.7759/cureus.41371

[230] Tan, L.J., Koh, C.P., Lai, S.K., Poh, W.C., Othman, M.S., Hussin, H. (2022) A systemic review and recommendation for an autopsy approach to death followed the COVID 19 vaccination. Forensic Sci Int. 340:111469. doi:10.1016/j.forsciint.2022.111469

[231] (2023) Morticians speak with the CCCA about abnormal blood clots in the COVID-19 vaccinated deceased. Canadian Covid Care Alliance. Rumble. Retrieved from https://rumble.com/v2au84s-morticians-discuss-abnormal-blood-clots-in-covid-19-vaccinated-patients.html

[232] Horwood, M. (2023) Exclusive: Embalmers speak out on unusual blood clots. The Epoch Times. Retrieved from https://www.theepochtimes.com/world/exclusive-embalmers-speak-out-on-unusual-parasite-blood-clots-5121795

[233] (2022) "Foot-long blood clots" from mRNA, says pathologist Dr. Ryan Cole w/ Dr. Kelly Victory – Ask Dr. Drew. YouTube. Retrieved from https://www.youtube.com/watch?v=2SLp6B_kkRI

homes primarily in the USA to determine if they were seeing unusual blood clots in corpses.[234] From 128 respondents: 68.75% had observed large whitish "fibrous" structures/clots in the corpses embalmed. Traditional "grape jelly" clots were reported by 66.4% of the respondents, especially in 2020, 2021 and 2022. In 2022, about 68.7% of the respondents observed large whitish, "fibrous" structures/clots, with 44% of the respondents finding these in cadavers 20% or more of the time. These clots were primarily found in the neck and legs. At the Canadian NCI Hearings on COVID-19, Laura Jeffrey noted that in her 27 years of experience as a funeral director, she observed these unusual clots starting in the Spring of 2021, and had not seen these before in all of her years in the industry.[235]

190. In view of the frequency and large size of these abnormal blood clots, the question arises why have they not been observed in living people? Surely individuals with such occlusions would be extremely sick and easily diagnosed. It seems more likely that they are a post-mortem artefact that is generated after death by a process involving aggregation of fibrin possibly induced by the SARS-CoV-2 Spike protein.[236, 237, 238, 239] With the termination of blood flow after death and cooling of the body temperature especially with refrigeration, the aggregation of microclots might accumulate over time and the compression of these clots as the embalming fluid is forced in and through the cadaver's circulatory system remains might account for the large size and shape of the clots observed by many morticians.

191. Since the spread of COVID-19 vaccine lipid nanoparticles occurs throughout the body and endothelial cells that line blood vessels are likely to have high Spike protein expression, it is feasible this might

[234] A Midwestern Doctor. (2023) Do the mysterious fibrous clots really exist? The Forgotten Side of Medicine Substack. Retrieved from https://www.midwesterndoctor.com/p/do-the-mysterious-fibrous-clots-really

[235] (2023) Funeral director Laura Jeffery on post-vaccine embalming. Canadian National Citizens Inquiry into COVID-19. Retrieved from https://www.youtube.com/watch?v=kYxUS9YO2rE

[236] Ryu, J.K., Sozmen, E.G., Dixit, K., Montano, M., Matsui, Y., *et al.* (2021) SARS-CoV-2 spike protein induces abnormal inflammatory blood clots neutralized by fibrin immunotherapy. bioRxiv (preprint). doi:10.1101/2021.10.12.464152

[237] Grobbelaar, L.M., Venter, C., Vlok, M., Ngoepe, M., Laubscher, G.J., *et al.* (2021) SARS-CoV-2 spike protein S1 induces fibrin(ogen) resistant to fibrinolysis: Implications for microclot formation in COVID-19. Biosci Rep. 41(8):BSR20210611. doi:10.1042/BSR20210611

[238] Montano, M., Ryu, J.K., Sozmen, E.G., Dixit, K., Matsui, Y., *et al.* (2022) SARS-CoV-2 spike binds fibrinogen-inducing abnormal inflammatory blood clots. Topics Antiviral Medicine. 30(1 SUPPL.):9. Retrieved from https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/pt/covidwho-1880599

[239] Kerr, R., Carroll, H.A. (2023) Long COVID is primarily a spike protein induced thrombotic vasculitis. Research Square. doi:10.21203/rs.3.rs-2939263/v1

contribute to the formation of microclots that in some people could develop into more serious blood clots. More research is required to establish the frequency of the abnormal blood clots identified by several morticians, and the underlying mechanisms that produce them.

2.9.3. Menstrual Cycles and Bleeding

192. Soon after the COVID-19 genetic vaccines were introduced into the general population, there were many anecdotal reports that vaccinated women were experiencing prolonged menstrual cycles and heavier menstrual bleeding, even including in some post-menopausal women.[240] A Facebook group featured over 20,000 testimonials regarding abnormalities in menstrual cycles before it was deleted in an act of censorship. Since then, other organizations such as My Cycle Story have emerged to record such experiences.[241] Initially these claims were largely dismissed by health officials. However, this has been investigated in several prospective studies, almost all of which support the finding of abnormal menstrual periods with COVID-19 vaccination, although to different degrees of severity.

193. In the Pregnancy Study Online (PRESTO) with 1,137 participants from the US and Canada, who were trying to conceive without fertility treatment, it was noted that the women "*had* [a] *1.1 day longer menstrual cycles after receiving the first dose of COVID-19 vaccine and 1.3 day longer cycles after receiving the second dose*."[242] The authors *"did not observe strong associations between COVID-19 vaccination and cycle regularity, bleed length, heaviness of bleed, or menstrual pain*." The participants were followed over 5 menstrual cycles and of the 437 that were vaccinated at least once, 93% of them received a COVID-19 RNA vaccine (60% Pfizer/BioNTech vaccine and 32.9% Moderna vaccine). Another larger US prospective study with 3,959 participants also noted a slight increase in the length of the menstrual cycle, but no change in the duration of the menses period.[243]

[240] Mercola, J. (2022) COVID Jabs impact both male and female fertility. Substack. Retrieved from https://takecontrol.substack.com/p/covid-vaccine-fertility-issues

[241] (2023) My Cycle Story Group. Retrieved from https://mycyclestory.com/

[242] Wesselink, A.K., Lovett, S.M., Weinberg, J., Geller, R.J., Wang, T.R., *et al.* (2023) COVID-19 vaccination and menstrual cycle characteristics: A prospective cohort study. Vaccine. 41(29):4327–4334. doi:10.1016/j.vaccine.2023.06.012

[243] Edelman, A., Boniface, E.R., Benhar, E., Han, L., Matteson, K.A., *et al.* (2022) Association between menstrual cycle length and Coronavirus Disease 2019 (COVID-19) vaccination: A U.S. Cohort. Obstet Gynecol. 139(4):481–489. doi:10.1097/AOG.0000000000004695

194. Another prospective study, the Nurses' Health Study 3, with 3,858 premenopausal American and Canadian female nurses that were not taking hormonal contraceptive medications, similarly found a change to longer menstrual cycles within the first 6 months after COVID-19 vaccination.[244] This was particularly evident among women who took the COVID-19 adenovirus vaccines, and whose cycles were short, long, or irregular before vaccination; by contrast SARS-CoV-2 infection did not produce any changes in menstrual cycle characteristics.

195. The delay in menstrual periods in recently vaccinated women was found to be reduced if they were taking hormonal contraceptive medications. In a study with 1,273 British and French women, and the study authors speculated "*that menstrual changes following vaccination may be mediated by perturbations to ovarian hormones*."[245] In this study, for participants with "progesterone-only contraception," their periods post-vaccination were significantly heavier than usual. Heavier menstrual bleed was also more evident in older women following vaccination.

196. Other studies have also described heavier and/or more prolonged bleeding during menses in women after COVID-19 vaccination. A Norwegian study of 3,972 women between 18 to 30 years of age found that while menstrual disturbances were common regardless of vaccination status, "*increased risks of prolonged bleeding, shorter interval between menstruations, and stronger pain during menstruation were also observed after both doses*" of COVID-19 vaccines.[246] This research group also tracked unexpected vaginal bleeding and COVID-19 vaccination in non-menstruating women both 3 months before and then after SARS-CoV-2 mRNA BNT162b2 vaccination.[247] The authors noted:

> *"Among 7,725 postmenopausal women, 7,148 perimenopausal women, and 7,052 premenopausal women, 3.3, 14.1, and 13.1% experienced unexpected vaginal bleeding during a*

[244] Wang, S., Mortazavi, J., Hart, J.E., Hankins, J.A., Katuska, L.M., *et al.* (2022) A prospective study of the association between SARS-CoV-2 infection and COVID-19 vaccination with changes in usual menstrual cycle characteristics. Am J Obstet Gynecol. 227(5):739.e1-739.e11. doi:10.1016/j.ajog.2022.07.003

[245] Alvergne, A., Woon, E.V., Male, V. (2022) Effect of COVID-19 vaccination on the timing and flow of menstrual periods in two cohorts. Front Reprod Health. 4:952976. doi:10.3389/frph.2022.952976

[246] Trogstad, L., Laake, I., Robertson, A.H., Mjaaland, S., Caspersen, I.H., *et al.* (2023) Heavy bleeding and other menstrual disturbances in young women after COVID-19 vaccination. Vaccine. 41(36):5271–5282. doi:10.1016/j.vaccine.2023.06.088

[247] Blix, K., Laake, I., Juvet, L., Robertson, A.H., Caspersen, I.H., *et al.* (2023) Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. *Science Advances*. 9(38):eadg1391. doi:10.1126/sciadv.adg1391

period of 8 to 9 months, respectively. In postmenopausal women, the risk of unexpected vaginal bleeding (i.e., postmenopausal bleeding) in the 4 weeks after COVID-19 vaccination was increased two- to threefold, compared to a prevaccination period. The corresponding risk of unexpected vaginal bleeding after vaccination was increased three- to fivefold in both nonmenstruating peri- and premenopausal women."[247]

197. Another study included women aged 18-50 years without known gynecologic comorbidities who regularly monitor their menstruation through electronic calendars.[248] A total of 219 women in this study met the inclusion criteria. Of these, 51 (23.3%) experienced irregular bleeding following the vaccine. Almost 40% (n = 83) of study participants reported a menstrual change following vaccination with the BNT162b2 SARS-CoV-2 mRNA vaccine.[248]

198. Likewise, in a cross-sectional European study with 14,153 women, who were double COVID-19 vaccinated at least three months before, 78% of them (many of them older or smokers) reported premenstrual symptoms including "*increased fatigue (43%), abdominal bloating (37%), irritability (29%), sadness (28%), and headaches (28%)*" and the predominant changes were "*more menstrual bleeding (43%), more menstrual pain (41%), delayed menstruation (38%), fewer days of menstrual bleeding (34.5%), and shorter cycle length (32%)*."[249]

199. In a large US study with 39,129 participants who were followed for 3 months after receiving two doses of a COVID-19 vaccine and had not contracted COVID-19, the authors reported:[250]

"42% of people with regular menstrual cycles bled more heavily than usual, while 44% reported no change after being vaccinated. Among respondents who typically do not menstruate, 71% of people on long-acting reversible contraceptives, 39% of people on gender-affirming hormones, and 66% of postmenopausal people reported breakthrough bleeding. We found that

[248] Lessans, N., Rottenstreich, A., Stern, S., Saar, T.D., Porat, S., Dior, U.P. (2023) The effect of BNT162b2 SARS-CoV-2 mRNA vaccine on menstrual cycle symptoms in healthy women. Int J Gynecol Obstet. 160(1):313–318. doi:10.1002/ijgo.14356

[249] Baena-García, L., Aparicio, V.A., Molina-López, A., Aranda, P., Cámara-Roca, L., Ocón-Hernández, O. (2022) Premenstrual and menstrual changes reported after COVID-19 vaccination: The EVA project. Womens Health (Lond). 18:17455057221112237. doi:10.1177/17455057221112237

[250] Lee, K.M.N., Eleanor J., Junkins, E.J., Luo, C., Fatima, U.A., *et al.* (2022) Investigating trends in those who experience menstrual bleeding changes after SARS-CoV-2 vaccination. Science Advances. 8(28):1–15. doi:10.1126/sciadv.abm7201

increased/breakthrough bleeding was significantly associated with age, systemic vaccine side effects (fever and/or fatigue), history of pregnancy or birth, and ethnicity."

200. As mentioned earlier, hormonal changes induced by the COVID-19 vaccines appear to partly underlie the menstrual changes observed with vaccination. Since the Pfizer COVID-19 vaccine lipid nanoparticles have been shown to accumulate in the ovaries, it is possible that this might contribute to the abnormal menstrual cycles in some fertile women following vaccination. The hypothalamus and pituitary glands in the brain and the ovaries hormonally control the menstrual cycle, so damage to the ovaries from an inflammatory attack might contribute to this effect, as well as platelet depletion following blood clotting induced by the COVID-19 vaccines.

201. It is important to appreciate that a female is born with all of the oocytes that she will have in her lifetime, and once she becomes fertile after puberty, she will have approximately 400 periods in which one (and sometimes more) oocyte is converted to a fertilizable egg by the process of meiosis. The vast majority of oocytes die off without undergoing meiosis during a woman's fertile life. Menopause occurs in women when they deplete their supply of oocytes. Inflammatory damage to the ovaries can endanger the overall supply of oocytes, and could lead to an earlier onset of menopause. In working women, there is a trend to delay having children, so if the ovaries are damaged by COVID-19 vaccine injury, there could possibly be a much shorter window in which they will be able to conceive. While this is a hypothetical risk, it is serious enough to warrant caution when weighing the risks and the benefits of the COVID-19 genetic vaccines.

2.9. Female and Male Fertility

2.9.1. Birth Rates

202. Although menstruation changes with COVID-19 vaccination appear to be reversible, there has been a reduction in the overall birth rates in Canada and many other countries since the introduction of the COVID-19 vaccines. This decrease may be over and above a steady decline in sperm counts in men since at least the early 1970s.[251] It should be appreciated that there may be significant differences in how

[251] Hagai, L., Jørgensen, N., Martino-Andrade, A., Mendiola, J., Weksler-Derri, D., *et al.* (2017) Temporal trends in sperm count: A systematic review and meta-regression analysis, Hum Reprod Update. 23(6):646–659. doi:10.1093/humupd/dmx022

males and females respond to the COVID-19 mRNA vaccines, particularly based on the biodistribution studies of the lipid nanoparticles used, which become enriched in the ovaries and testes.[196]

203. From 2019 to 2020, the Canadian fertility rate declined by 4.1% from 1.47 children per woman in 2019 to 1.41.[252] In 2021, it slightly increased by 2.1% to 1.44 children per woman, but then dropped by 7.6% to 1.33 in 2022.[253] The highest decline in birthrate was in women 20 to 24 years with a 37.5% decline, followed by 34% in 15- to 19-year-olds, 17% in 25- to 29-year-olds, then dropping to 7.6% in 30- to 34-year-olds, and leveling off after that for 35- to 49-year-olds.[254] From 2019 to 2022 in Canada, the crude birth rate decline was 8.6%; the total fertility rate decline was 12%.

204. By contrast in the US, there has been a steady rise in the fertility rates of 0.06% to 0.11% per year from 2019 through to 2023, which is currently around 1.78 births per woman.[255] US birthrates declined by 1.6% in this period, but these data were not broken down by age.[256]

205. Reductions in fertility rates of women have also been noted in England and Wales, where the number of live births declined by 3.1% in 2022 compared to 2021.[257] There was a 2.0% increase in births in England and Wales from 2020 to 2021, but the number of births had previously declined by 4.2% from 2019 to 2020, and followed a downward trend since 2012. In the European Union, the total number of live births also declined by 2.4% from 2019 to 2020, was unchanged from 2020 to 2021, and then further decreased by another 4.4% from 2021 to 2022.[258]

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[252] (2022) Fewer babies born as Canada's fertility rate hit a record low in 2020. Statistics Canada. Retrieved from https://www.statcan.gc.ca/o1/en/plus/960-fewer-babies-born-canadas-fertility-rate-hits-record-low-2020

[253] (2023) Fertility indicators, provinces and territories: Interactive dashboard. Statistics Canada. Retrieved from https://www150.statcan.gc.ca/n1/pub/71-607-x/71-607-x2022003-eng.htm

[254] (2023) Crude birth rate, age-specific fertility rates and total fertility rate (live births). Statistics Canada. Retrieved from https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310041801

[255] (2023) U.S. Fertility rate 1950–2023. Macrotrends. Retrieved from https://www.macrotrends.net/countries/USA/united-states/fertility-rate

[256] (2023) Total fertility rate of United States of America. Database Earth. Retrieved from https//database.earth/population/united-states-of-america/fertility-rate

[257] (2023) Births in England and Wales: 2022. Office for National Statistics. Retrieved from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2022

[258] (2023) Number of live births in the European Union (EU27) from 2009 to 2022. Statista. Retrieved from https://www.statista.com/statistics/253401/number-of-live-births-in-the-eu/

206. Worldwide, the decline in fertility during the pandemic period of 2019 to 2023 in fertility has continued, but includes both countries with high mRNA vaccine uptake, as well as those with very low rates. It should be appreciated that birthrates have declined yearly by approximately 4% per annum since the 1950s in most nations.[259]

207. The reduction in birthrates from the beginning of the COVID-19 pandemic to the later introduction of mRNA and other COVID-19 vaccines may be due to a number of possibilities such as: the influence of COVID-19 or the COVID-19 genetic vaccines on fertility, the overall decline in male sperm levels, increased economic hardship and social impacts of the pandemic, as well as concerns about having children given the current world situation. In Canada, conscious decisions not to have children during the current uncertain period and the lack of available housing in addition to these other factors, have contributed to the lower birth rate during the COVID-19 crisis.[260] Thus, while it may be tempting to attribute the decline in birthrates at least in part to COVID-19 vaccines, it is premature to make this a solid conclusion.

2.9.2. Sperm Counts and Motility

208. Another possible factor that may have contributed to the reduction in the birth rate is a temporary reduction in the production of sperm in men following COVID-19 vaccination. Gat *et al.* (2022) reported that inoculation with two doses of the Pfizer/BioNTech BNT162b2 COVID-19 vaccine in 37 Israeli males (median age of 28 years) was associated with a 15.4% and 22.1% temporary decline, respectively, in total spermatozoa concentration in semen and in their motility 75 to 125 days after the second inoculation, which was largely recovered by 145 days later.[261] Abd *et al.* (2022) tested 60 Iraqi males (18 to 50 years of age), and found that their sperm concentrations and sperm motility were reduced

[259] (2023) World fertility rate 1950–2023. MacroTrends. Retrieved from https://www.macrotrends.net/countries/wld/world/fertility-rate

[260] Hopper, T. (2023) First Reading: Canada's birth rate has dropped off a cliff (and it's likely because nobody can afford housing). National Post. Retrieved from https://nationalpost.com/opinion/canadas-birth-rate-has-dropped-off-a-cliff-and-its-because-nobody-can-afford-housing

[261] Gat, I., Kedem, A., Dviri, M., Umanski, A., Levi, M., *et al.* (2022) COVID-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count among semen donors. Andrology. 10:1016–1022. doi:10.1111/andr.13209

by 6%, at least 90 days after a second vaccination with a COVID-19 vaccine as compared to any prior vaccination.[262]

209. In a meta-analysis of seven publications (which excluded the study by Gat *et al.* (2022)[261] mentioned above but included the Abd *et al.* (2020) report) where investigators examined sperm concentration and quality, the authors noted that most studies failed to observe differences in total sperm count, semen volume, sperm concentration, total sperm motility, and morphological changes with COVID-19 vaccination after two doses.[263] Gonzalez *et al.* (2021) actually reported increases in sperm counts and motility about 70 days after double vaccination in their study of 45 men (median age of 28 years).[264] Likewise, Barda *et al.* (2022) reported slight increases in sperm counts and total motility counts in 33 sperm donors (median age of 27 years) 72 days or later after a second dose of the Pfizer/BioNTech BNT162b2 vaccine.[265] Safrai *et al.* (2022) failed to observe any significant changes in sperm volume, counts and motility in their study of 72 men (median age of 35.7 years) about 50 days after their second dose of the BNT162b2 vaccine, but there were large differences in these parameters within each pre- and post-vaccination subgroup (as much as 16-fold for sperm motility).[266] In 106 men (older than 18 years) undergoing assisted reproduction technology, a pairwise comparison between the first (while unvaccinated) and second attempt (median of 75 days after COVID-19 vaccination) did not reveal any changes in the sperm quality or successful fertilization rates.[267] However, their sperm counts were likely to be low to begin with. Olano *et al.* (2022) also did not find any changes in sperm counts or motility in 47 males (median age of 29 years) tested 70 days after a second inoculation with

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[262] Abd, Z.H., Muter, S.A., Saeed, R.A.M., Ammar, O. (2022) Effects of CCOVID-19 vaccination on different semen parameters. Basic Clin Androl. 32(1):13. doi:10.1186/s12610-022-00163-x

[263] Ma, Y.-C., Chao, C., Chi, Y., Xiang, L.-Y., Wen, J., Xi, J. (2023) The effect of COVID-19 vaccines on sperm parameters: A systematic review and meta-analysis. Asian J. Andrology. 25(4):468–473. doi:10.4103/aja2022100

[264] Gonzalez, D.C., Nassau, D.E., Khodamoradi, K., Ibrahim, E., Blachman-Braun, R., *et al.* (2021) Sperm parameters before and after COVID-19 mRNA vaccination. JAMA. 326(3):273–274. doi:10.1001/jama.2021.9976

[265] Barda, S., Laskov, I., Grisaru, D., Lehavi, O., Kleiman, S., *et al.* (2022) The impact of COVID-19 vaccine on sperm quality. Int J Gynaecol Obstet. 158(1):116–120. doi:10.1002/ijgo.14135

[266] Safrai, M., Herzberg, S., Imbar, T., Reubinoff, B., Dior, U., Ben-Meir, A. (2022) The BNT162b2 mRNA COVID-19 vaccine does not impair sperm parameters. Reprod Biomed Online. 44(4):685–688. doi:10.1016/j.rbmo.2022.01.008

[267] Reschini, M., Pagliardini, L., Boeri, L., Piazzini, F., Bandini, V., *et al.* (2022) COVID-19 vaccination does not affect reproductive health parameters in men. Front Public Health. 10:839967. doi:10.3389/fpubh.2022.839967

BNT162b2.[268] Examination of sperm production and quality in 75 Israeli men (younger than 45 years) one to two months after a second dose of the BNT162b2 vaccine only showed one participant that had reduced sperm motility and another participant with a sperm concentration that was below the normal expected range.[269] However, in this study the sperm counts and motility of the participants were not determined prior to vaccination. In a study performed by Xia *et al.* (2022) with the Sinovac and Sinopharm recombinant Spike protein vaccines, vaccination of 105 men (median of 33 to 34 years of age) did not appear to significantly affect semen volume, and sperm count and motility.[270] The difference in time between vaccination and sperm acquisition for testing was a median of 80.6 days.

210. In most of the aforementioned studies, sperm samples were typically taken about 75 days or less after the participants' second vaccination, whereas the reduction of sperm numbers and motility in the Gat *et al.* (2022)[261] study were between 75 and 125 days later. Most of the male participants in all studies were under 40 years of age, and often excluded those with low sperm counts to begin with. The vast differences in parameters from these studies in men who were vaccinated or not, make it difficult to determine if alteration in sperm concentration and mobility may be vaccine-induced.[263] At the very least, any reductions in sperm counts and motility with the COVID-19 vaccines appeared to be reversible.

211. It would be remiss not to mention that SARS-CoV-2 infection is strongly associated with a temporary reduction in sperm levels and motility as reviewed by Pourmasumi *et al.* (2022).[271] In many of these studies of the effects of COVID-19 on sperm concentration and quality, the COVID-19 vaccination status of the participants was not defined.

2.10. Impact of COVID-19 Vaccines on Pregnancy and Postnatal Development

[268] Olana, S., Mazzilli, R., Salerno, G., Zamponi, V., Tarsitano, M.G., *et al.* (2022) 4BNT162b2 mRNA COVID-19 vaccine and semen: What do we know? Andrology. 10(6):1023–1029. doi:10.1111/andr.13199

[269] Lifshitz, D., Haas, J., Lebovitz, O., Raviv, G., Orvieto, R., Aizer, A. (2022) Does mRNA SARS-CoV-2 vaccine detrimentally affect male fertility, as reflected by semen analysis? Reprod Biomed Online. 44(1):145–149. doi:10.1016/j.rbmo.2021.09.021

[270] Xia, W., Zhao, J., Hu, Y., Fang, L., Wu, S. (2022) Investigate the effect of COVID-19 inactivated vaccine on sperm parameters and embryo quality in *in vitro* fertilization. Andrologia. 54(6):e14483. doi:10.1111/and.14483

[271] Pourmasumi, S., Nazari, A., Ahmadi, Z., Kouni, S.N., de Gregorio, C., *et al.* (2022) The effect of Long COVID-19 infection and vaccination on male fertility: A narrative review. Vaccines (Basel). 10(12):1982. doi:10.3390/vaccines10121982

2.10.1. Efficacy and Safety for Pregnant Women

212. This section primarily examines the evidence for the efficacy and safety of the mRNA vaccines against COVID-19 that were administered to women before or during pregnancy. To do so effectively requires consideration of the following concerns where some, often very limited, data may be available for evaluation:

a. The efficacy and safety of the mRNA vaccines in non-pregnant women in general, mostly based on the initial phase trials of the mRNA manufacturers, and some later studies in the scientific literature;
b. The impact of these vaccines on fertility;

c. The impact of these vaccines on pregnancy during the various trimesters, including any changes in rates of spontaneous abortions and miscarriages;

d. Health outcomes for infants born to mothers vaccinated against COVID-19; and

e. Finally, the evidence, if any, that the vaccines may induce developmental disorders, particularly of the nervous system, in some children.

213. Taking these in order, what does the existing literature show about efficacy or safety for women in general following vaccination with any of the COVID-19 mRNA vaccines? The efficacy of any intervention in health is typically assessed by the use of a double-blind, randomized clinical trial (RCT), as described in previous sections. This level of evaluation was never done for pregnant or potentially future pregnant women before the deployment and recommendation of the COVID-19 vaccines to the entire population. In fact, pregnant women were excluded from the initial Phase 3 studies. Remarkably, this omission did not stop medical authorities in various countries from recommending COVID-19 vaccination for women before, or during any trimester of pregnancy on the assumption, never tested, that infection with COVID-19 *might* be more serious for the mother and potentially harmful to the fetus. The same authorities then opted to measure effectiveness (real world data), in place of efficacy. Note that efficacy can only be determined prospectively in the context of a randomized control trial (RCT). To do so, often unblinded data was frequently used (mostly from registries), often retrospectively, using different definitions of what a COVID-19 case was (typically positive PCR testing exclusively), from symptomatic COVID-19 diagnoses, to hospitalizations based on PCR tests, *etc*. More

importantly, studies determining effectiveness, almost never investigated adverse events in the same populations, so a risk/benefit analysis in the pregnant population is non-existent when it should be the basis of any rational consideration of whether COVID-19 vaccination during pregnancy is indeed "safe and effective."

214. After more than three and a half years since the COVID-19 crisis started, there has been more than enough time to undertake a double blind RCT in pregnant women with a large enough sample to be able to extrapolate results to the general pregnant population. However, the latest results from Pfizer, published in the US Clinical Trials.gov website,[272] regarding the Phase 2-3 placebo-controlled, randomized, observer-blind trial in pregnant women, had managed to recruit only 174 women in each group (*i.e.,* total of 348 women) which is statistically insufficient to detect all potential poor outcomes, and makes extrapolation to the full population of pregnant women impossible. Comparatively, the retrospective design studies with statistical corrections that allegedly equalize the differences across groups (*e.g.,* the study of Fell *et al*. (2022)[273] have managed to compare 43,099 vaccinated women versus 42,063 non-vaccinated women. So, the question that needs to be answered is why are there no larger RCTs under way given how important the issue is?

215. It should also be noted that the cited Pfizer study did not administer the vaccine before week 24 or 27 of gestational age, so there is little to no data related to miscarriages (defined as pregnancy before 20 weeks), which has been one (or the main) point of debate regarding administering mRNA vaccines to pregnant women.[210] Indeed, Table 6 of the Pfizer report may deliberately blend data across trimesters giving the impression that vaccinated and non-vaccinated have the same level of miscarriages when Pfizer's own data may support the opposite. The above concerns render the pregnancy data far less than evidence-based. Sadly, the data for fertility, lactation and postpartum adverse events are even less acceptable. In conclusion, the data presented in support of COVID-19 vaccination during pregnancy fails to make a successful case that the vaccines are safe or effective.

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[272] (2023) History of changes for study: NCT04754594. To evaluate the safety, tolerability, and immunogenicity of BNT162b2 against COVID-19 in healthy pregnant women of 18 years of age and older. Clinical Trial.gov Archive. Retrieved from https://classic.clinicaltrials.gov/ct2/history/NCT04754594?V_21=View#StudyPageTop

[273] Fell, D.B., Dimanlig-Cruz, S., Regan, A.K., Håberg, S.E., Gravel, C.A., *et al.* (2022) Risk of preterm birth, small for gestational age at birth, and stillbirth after COVID-19 vaccination during pregnancy: Population based retrospective cohort study. BMJ. 378:e071416. doi:10.1136/bmj-2022-071416

216. Almost all the studies supposedly designed to evaluate the safety of mother and baby were determined retrospectively in case control studies, using registry data, which did not match groups of vaccinated and unvaccinated pregnant women, that is women with similar characteristics (*i.e*., demographic, ethnic, socioeconomic characteristics, substance consumption profile, comorbidities, *etc*.). Such matching is essential since these different characteristics (regardless of the vaccination status of the mother) may be responsible for differences in the outcome of the pregnancy and the overall health of the mother and the baby. Instead of attempting to match the groups, many researchers opted for complicated statistical corrections which tended to make the different characteristics across groups disappear, leading to a conclusion that the vaccinations were not responsible for any differences in outcomes. However, some of the most striking differences between the vaccinated versus the unvaccinated for COVID-19 were not separately considered. These variables, such as cigarette use, consumption of other substances, and socioeconomic income or poverty index, known to negatively impact pregnancy were higher in the unvaccinated group.[273]

217. An important question to consider in relation to such data is how good are the statistical methods to erase differences between unvaccinated mothers who consumed cigarettes or other drugs, and lived in more impoverished conditions (which generally entail worse overall health status and nutritional status) versus vaccinated mothers who did not consume any substances and who benefited from a better socioeconomic status (which generally means better overall health baseline status)? Can one be certain that a lower number of adverse events in vaccinated pregnant women means that the vaccination is not associated with poorer outcomes (*i.e*., harms), or could it be that the harms in the healthier vaccinated population becomes like that of unvaccinated mothers dealing with worse overall health conditions, cigarette consumption and/or other substance use issues, all of which are known to produce poorer outcomes during pregnancy? This is a key question to resolve.

218. The initial Phase 3 trials for mRNA vaccines, specifically those by Pfizer, did not separate the male and female participants such that women of reproductive age were not separately assessed. Additionally, any women who might be pregnant were excluded from the trials. Moderna's initial trials also assessed the efficacy and safety data for both sexes, without considering a separate analysis in woman of reproductive age.

219. Based on these evaluations of male and female efficacy and safety data, few sex-based conclusions about the impact of mRNA vaccines can be used as baseline values. Further, such data cannot really be used as a comparator to women during the various trimesters of pregnancy.

220. In place of this, is a 2021 report by Pfizer/BioNtech on BNT162B2 entitled "Cumulative Analysis of Post-Authorization Adverse Event Reports of PF-07302048 (BNT162B2) Received Through 28-FEB-2021."[211] This analysis covered through to the end of February 2021. It evaluated 42,086 vaccine recipients, of whom 29,214 were female and 9,182 were male. A further 2,990 patients were listed as "No data", which may simply mean that the sex of some participants was not recorded, as odd as that conclusion might be. The data were gathered from reports in 26 countries in which the trials were held.

221. In regard to safety as measured by adverse events in pregnant women, Tables 5 and 6 of the document are revealing. In Table 5, the report discusses "Vaccine-Associated Enhanced Disease" (VAED) or Vaccine-Associated Enhanced Respiratory Disease (VAERD). It lists 138 cases including 317 "potentially relevant events." The authors write:

> *"Conclusion: VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 37 subjects with suspected COVID-19 and 101 subjects with confirmed COVID-19 following one or both doses of the vaccine; 75 of the 101 cases were severe, resulting in hospitalization, disability, life-threatening consequences or death. None of the 75 cases could be definitively considered as VAED/VAERD. In this review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERD remains a theoretical risk for the vaccine. Surveillance will continue."* [211]

222. Whether these cases might represent antibody-dependent enhancement (ADE) was not clear, nor was it apparently evident to Pfizer, assuming the company even acknowledged that ADE exists.

223. Table 6 in the Pfizer report listed 413 adverse event cases, of which 84 were listed as "serious" and 329 as "non-serious." How these descriptions were determined is not specified. Of these overall adverse events, in the presumably serious cases, 23 showed spontaneous abortions, premature death with neonatal death (2) and spontaneous abortion with intrauterine death (2) (for a total of 27). The adverse events during pregnancy listed as "non-serious" included those in the first trimester (15), second trimester (7) and third trimester (2).[211]

224. In the next paragraph of the report, it listed 124 “mother cases”, with 49 cases characterized as non-serious and 75 cases as serious.[211] Why the numbers varied was not clear. In this paragraph, spontaneous abortions included 25 of the cases. Taking the latter number and not being certain in which trimester the 25 spontaneous abortions occurred (although the first trimester would be most likely) would give a rate of 29.98 % for “serious cases” (which one would have to conclude these cases were) or 7.6% of those deemed “non-serious.” In comparison, US data for pregnancy in general shows the percentage of the first trimester spontaneous abortions were highly dependent on the mother’s age, with 15% occurring in those under 35 years, 20-35% in the 35-45 age range, and 50% in the over 45 age group.[274]

225. A clearer answer to the question of the potentially negative impacts of COVID-19 vaccines on pregnancy would be to look at stillbirth data, which is the death of fetuses over 20 weeks of gestational age. In the richer countries with advanced medical care, stillbirths are quite uncommon so it would be extremely concerning if the numbers of stillbirths in women taking the COVID-19 vaccines just before or during the pregnancy were higher. However, the Pfizer study did not appear to clearly distinguish spontaneous abortions from stillbirths. Some insights into this issue can be found in the last paragraph of page 12 in the report in the section on “Pregnancy cases.” Of the 270 adverse effects reported, 4 were described as “serious foetus/baby cases” of which 2 were “premature baby” and 1 death. Two of these are described as occurring in the first trimester.

226. Taking the numbers of spontaneous abortions in this report as accurate, the Pfizer mRNA vaccines would seem to have almost doubled the number of such cases for under 35-year-olds, coming in at about the same in the 35- to 45-year-old group, and showing lower numbers than in the over 45 years and up age group. It should be stressed however, that the overall numbers in the Pfizer data were small and will thus not have the same accuracy and statistical power to make valid conclusions or extrapolation of the data to the general pregnant population.

227. During the same time period as when the Pfizer report came out, a number of studies appeared in the peer-reviewed literature as referenced below. The main issues for these studies include concerns about study design, exclusion criteria, the use of PCR testing at too high thermal cycle thresholds (see

[274] Villines, D. (2021) What are the average miscarriage rates by week? Medical News Today. Retrieved from https://www.medicalnewstoday/com/articles/322634#miscarriage

Exhibit C, Chapter 4.2), and the fundamental differences between the use of relative risk reduction and safety versus absolute risk reduction (see Section 2.6.2) and safety values.

228. An article by Morgan *et al.* (2022) also demonstrated other study design issues, namely that non-vaccinated women were younger, belonged to the Hispanic or the African-American community, had a higher BMI (body mass index) and a positive smoking status.[275] The authors attempted to deal with these issues by statistical correction. Additionally, Remdesivir had been taken by 20 women in the unvaccinated group compared to none in the vaccinated group, a variable that was not corrected for.[275, 276, 277, 278, 279] Remdesivir itself can have profound side-effects.

229. In terms of effectiveness, the relative rate reported by these studies ranged from 71% to 88%; the absolute rate was between 0.1% to 5.6%. Effectiveness was also assessed in relation to specific severe forms of COVID-19, such as cases requiring hospitalization, with a relative risk reduction of 71.4%, but an absolute risk reduction of only 0.1%.[276] In one retrospective observational study, researchers from Tel Aviv and the US carefully matched 15,060 pregnant women in Israel according to age, gestational age, residential area, population subgroup, parity, and influenza immunization status, into vaccinated/unvaccinated pairs.[278] Their findings indicated that vaccination with BNT162b2 in pregnant women lowered the risk of SARS-CoV-2 infection, with a relative efficacy rate of 78%, but an absolute difference of only 1.31%. In both the vaccinated and non-vaccinated women that were infected with SARS-CoV-2, about 16% were asymptomatic. Of 88 pregnant women who were symptomatic for COVID-19 in the vaccinated group, 10 were hospitalized (11.4%), whereas 23 of the 149 non-vaccinated

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[275] Morgan, J.A., Biggio, J.R., Jr., Martin, J.K, Mussarat N., Chawla, H.K., *et al.* (2022) Maternal outcomes after Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in vaccinated compared with unvaccinated pregnant patients. Obstet Gynecol. 2022 Jan 1;139(1):107–109. doi:10.1097/AOG.0000000000004621

[276] Dagan, N., Biron-Shental, T., Makov-Assif, M., Key, C., Kohane, I.S., *et al.* (2021) Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nat Med. 27(10):1693–1695. doi:10.1038/s41591-021-01490-8

[277] Butt, A.A., Chemaitelly, H., Al Khal, A., Coyle, P.V., Saleh, H., *et al.* (2021) SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. J Clin Invest. 131(23):e153662. doi:10.1172/JCI153662

[278] Goldshtein, I., Nevo, D., Steinberg, D.M., Rotem, R.S., Gorfine, M., *et al.* (2021) Association between BNT162b2 vaccination and incidence of SARS-CoV-2 infection in pregnant women. JAMA. 326(8):728-735. doi:10.1001/jama.2021.11035

[279] Kadour-Peero, E., Sagi-Dain, L., Sagi, S. (2021) Early exploration of COVID-19 vaccination safety and effectiveness during pregnancy: Interim descriptive data from a prospective observational study. Vaccine. 39(44):6535–6538. doi:10.1016/j.vaccine.2021.09.043

pregnant women were hospitalized (15.4%). Therefore, there appeared to be little difference with respect to the severity of COVID-19 once it was acquired in either vaccinated or nonvaccinated women. The authors noted that *"there were no notable differences between the vaccinated and unvaccinated groups regarding preeclampsia, intrauterine growth restriction, infant birth weight, abortions, stillbirth, maternal death, or pulmonary embolism*." While 68/7,530 (0.9%) of the vaccinated women experienced vaccine-related adverse events, none of these were considered severe.[278]

230. Bookstein Peretz *et al*. (2021) compared 390 pregnant Israeli women who were vaccinated with 260 non-pregnant women who were also vaccinated between January and February of 2021, and concluded that there were no significant differences in reported side-effects of Pfizer-BioNTech vaccinations after two doses associated with pregnancy.[280] However, in this retrospective study, the pregnant women had 21% lower serum SARS-CoV-2 IgG levels compared to non-pregnant, vaccinated women ($p < 0.001$)). This study had no comparable cohort of unvaccinated pregnant women with which to compare, and it did not evaluate whether vaccination reduced the incident of COVID-19.

231. In several studies, most of the pregnant women who were admitted to hospital that were positive for SARS-CoV-2 had no symptoms of COVID-19 at presentation. This amounted to 87.9% of 33 PCR-positive obstetrics patients at the New York–Presbyterian Allen Hospital and Columbia University Irving Medical Center,[281] 52.2% of 23 PCR-positive pregnant patients at an Indonesian hospital,[282] and in a meta-analysis of five studies, between 45% to 100% of 131 PCR-positive obstetric patients presenting to hospitals, of which 49% to 68% remained asymptomatic for COVID-19 during their hospital stay.[283]

232. Cumulatively, a summary of the existing data on vaccine effectiveness in vaccinated versus unvaccinated women during pregnancy shows major flaws in study design and interpretation, much

[280] Bookstein Peretz, S., Regev, N., Novick, L., Nachshol, M., Goffer, E., *et al.* (2021) Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. Ultrasound Obstet Gynecol. 58(3):450–456. doi:10.1002/uog.23729

[281] Sutton, D., Fuchs, K., D'Alton, M., Goffman, D. (2020) Universal screening for SARS-CoV-2 in women admitted for delivery. N Engl J Med. 382(22):2163–2164. doi:10.1056/NEJMc2009316

[282] Wardhana, M.P., Maniora, A., Maniora, M.C., Aryananda, R.A., Gumilar, K.E., *et al.* (2021) *Lesson from Indonesia: COVID-19 testing strategy in obstetric emergency cases at low-resource health care setting.* Pakistan J Med Health Sci. 15(2):508–513. ISSN 1996-7195

[283] Yanes-Lane, M., Winters, N., Fregonese, F., Bastos, M., Perlman-Arrow, S., *et al*. (2020) Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. PLOS One. 15(11):e0241536. doi:10.1371/journal.pone.0241536

like that which attended the Phase 3 trials discussed earlier. First, claims made that the COVID-19 genetic vaccines may be effective in pregnant women to prevent infection with SARS-CoV-2 are speculative, especially given the absolute efficacy numbers. Also, because a woman's immune system is distinctly different during pregnancy than in non-pregnant states, any statements about how well the COVID-19 mRNA vaccines work in pregnant women based on studies that excluded these women as in the original Phase 3 trial data are largely conjecture. Also, of note, a key problem in most studies has been the short reporting time post vaccination and the small sample sizes. In some cases, they are simply based on surveys that are filled retrospectively by study participants, as exemplified in the Canadian COVERED study by McClymont *et al.* (2023).[284]

233. In the COVERED study with 4,528 respondents,[284] 99% were either vaccinated before, during and/or after their pregnancy. Less than a percent remained unvaccinated. About 80% of the participants were white and only 3.4% had a maximum of a high school education or less. The extent of natural immunity in all of the study respondents from previous SARS-CoV-2 infections prior to pregnancy was not considered, although this would be difficult to ascertain without serological testing since about 41% of adults are asymptomatic for COVID-19 following infection with this virus.[285] About 27.4% of the vaccinated study participants tested positive for an active SARS-CoV-2 infection after vaccination. While none of these infected individuals experienced more than mild symptoms of COVID-19, the study was silent about the severity of COVID-19 cases in the unvaccinated group. However, the authors did note that the side-effects of COVID-19 vaccination (redness, pain or swelling at the site of injection (in over 65% of vaccinated participants), tiredness, headache, muscle pain, chills, fever and nausea) in the pregnant women were more commonly observed than evident in non-pregnant COVID-19 vaccinated women, and these were generally more pronounced after the second dose of a COVID-19 vaccine. Only 23.6% of the vaccinated group received one or two doses of a COVID-19 vaccine in the first trimester, which would be the most dangerous to the developing fetus as Spike levels would be at their peak soon after vaccination. Since the study was underpowered in the number of participants, rarer adverse

[284] McClymont, E., Atkinson, A., Albert, A., Av-Gay, G., Andrade, J., *et al.*; COVERED Team. (2023) Reactogenicity, pregnancy outcomes, and SARS-CoV-2 infection following COVID-19 vaccination during pregnancy in Canada: A national prospective cohort study. Vaccine. S0264-410X(23)01215-X. doi:10.1016/j.vaccine.2023.10.032

[285] (2023) Between April and August 2022, 98% of Canadians had antibodies against COVID-19 and 54% had antibodies from a previous infection. Statistics Canada. Retrieved from https://www150.statcan.gc.ca/n1/daily-quotidien/230327/dq230327b-eng.htm

effects of the COVID-19 vaccinations would be harder to identify. Receiving a vaccination in the latter half of the second trimester (weeks 13 through 27 of pregnancy) or in the third trimester (weeks 28 to 40) would not cause a spontaneous abortion (which by definition occurs before the 20th week of pregnancy). Even so, the higher rate of spontaneous abortions in the vaccinated group (18/2,868) as compared with the unvaccinated group (4/1,660) (*i.e.,* 0.63% vs 0.24%) was dismissed on the basis that the survey was retrospective and the number of respondents between the two groups was unequal, even though the rates were adjusted for this by percentage. It was also evident that there were 5 stillbirths and 3 neonatal deaths in the COVID-19 vaccinated group and none in the unvaccinated group. While not statistically significant, there were seizures in 9 babies born to vaccinated mothers (0.32%) compared to 4 babies with unvaccinated mothers (0.24%).[284]

234. To draw a meaningful conclusion regarding the effects of vaccines on pregnancy, the outcomes should be recorded from vaccination until birth. Moreover, a snapshot of 7-day post-vaccination (as recorded in certain studies, such as that of Sadarangani *et al.* (2022),[286] seems meaningless when the health authorities themselves consider people who received one dose of the vaccine less than 14 days prior as unvaccinated, and people with two doses were only considered fully vaccinated more than seven days post-second dose. So, as per the definition of health authorities, when counting hospitalized vaccinated patients, these vaccinated-pregnant women would have fallen in the category of unvaccinated for the one-dose recipients (unvaccinated and one dose less than 14 days), and of one-dose patients (one dose greater than 14 days) for the two-dose recipients. They would have never counted in the fully vaccinated hospitalized patients. Immune-mediated mechanisms (such as autoimmunity or molecular mimicry) typically takes longer to manifest, as opposed to local reactions, general systemic reactions (like fever or malaise) and allergies.

235. Among other concerns is the lack of animal or Phase 1/2 studies in humans that addressed teratogenic/toxic effects of individual components of these vaccines, for example, lipids used in the nanoparticles and the Spike protein and its potential truncated versions. Another issue is the low numbers of participants in the clinical trials, particularly in the first trimester when most miscarriages typically occur. In these studies, where there were claims of no increased risk of miscarriage, these

[286] Sadarangani, M., Soe, P., Shulha, H.P., Valiquette, L., Vanderkooi, O.G., *et al.* (2022) Safety of COVID-19 vaccines in pregnancy: A Canadian National Vaccine Safety (CANVAS) network cohort study. Lancet Infect Dis. 22(11):1553–1564. doi:10.1016/S1473-3099(22)00426-1

statements were based on comparison to historic cohorts, where the frequency of miscarriages varies widely between 8 and 20%.

236. Finally, the data for adults using a non-vaccine immune population may be clinically irrelevant since at the time of the trial most people already had some level of immunity – either acquired naturally or vaccine-induced.

237. Despite of all of the aforementioned caveats, it is still important to collectively review the data that is available with respect to the maternal and neonatal outcomes of COVID-19 vaccination during pregnancy. Amongst the best available is a meta-analysis of 37 published studies that together tracked maternal, neonatal and immunological outcomes in 141,107 pregnant women (36.8% vaccinated) performed by Marchand *et al.* (2023).[287] I was originally one of the peer-reviewers for the journal that eventually published this meta-analysis. The extent of SARS-CoV-2 infections in the vaccinated women was 13.1% and in the non-vaccinated women was 19.1%. Such a difference can easily be accounted for by extra testing in non-vaccinated women who were pregnant from strong encouragement from their biased health care providers. The meta-analysis revealed that vaccination for COVID-19 was associated with what was described as a reduced risk of premature delivery (Odds Ratio of 0.71; $p<0.00001$) by a day or so, and slightly increased risk for a Cesarean section delivery (Odds Ratio of 1.20; $p=0.007$) as compared to non-vaccinated pregnant women. (Odds Ratios provide a measure of the association of an exposure with an outcome. If the Odds Ratio is close to 1, there is no association. A positive number supports a positive relationship, where a negative number supports an inverse relationship.) The authors described the delivery of the babies as occasionally slightly more premature in the non-vaccinated mothers. However, presumably the non-vaccinated mothers should be considered as the expected normal controls, especially since 80.9% of them were apparently not infected with the SARS-CoV-2 virus during their pregnancies. Thus, it is more appropriate to suggest that the vaccinated women may have a slight risk of a delay in their deliveries. Although not quite statistically significant in their analysis, there also appeared to be a small trend towards increased gestational diabetes in the

[287] Marchand, G., Masoud, A.T., Grover, S., King, A., Brazil, G., *et al.* (2023) Maternal and neonatal outcomes of COVID-19 vaccination during pregnancy, a systematic review and meta-analysis. NPJ Vaccines. 8(1):103. doi:10.1038/s41541-023-00698-8

vaccinated pregnant women (Odds Ratio of 1.28 based on two studies; 10.6% vs 8.96%) and postpartum hemorrhage (Odds Ratio of 1.68 based on 3 studies; 3.9% versus 3.4%; p=0.08).[286]

238. A recent retrospective cohort of 6,057 women by Dick *et al.* (2023) also found a slightly higher rate of gestational diabetes (47% increase; 12.2% versus 8.3%; p=0.02) amongst vaccinated pregnant women, and in triple-vaccinated women as compared to non-vaccinated mothers slightly more Cesarean deliveries (12% increase; 18.6% versus 16.6%, p=0.52), as well as higher rates of postpartum hemorrhage (195% increase; 9.5% versus 3.21%; p<0.001).[288] Another meta-analysis of the literature by Pratama *et al.* (2023) based on 13 observational studies with COVID-19 mRNA vaccines with 48,039 pregnant women failed to detect any differences between vaccinated and non-vaccinated women with respect to maternal, delivery and neonatal outcomes.[289]

2.10.2. Breast Feeding

239. In regard to lactation, there are limited studies, of which the work of Kachikis *et al.* (2022), may be the most representative.[290] One of the possible adverse effects reported by 355 of 10,278 (3.5%) lactating women included a decrease in their breast milk supply. However, all signs and symptoms were recorded during the first 24 hours post-vaccination and from a pre-determined list of options. When asked about other signs and symptoms post-vaccination, the participants were instructed to record them only if they thought they were related to vaccination, which makes the data collection subjective to the participants' own biases.

240. In a Pfizer analysis,[210] the authors considered 133 reports of breast feeding in vaccinated mothers, where 116 were taken to be normal and 17 cases included adverse events with 3 that were considered as "serious" and 14 "as non-serious." The symptoms in the infants included: pyrexia (fever), rash, irritability, vomiting, diarrhea, insomnia, poor feeding, lethargy, abdominal discomfort, allergy to

[288] Dick, A., Rosenbloom, J.I., Karavani, G., Gutman-Ido, E., Lessans, N., Chill, H.H. (2022) Safety of third SARS-CoV-2 vaccine (booster dose) during pregnancy. Am J Obstet Gynecol MFM. 4(4):100637. doi:10.1016/j.ajogmf.2022.100637

[289] Pratama, N.R., Wafa, I.A., Budi, D.S., Putra, M., Wardhana, M.P., Wungu, C.D.K. (2022) mRNA COVID-19 vaccines in pregnancy: A systematic review. PLOS One. 17(2):e0261350. doi:10.1371/journal.pone.0261350

[290] Kachikis, A., Englund, J.A., Covelli, I., Frank, Y., Haghighi, C., *et al.* (2022) Analysis of vaccine reactions after COVID-19 vaccine booster doses among pregnant and lactating individuals. JAMA Netw Open. 5(9):e2230495. doi:10.1001/jamanetworkopen.2022.30495

vaccine, increased appetite, anxiety, crying, poor sleep quality, belching (eructation) agitation, pain and hives (uticaria).

241. Fu *et al.* (2022) conducted a meta-analysis of 23 studies that examined the immune response in pregnant and lactating individuals to COVID-19 vaccination.[291] They noted that these individuals experienced vaccine-related reactions at a similar rate to the general population. With respect to whether the levels of IgA anti-Spike protein in breast milk was higher following vaccination against COVID-19 or if it was higher in lactating mothers who had previously been infected with SARS-CoV-2, the authors noted that the findings in the literature were conflicting.

242. In addition to the previously mentioned problems with the published studies on vaccination of pregnant women in general and with breast feeding specifically, other issues included small sample sizes and lack of control groups, as well as short duration follow up of 4.6 to 17 weeks.[292] A small sample size was also used by Blakeway *et al.* (2023),[293] none of whom were vaccinated during the first trimester with 85.7% vaccinated in the third trimester, thus limiting the ability to monitor stillbirths. Additionally, many of the reporting authors had conflicts of interest with relationships with COVID-19 vaccine companies.

2.10.3. Impacts of mRNA Vaccines on Early Infant Health

243. Much of the literature about this age range is based on the official reports from health agencies such as NIH, CDC, Health Canada and others. These simply repeat the mantra that the mRNA vaccines are "safe and effective" without critical analysis. However, in the Pfizer report,[210] part of the list in Table 6 may provide some insight, primarily into what was not analyzed. In a section entitled "Use in Paediatric Individuals <12 years of Age", it listed 34 cases ranging from 2 months of age to 9-year-olds. The following adverse effects are reported: vaccination site pain (3), upper abdominal pain (2), COVID-19

[291] Fu, W., Sivajohan, B., McClymont, E., Albert, A., Elwood, C., *et al.* (2022) Systematic review of the safety, immunogenicity, and effectiveness of COVID-19 vaccines in pregnant and lactating individuals and their infants. Int J Gynaecol Obstet. 156(3):406–417. doi:10.1002/ijgo.14008

[292] Trostle, M.E., Limaye, M.A., Avtushka, V., Lighter, J.L., Penfield, C.A., Roman, A.S. (2021) COVID-19 vaccination in pregnancy: Early experience from a single institution. Am J Obstet Gynecol MFM. 3(6):100464. doi:10.1016/j.ajogmf.2021.100464

[293] Blakeway, H., Prasad, S., Kalafat, E., Heath, P.T., Ladhani, S.N., *et al.* (2022) COVID-19 vaccination during pregnancy: Coverage and safety. Am J Obstet Gynecol. 226(2):236.e1-236.e14. doi:10.1016/j.ajog.2021.08.007

(2), facial paralysis (2), lymphadenopathy (disorder of the lymph nodes) (2), malaise (2), pruritus (itchy skin) and swelling (2). From this, the authors concluded that there was no significant difference compared to "the non-paediatric population."

2.10.4. Impacts of mRNA Vaccines on Neurological Development in Children

244. Finally, the question about whether children born to women vaccinated against COVID-19 have more developmental delays is a question that cannot yet be answered, and especially for neural development. For example, autism spectrum disorder (ASD) remains a neurological disorder of unknown etiology. While claims have been made that ASD levels have risen in lock step to the increase in pediatric vaccines that are recommended for children, clearly, correlation, even if suggestive, does not equal causation. Other environmental insults have also been proposed and there are indications that ASD has a genetic component, although one that likely involves at most selected nucleotide sequences, often in non-coding regions of DNA. (For references to these and other points, see Shaw, *Dispatches from the Vaccine Wars*, 2021.[294]) Regardless, while ASD may be diagnosed as early as 18 months of age, it is not usually diagnosed prior to a mean age of 5.5 years of age.[295]

245. This fact alone would preclude an early answer to the question of mRNA vaccines in pregnancy and neural outcomes in postnatal life. In addition, such a study would be highly complicated by the numerous other prenatal and postnatal events to which children might be exposed.

2.10.5. Concluding Remarks on Vaccine Safety in Pregnant Mothers and Their Babies

246. FDA's February 28, 2021, review of Pfizer's early pharmacovigilance safety database clearly showed that mRNA product (BNT162b2) injections may cause harm to mothers, pregnancy, lactation, and breastfeeding infants. This review makes clear that this database cannot be used to calculate incidence rates or test hypotheses, but that it should be used to detect potential indicators of harm or safety

[294] Shaw, C.A. (2021) Dispatches from the Vaccine Wars: Fighting for human freedom during the Great Reset. New York: Skyhorse Publishers

[295] Van T'Hof, M., Tisseur, C., Berckelear-Onnes, I., Van Nieuwenhozen, A., Daniels, A.M., *et al.* (2020) Age at autism spectrum disorder diagnosis: A systematic review and meta-analysis from 2012 to 2019. Sage Journals. Autism. 25(4):862–873. doi:10.1177/1362361320971107

signals. This raises the question of how much harm is acceptable before halting use of these products. Despite a deficiency of safety data, these products continue to be declared as "safe" in pregnancy.

247. Studies used to support these claims are generally of poor quality, consisting mainly of observational studies and voluntary registries. As such, they are only able to speculate that associations seen between suspected injuries and the mRNA product are not due to the COVID-19 mRNA products. The primary limitation of most of these studies is that they focus on short-term harms to the mother or only highly observable immediate harms such as miscarriage, stillbirth, preterm birth, or infant size at birth. None of the studies monitored the health of the mother and child carefully enough – or long enough – to detect subtle but significant changes to maternal or infant bodily systems, including but not limited to, the reproductive, immune, or cardiovascular system. Additionally, these studies have significant statistical issues that further bring their findings into question. They lacked any reliable denominators, standardization, stratification of significant variables, adequate tracking and follow-up of participants, and they incorrectly interpreted what data is available. Recently meta-analyses of these same observational trials have been published and have failed to establish safety risks for these COVID-19 mRNA products in pregnant women. These analyses suffer from the same limitations as the observational trials and are no substitute for the robust and long-term RCT data that is required to prove product safety.

2.11. Myocarditis and Myopericarditis

2.11.1. Nature of Myocarditis and Incidence Pre-COVID-19

248. Myocarditis, also known as inflammatory cardiomyopathy, is a disease that results from infiltration of heart muscle with immune cells that attack, damage and may kill cardiomyocytes. These are the contractile cells of the middle layer of the heart that permit it to beat and pump blood through the circulation. If the cardiomyocytes are killed, they are replaced by non-contractile scar tissue, and the surviving heart cells have to expand in size to maintain circulation and blood pressure, which results in enlargement of the heart. **Myocarditis is the principal cause of about 20% of sudden cardiac death in people under 40 years of age**.[296] It can occur within an hour of symptoms, such as dizziness, chest pain,

[296] Drory, Y., Turetz, Y., Hiss, Y., Lev, B., Fisman, E.Z., *et al.* (1991) Sudden unexpected death in persons less than 40 years of age. Am J Cardiol. 68(13):1388–1392. doi:10.1016/0002-9149(91)90251-f

sudden loss of consciousness, lack of pulse and no breathing. Continuing symptoms include feeling fatigued, short of breath, chest pains and palpitations (sensation of heart racing). While the symptoms of myocarditis subside gradually, the actual physical damage to the heart may become permanent, although full recovery is usually observed. Myopericarditis has a similar pathology to myocarditis, and involves damage to the pericardium muscle tissue that envelopes and protects the heart. It tends to be less severe than myocarditis. Both myocarditis and myopericarditis can be triggered by a wide range of factors such as kidney failure, cancer, drugs, toxins and many viruses, including SARS-CoV-2.[297] It can also be induced by COVID-19 vaccines.

249. Historically, the outcomes from myocarditis are usually favorable. However, since the damage from myocarditis can be irreversible and may be cumulative, it is inappropriate to suggest that a person can have a mild case of myocarditis based on symptoms. The acute observable effects may be experienced as mild, and apparently asymptomatic in most cases, but it may induce more serious heart issues in the longer term. The scarring that may result with myocarditis can cause life-threatening arrhythmia of the heart. While the long-term outcomes of COVID-19 vaccine-induced myocarditis are yet unknown, viral induced myocarditis causes death in about 20% of those afflicted within 6 years.[298] The lethality of myocarditis is also highlighted in *The Journal of Clinical Medicine* article: "Occurrence, Trends, Management and Outcomes of Patients Hospitalized with Clinically Suspected Myocarditis—Ten-Year Perspectives from the MYO-PL Nationwide Database*."* [299] which concluded that:

> *"Myocarditis has been shown in post-mortem studies to be a major cause (up to 42% of cases) of sudden and unexpected death in children and young adults. In contrast, a recently published study on autopsies reported that 6% of 14,294 sudden deaths were assigned as being caused by myocarditis. In patients with biopsy-proven myocarditis in long-term observation (the median*

[297] Castiello, T., Georgiopoulos, G., Finocchiaro, G., Claudia, M., Gianatti, A., *et al*. (2022) COVID-19 and myocarditis: A systematic review and overview of current challenges. Heart Fail Rev. 27(1):251–261. doi:10.1007/s10741-021-10087-9

[298] Kang, M. (2022) Viral myocarditis. An J. Viral Myocarditis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK459259/

[299] Ozierański, K., Tymińska, A., Kruk, M., Koń, B., Skwarek, A., *et al.* (2021) Occurrence, trends, management and outcomes of patients hospitalized with clinically suspected myocarditis – ten-year perspectives from the MYO-PL nationwide Database. J Clin Med. 10(20):4672. doi:10.3390/jcm10204672

follow up of 4.7 years), all-cause mortality was 19.2%, while sudden death occurred in 9.9% of cases." [299]

250. Another older report noted that:

> *"The Myocarditis Treatment Trial reported mortality rates for biopsy-verified myocarditis of 20% and 56% at 1 year and 4.3 years, respectively. These outcomes are similar to the Mayo Clinic's observational data of 5-year survival rates that approximate 50%. Survival with giant cell myocarditis is substantially lower, with <20% of patients surviving 5 years."* [300]

251. The global incidence of myocarditis and deaths from this disease steadily climbed over 30 years between 1990 and 2019 by 62% and 65%, respectively, although the age-standardized death rate (ASDR) (about 16 per 100,000) was stable during this period.[301] The age-standardized incidence rate (ASIR) in North America during this period for all ages and sexes was 18.2 per 100,000, and this serves as a useful bench mark for consideration of the expected background rates of myocarditis during the COVID-19 pandemic. World-wide in 2019, men were on average 35% more likely than women to get myocarditis. The risk of myocarditis increases with age; in 2019, 77.76% of cases were in those 65 years and older, 12.26% in 40- to 64-year-olds, and 9.98% in those under 40 years of age. The ASDR from myocarditis is less than 1 in 100,000 for those under 70 years of age. In the 15 to 24 years-old bracket, the ASIR were 12.3 in males and 7.3 in females per 100,000, and the ASDR were 0.13 in males and 0.07 in females per 100,000.[301] Due to the rarity of myocarditis in children and young adults, it is much easier to observe unusual incidence of this disease in these populations, including from COVID-19 and COVID-19 vaccines.

252. Another study by Nasreen *et al.* (2022) examined the historical rates in Ontario between 2015 and 2022 of myocarditis and myopericarditis along with a range of other diseases that have been linked to COVID-19 vaccine adverse events.[302] They noted:

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[300] Magnani, J., Dec, G. (2006) Myocarditis: Current trends in diagnosis and treatment. Circulation. 113(6):876–890. doi:10.1161/CIRCULATIONAHA.105.584532

[301] Wang, T.-W.-Y., Lui, R.-B., Huang, C.-Y., Li, H.-Y., Zhang, Z.-X., *et al.* (2023) Global, regional, and national burdens of myocarditis, 1990–2019: Systematic analysis from GBD 2019. BMC Public Health. 23(1):714. doi:10.1186/s12889-023-15539-5

[302] Nasreen, S., Calzavara, A., Buchan, S.A., Thampi, N., Johnson, C., *et al.* (2022) Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Ontario investigators. Background

"The average annual population was 14 million across all age groups with 51% female. The pre-pandemic mean annual rates per 100,000 population during 2015-2019 were 191 for acute myocardial infarction, 43.9 for idiopathic thrombocytopenia, 28.8 for anaphylaxis, 27.8 for Bell's palsy, 25.0 for febrile convulsions, 22.8 for acute disseminated encephalomyelitis, 11.3 for myocarditis/pericarditis, 8.7 for pericarditis, 2.9 for myocarditis, 2.0 for Kawasaki disease, 1.9 for Guillain-Barré syndrome, and 1.7 for transverse myelitis. Females had higher rates of acute disseminated encephalomyelitis, transverse myelitis and anaphylaxis while males had higher rates of myocarditis, pericarditis, and Guillain-Barré syndrome. Bell's palsy, acute disseminated encephalomyelitis, and Guillain-Barré syndrome increased with age. The mean rates of myocarditis and/or pericarditis increased with age up to 79 years; males had higher rates than females: from 12 to 59 years for myocarditis and ≥12 years for pericarditis."[302]

2.11.2. Myocarditis from COVID-19

253. Early on in the COVID-19 pandemic, health officials widely proclaimed that a person who got COVID-19 was much more likely to get myocarditis than from a COVID-19 vaccine. For example, as part of a resource guide produced by the Office of the Chief Medical Officer for Ontario, which was presented in information sessions to doctors, nurses and pharmacists to encourage COVID-19 vaccination of children 5 to 11 years of age, in slide number 41, it is indicated that for those under 16 years of age, the risk of hospitalized myocarditis is "*133 per 100k COVID-19 infections or 1 in almost every 750 infections*."[303] The citation provided in the slide was Boehmer *et al.* (2021),[304] which was based on the number of US children under 16 years of age that showed up in hospitals and clinics, between March 2020 and January 2021, with COVID-19. This was not the total number of children who were actually infected with SARS-CoV-2, which should include those that were asymptomatic or mildly sick, and

incidence rates of adverse events of special interest related to COVID-19 vaccines in Ontario, Canada, 2015 to 2020, to inform COVID-19 vaccine safety surveillance. Vaccine. 40(24):3305–3312. doi:10.1016/j.vaccine.2022.04.065

[303] Office of the Chief Medical Officer for Ontario. (2021) COVID-19 vaccination in children aged 5–11. Ontario Ministry of Health. Retrieved from https://www.ontariofamilyphysicians.ca/tools-resources/covid-19-resources/covid-19-vaccines/covid-19-vaccination-children-2021-11-26-session-slides.pdf

[304] Boehmer, T.K., Kompaniyets, L., Lavery, A.M., Hsu, J., Ko, J.Y., *et al.* (2021) Association between COVID-19 and myocarditis using hospital-based administrative data – United States, March 2020–January 2021. MMWR Morb Mortal Wkly Rep. 70(35):1228–1232. doi:10.15585/mmwr.mm7035e5

would be about a 100-fold higher (see Table 1). The total number of children tracked in this age group was 3,735,660, of which only 1.7% were reported to be infected with SARS-CoV-2. The number of children under 16 years of age presenting at hospitals with myocarditis was 132 with COVID-19 and 86 without COVID-19. The incidence of myocarditis in all ages groups was only 42.3% higher in 2020 than in pre-pandemic 2019. When all age groups were considered in aggregate, there were 2,116 cases presenting at hospitals with symptomatic myocarditis with COVID-19 and 2,953 cases without COVID-19. Only about 4% of the total number of people tracked in this study (*i.e.,* 36,005,294) had been diagnosed with COVID-19, but the actual number was likely substantially higher as only about 5.7% of known COVID-19 cases were likely hospitalized (Table 1).

254. Interestingly, when Nasreen *et al.* (2022)[302] examined the prevalence rates of various diseases using the mean of incidence values from 2015 to 2019 and compared them with 2000, the first year of the pandemic in Ontario, there were no increases in the total incidence of myocarditis and pericarditis, and actually slight decreases of 15% and 2.5%, respectively. They also noted that the rates of **Guillain-Barré syndrome also decreased by 28%, and acute myocardial infarctions (heart attacks) by 11%.** The authors ascribed the reduced myocarditis due to the effectiveness of lockdown measures and less influenza in 2020.

255. Another study by Singer *et al.* (2021) has been used to support the contention that the risk of myocarditis is substantially higher from COVID-19 than from COVID-19 vaccines for those under 20 years of age. [305] The authors used proprietary data for over 60 million people tracked by 48 US health care organizations in aggregate to examine the general population of 12- to 19- year-olds who were pre-screened to have had COVID-19. There were only 6 out of 6,846 reported COVID-19 cases (0.09%) for 12- to 17-year-old males tracked from April 2020 to March 2021 who had symptomatic myocarditis, which is about a 1 in 1,141 rate. Apart from being a very low number of symptomatic myocarditis cases, it is clear that the total number of male teenagers in this age group in the database likely exceeded 1.5 million, which would indicate an infection rate of with SARS-CoV-2 of only around 0.45%, which is highly unlikely, and even the authors considered that about 9.2% of the 12- to 17-year-olds were infected by this point. This and other dubious assumptions led the authors to suggest an adjusted rate for

[305] Singer, M.E., Taub, I.B., Kaelber, D.C. (2021) Risk of myocarditis from COVID-19 infection in people under age 20: A population-based analysis. medRxiv (preprint). doi:10.1101/2021.07.23.21260998

symptomatic myocarditis of 45 per 100,000 for males, and 21.3 per 100,000 females following SARS-CoV-2 infection. Since about 99.5% of people with symptomatic myocarditis are typically admitted to a hospital, it is likely that total symptomatic myocarditis cases were captured in the study, but the number of SARS-CoV-2 infections was likely underestimated by more than an order of magnitude.

256. Yet another multicenter, retrospective study by Kamath *et al.* (2023) of the Hospital Corporation of America enterprise-wide database identified 8,162 patients 18 years and older with SARS-CoV-2 infections from January 1, 2020, to May 14, 2020.[306] They reported that 929 (11.38%) of these patients met their diagnostic criteria for myocarditis, which was elevated blood troponin T (a marker of heart damage) and brain natriuretic peptide as proxies (as observed in other studies of COVID-19-induced myocarditis[307]). About 48% of the patients had European ethnicity, 26.3% has African ancestry and the rest were from other races, and most of them had pre-existing medical conditions, including over a quarter with previous heart disease. Of the COVID-19 patients with acute myocarditis, 37.9% required respiratory support via ventilation during their hospital stay and 29.8% died, compared to only 9% of COVID-19 patients without acute myocarditis that required ventilation and 5.8% that experienced in-hospital mortality.[306] These findings were similar to another earlier study that was performed with 187 patients with myocarditis in Wuhan, China from January 23, 2020, to February 23, 2020.[308] These studies indicate that COVID-19 can have very serious consequences for hospitalized patients with pre-existing conditions, but these rates of myocarditis with COVID-19 should not be taken as applicable to young, healthy individuals that become infected with SARS-CoV-2, the majority of which are symptom-free.

257. There have been very few studies that have accessed the incidence of myocarditis amongst otherwise healthy young adults who get COVID-19. For high performance athletes under 24 years who had COVID-19, the occurrence of clinical symptomatic myocarditis was estimated in one study to be about 1 in 177. This number was based on full testing with cardiac magnetic resonance imaging (MRI) of 1,597

[306] Kamath, S., Gomah, M.T., Stepman, G., DiMartino, P., Adetula, I. (2023) COVID-19-associated acute myocarditis: Risk factors, clinical outcomes, and implications for early detection and management. Cureus. 15(9):e44617. doi:10.7759/cureus.44617

[307] Pirzada, A., Mokhtar, A.T., Moeller, A.D. (2020) COVID-19 and myocarditis: What do we know so far? CJC Open. 2(4):278–285. doi:10.1016/j.cjco.2020.05.005

[308] Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., *et al.* (2020) Cardiovascular implications of fatal outcomes of patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 5(7):811–818. doi:10.1001/jamacardio.2020.1017

COVID-19-recovered athletes (60.4% males) from 13 US universities from March 1, 2020, through December 15, 2020, for myocarditis. Only 9 participants were symptomatic for myocarditis, and another 28 were subclinical and asymptomatic (27 of the 38 were males).[309] Data on age and race were not collected. The higher rates of COVID-19-associated myocarditis with this particular select group of athletes likely reflects the extreme physical exertions that come with practice from training and competition. It appeared that there were 3-times more asymptomatic myocarditis, but underlying heart damage was still evident based on cardiac MRI. It is reasonable that high performance athletes are much more likely to develop symptomatic myocarditis than the general public, as the intense exercise can precipitate symptomatic myocarditis. It is important to note that 2,461 athletes in this study were identified as COVID-19 cases based on PCR testing for SARS-CoV-2, but many asymptomatic individuals may not have been tested. Some 9000 athletes would have been training in the 13 universities at the time. A higher proportion of the athletes in the study were likely infected by the virus by the end of 2020, higher than 27%. Thus, the risks of SARS-CoV-2-induced myocarditis were likely lower than represented. However, these studies demonstrate that most people with asymptomatic myocarditis from SARS-CoV-2 infection are unaware of the damage to their hearts from the underlying inflammation. This would also be true with asymptomatic myocarditis and myopericarditis from COVID-19 vaccines.

258. A significant advantage of these early studies is that COVID-19 vaccines were not yet available, so the impacts of vaccination on the rates of myocarditis and myopericarditis are not a confounding issue. However, previous exposure to SARS-CoV-2 might have a significant impact on COVID-19 vaccine-induced rates of myocarditis and myopericarditis. Furthermore, the Wuhan SARS-CoV-2 virus was more virulent than later variants that predominated, so this may have also reduced the risks of myocarditis and myopericarditis as the COVID-19 pandemic progressed, at least for the un-vaccinated. The previous infection and development of natural immunity, followed by COVID-19 vaccination that became mandatory in 2021 in most of these colleges may have caused even higher rates of myocarditis and myopericarditis in college athletes, but this has not been formally tested as in the 13 US universities study.

[309] Daniels, C.J., Rajpal, S., Greenshields, J.T., *et al.* (2021) Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: Results from the Big Ten COVID-19 Cardiac Registry. JAMA Cardiol. 6(9):1078–1087. doi:10.1001/jamacardio.2021.2065

259. Based on PCR testing alone, by April 26, 2023, over 104 million Americans had been infected with SARS-CoV-2.[310] Studies of serological testing for SARS-CoV-2 anti-nucleocapsid antibodies in Canada up to the same time indicate that at least 75% of Canadians had been infected with SARS-CoV-2,[311] and this is probably true for Americans as well. If the risks of myocarditis and myopericarditis from SARS-CoV-2 viral infections were as high as suggested in these earlier studies, then a very much higher rate of these diseases would have been evident in North America and world-wide, which apparently has not transpired. One might suggest that this was circumvented due to the wide-spread adoption of COVID-19 vaccines. However, as will be evident in the next subsection, the COVID-19 vaccines have been linked to increased rates of myocarditis. So, for at least healthy men under 30 years of age, there is a greater risk of myocarditis and myopericarditis from these vaccines than from a SARS-CoV-2 infection.

2.11.3. Myocarditis and Myopericarditis from COVID-19 Vaccines

260. In the Phase 3 clinical studies with COVID-19 vaccines, the risks of myocarditis and pericarditis following inoculation were not readily apparent. Tracking for COVID-19 vaccine-induced adverse events in the VAERS after the dissemination of these vaccines soon flagged this as a problem (Figure 12).[312] A very comprehensive, early Israeli study by Barda *et al.* (2021) compared pathology from COVID-19 vaccine injury to that produced with COVID-19 from SARS-CoV-2 infection.[313] However, this study, which covered the first five months of the start of the vaccination program in Israel, reflected only up to a second dose of the Pfizer/BioNTech vaccine, and provided comparisons with the risks of COVID-19 injury associated with the Wuhan and earlier variants of COVID-19 that were more severe than from the Omicron variant. The most problematic aspect of this study, despite its comprehensive approach, is that it did not provide a breakdown of the risks by age group or gender. In this study, it was suggested that there was an overall risk of about 1 in 45,000 in getting symptomatic myocarditis from the

[310] Silk, B.J., Scobie, H.M., Duck, W.M., Palmer, T., Ahmad, F.B., *et al.* (2023) COVID-19 surveillance after expiration of the Public Health Emergency Declaration – United States, May 11, 2023. MMWR Morb Mortal Wkly Rep. 72(19):523–528. doi:10.15585/mmwr.mm7219e1

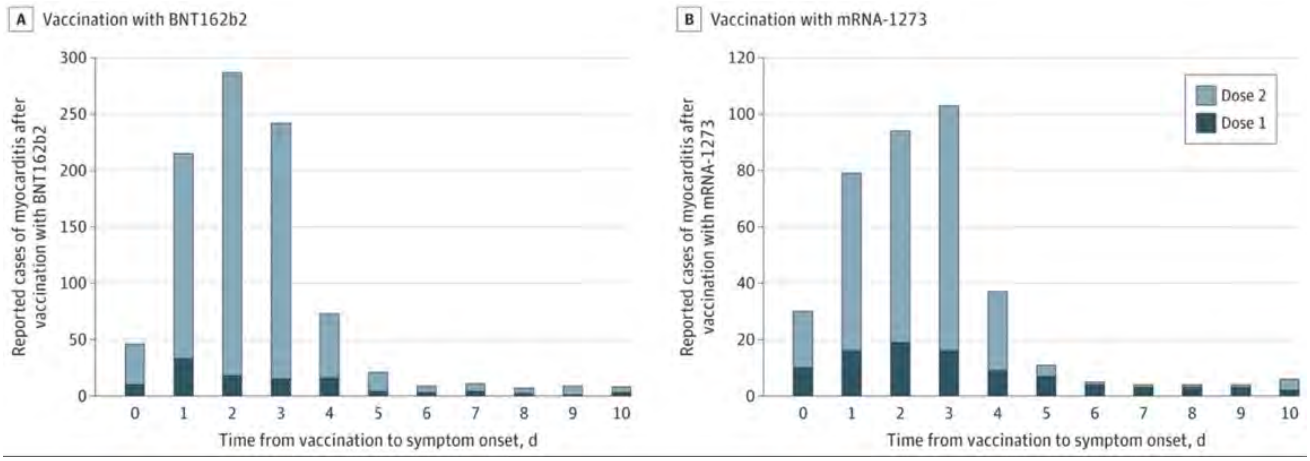
[311] Murphy, T.J., Swail, H., Jain, J., Anderson, M., Awadalla, P., *et al.* (2023) The evolution of SARS-CoV-2 seroprevalence in Canada: A time-series study, 2020–2023. CMAJ. 195(31):E1030-E1037. doi:10.1503/cmaj.230949

[312] Oster, E.O., Shay, D.K., Su, J.R. *et al.* (2022) Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. JAMA. 327(4):331-340. https://jamanetwork.com/journals/jama/fullarticle/2788346)

[313] Barda, N., Dagan, N., Ben-Shlomo, Y., Kepten, E., Waxman, J., *et al.* (2021) Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med. 385(12):1078–1090. doi:10.1056/NEJMoa2110475

Pfizer/BioNTech vaccine for those over 18 years of age, but this was still about 3.24-times higher than in the unvaccinated when all ages groups were aggregated.

Figure 12. Daily US VAERS myocarditis cases reported for COVID-19 vaccines. Reproduced from Figure 2 of Oster *et al.* (2022).[312]



261. Montag and Kampf (2022) following analysis of German hospitalized cases of myocarditis or pericarditis noted that "*In 2019 and 2020, there were no or only very few cases (<4) of myocarditis or pericarditis described as adverse events after any type of vaccination*."[314] Of these, none of them required intensive-care treatment. In 2020, there were 32 hospitalized COVID-19 patients that had myocarditis or myopericarditis and 15 of them needed intensive-care treatment. However, in 2021, the number of hospitalized myocarditis or pericarditis cases among juveniles (10– to 17-year-olds) more than doubled from 270 (2019) and 196 (2020) to 506 (2021). In total, only 11 cases (2.2%) were associated with SARS-CoV-2 infection, whereas 160 cases (31.6%) were associated with a COVID-19 vaccine or vaccination in general, and 32 of these cases required intensive-care treatment. Similar results were also described for young adults of 18- to 29-years of age.[314]

262. In a meta-analysis of 22 published studies following administration of 405 million doses of COVID-19 vaccines, Li *et al.* (2022) concluded that "*there was no statistically significant difference in the overall incidence of myocarditis or pericarditis between those with COVID-19 vaccination and those without. It*

[314] Montag, K., Kampf, G. (2022) Hospitalised myocarditis and pericarditis cases in Germany indicate a higher post-vaccination risk for young people mainly after COVID-19 vaccination. J Clin Med. 11(20):6073. doi:10.3390/jcm11206073

was also found that the risk of myocarditis was higher with mRNA-based vaccines as compared to non-mRNA vaccines as well as the second vaccination dose posing a higher risk for myocarditis than the first-time doses."[315] The authors also noted that in seven studies of adolescents aged 12- to 19-years-old that 111 of 1,008,753 (1 in 9088, or 11 in 100,000) vaccinated youth developed symptomatic myocarditis or myopericarditis, with females in this age group being about 13.9-fold less likely to be afflicted with these diseases.

263. It is now well recognized that the incidence of symptomatic myocarditis in males who are from 12- to 29-years of age with the second shot of the BNT162b2 vaccine ranges from 1 in 5,000 to 1 in 15,000 depending on the study (Table 5). For Moderna's mRNA-1273, with this demographic, the risk of myocarditis is even higher, at around 1 in 4,400.[316] Similar risks are observed with symptomatic myopericarditis in male adolescents and young adults. When the risks of either symptomatic myocarditis or myopericarditis are considered together, the chances of acquiring one of these diseases becomes even greater, as high at 1 in 704 with BNT162b2 and 1 in 264 for 16- to 24-years-old males following a second dose in one Nordic study.[317] By contrast, in these same studies, there were no recorded female cases with symptomatic myocarditis or myopericarditis (*i.e.*, no measurable risk). However, in most studies with 12- to 39-year-olds, the risks of these diseases in young females can be calculated from Table 5 to be about 6.2-fold lower on average than in their male counterparts. The reasons for the predominance in myocarditis and myopericarditis in men is not known, but may relate to sex hormone differences in the immune response and myocarditis, and possibly the under diagnosis of cardiac disease in women.

264. The incidence of myocarditis and myopericarditis following a third dose of BNT162b2 continued to be high in males under 30 years of age according to the data presented from a study conducted in British Columbia by *Naveed et al.* (2020), and was further increased for older men in the 30- to 49-years- old

[315] Li, M., Wang, X., Feng, J., Feng, Z., Li, W., Ya, B. (2022) Myocarditis or pericarditis following the COVID-19 vaccination in adolescents: A systematic review. Vaccines (Basel). 10(8):1316. doi:10.3390/vaccines10081316

[316] Klein, N.P. (2021) Myocarditis analyses in the Vaccine Safety Datalink: Rapid cycle analyses and "head-to-head" product comparisons. ACIP meeting COVID-19 Vaccines. Retrieved from https://stacks.cdc.gov/view/cdc/110921

[317] Karlstad, Ø., Hovi, P., Husby, A., Härkänen, T., Selmer, R.M., *et al.* (2022) SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. JAMA Cardiol. 7(6):600–612. doi:10.1001/jamacardio.2022.0583

age bracket.[318] For example, with the booster dose of BNT162b2 in men between 40- and 49- years of age, the incidence of symptomatic myocarditis was 1 in 3922. For males under under 69 years of age, there was also trend toward increased myopericarditis with the third dose of BNT162b2, and in the 12- to 17-years-old males, the risk of myopericarditis increased to 1 in 4,024 compared to 1 in 6,281 with the second dose. These increases in the rates of myocarditis and myopericarditis were not evident with the mRNA-1273 booster, and were lower than seen following the second dose. This may have been in part because fewer people took a third shot of this mRNA vaccine after the stronger adverse effects experienced with earlier inoculations discouraged them. In an examination of the Permanente Northwest Health Plan with male and female members aged 18- to 39-years in the US, Sharff *et al.* (2022) recorded 4 males and 2 females with symptomatic myopericarditis.[319] In the case of the males in the study, the incidence of symptomatic myopericarditis with the BNT162b2 booster worked out to 1 in 6,800.

Table 5. Rates of COVID-19 vaccine induced myocarditis and myopericarditis in people under 40 years after a second dose of the same COVID-19 vaccine.

Vaccine	Disease	Incidence per 100,000	Incidence/ Vaccinated Study Participants	Demo-graphic	Country	Study Period	Reference
Pfizer/ BioNTech - BNT162b2	Myocarditis	6.73	9/133,633	Males, 12-17 years	Canada, BC	December 15, 2020 to March 10, 2022	Naveed *et al.* (2022) [318]
		1.53	2/130,628	Females, 12-17 years			
Moderna - mRNA-1273	Myocarditis	22,97	25/108,820	Males, 18-29 years	Canada, BC	December 15, 2020 to March 10, 2022	Naveed *et al*. (2022) [318]
		2	2/99,895	Females, 18-29 years			
Pfizer/ BioNTech - BNT162b2	Myopericarditis	9	12/133,633	Males, 12-17 years	Canada, BC	December 15, 2020 to March 10, 2022	Naveed *et al*. (2022) [318]
		3.1	4/130,628	Females, 12-17 years			
Moderna - mRNA-1273	Myopericarditis	32.2	35/108,820	Males, 18-29 years	Canada, BC	December 15, 2020 to March 10, 2022	Naveed *et al*. (2022) [127]
		5	5/99,895	Females, 18-29 years			

[318] Naveed, Z., Li, J., Spencer, M., Wilton, J., Naus, M., García, H.A.V., *et al.* (2022) Observed versus expected rates of myocarditis after SARS-CoV-2 vaccination: A population-based cohort study. CMAJ. 94(45):E1529-E1536. doi:10.1503/cmaj.220676

[319] Sharff, K.A., Dancoes, D.M., Longueil, J.L., Lewis, P.F., Johnson, E.S. (2022) Myopericarditis after COVID-19 booster dose vaccination. Am J Cardiol. 172:165–166. doi:10.1016/j.amjcard.2022.02.039

Vaccine	Disease	Incidence per 100,000	Incidence/ Vaccinated Study Participants	Demo-graphic	Country	Study Period	Reference
Pfizer/ BioNTech - BNT162b2	Myocarditis	5.24	6/114,450*	Males, 20-51 years (median 25)	United States Military	January to April, 2021	Montgomery *et al.* (2021) [320]
		0	0/28,350*	Females, 20-51 years (median 25)			
Moderna - mRNA-1273	Myocarditis	4.35	14/321,550*	Males, 20-51 years (median 25)	United States Military	January to April, 2021	Montgomery *et al.* (2021) [320]
		0	0/79,650*	Females, 20-51 years (median 25)			
Pfizer/ BioNTech - BNT162b2	Myocarditis and myopericarditis	19.31	44/?	Mixed, 12-39 years	United States	December 2020 to October 9, 2021	Klein (2021) [316]
Moderna - mRNA-1273	Myocarditis and myopericarditis	37.51	22/?	Mixed, 18-39 years	United States	December 2020 to October 9, 2021	Klein (2021) [316]
Pfizer/ BioNTech - BNT162b2	Myocarditis and myopericarditis	11.65	56/480,407	Males, 18-25 years	United States	December 18, 2020, to December 25, 2021	Wong *et al.* (2022) [321]
		3.49	20/572,330	Females, 18-25 years			
Moderna - mRNA-1273	Myocarditis and myopericarditis	14.20	34/239,420	Males, 18-25 years	United States	December 18, 2020, to December 25, 2021	Wong *et al.* (2022) [321]
		2.84	8/282,057	Females, 18-25 years			
Pfizer/ BioNTech - BNT162b2	Myocarditis and myopericarditis	1.70	60/3,535,806	Males, 13-39 years	England	December 1 2020, to December 15, 2021	Patone *et al.* (2022) [322]
		0.22	9/4,131,123	Females, 13-39 years			
Moderna - mRNA-1273	Myocarditis and myopericarditis	102.60	36/35,074	Males, 13-39 years	England	December 1 2020, to December 15, 2021	Patone *et al.* (2022) [322]
		0	0/328,311	Females, 13-39 years			

[320] Montgomery, J, Ryan, M., Engler, R., Hoffman, D., McClenathan, B., *et al.* (2021) Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US Military. JAMA Cardiol. 6(10):1202–1206. doi:10.1001/jamacardio.2021.2833

[321] Wong, H.L., Hu, M., Zhou, C.K., Lloyd, P.C., Amend, K.L., *et al.* (2022) Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: A cohort study in claims databases. Lancet. 399(10342):2191–2199. doi:10.1016/S0140-6736(22)00791-7

[322] Patone, M., Mei, X.W., Handunnetthi, L., Dixon, S., Zaccardi, F., *et al.* (2022) Risk of myocarditis after sequential doses of COVID-19 vaccine and SARS-CoV-2 infection by age and sex. Circulation. 146(10):743–754. doi:10.1161/CIRCULATIONAHA.122.059970

Vaccine	Disease	Incidence per 100,000	Incidence/ Vaccinated Study Participants	Demo-graphic	Country	Study Period	Reference
AstraZeneca - ChAdOx1	Myocarditis and pericarditis	2.21	21/949,865	Males, 13-39 years	England	December 1 2020, to December 15, 2021	Patone *et al.* (2022) [322]
		0	0/1,437,517	Females, 13-39 years			
Pfizer/ BioNTech - BNT162b2	Myocarditis and myopericarditis	9.42	48/509,590	Mixed, 12-39 years	Denmark	October 1, 2020 to October 5, 2021	Husby *et al.* (2021) [323]
Moderna - mRNA-1273	Myocarditis and myopericarditis	28.21	21/74,441	Mixed, 12-39 years	Denmark	October 1, 2020 to October 5, 2021	Husby *et al.* (2021) [323]
Pfizer/ BioNTech - BNT162b2	Myopericarditis	9.74	13/133,477	Males, 12-17 years	Denmark	May 15 to September 15, 2021	Nygaard *et al.* (2022) [324]
		1.56	2/127,857	Females, 12-17 years			
Pfizer/ BioNTech - BNT162b2	Myocarditis and myopericarditis	142	59/?	Males, 16-24 years	Denmark, Finland, Norway, Sweden	December 27, 2020 to October 5, 2021	Karlstad *et al.* (2022) [317]
		0	0/?	Females, 16-24 years			
Moderna - mRNA-1273	Myocarditis and myopericarditis	379	22/?	Males, 16-24 years	Denmark, Finland, Norway, Sweden	December 27, 2020 to October 5, 2021	Karlstad *et al.* (2022) [317]
		0	0/?	Females, 16-24 years			
Pfizer/ BioNTech - BNT162b2	Myocarditis	8.68	8/92,200	Males, 16-29 years	Israel	June 2 to November 30, 2021	Witberg *et al.* (2022) [325]
		1.08	1/90,405	Females, 16-29 years			
Pfizer/ BioNTech - BNT162b2	Myocarditis and myopericarditis	13.23	58/438,511	Males, 16-24 years	Israel	December 20, 2020 to May, 2021	Mevorach *et al.* (2021) [326]
		1.85	8/431,666	Females, 16-24 years			

[323] Husby, A., Hansen, J.V., Fosbøl, E., Thiesson, E.M., Madsen, M., *et al.* (2021) SARS-CoV-2 vaccination and myocarditis or myopericarditis: Population based cohort study. BMJ. 375:e068665. doi:10.1136/bmj-2021-068665

[324] Nygaard, U., Holm, M., Bohnstedt, C., Chai, Q., Schmidt, L.S., *et al.* (2022) Population-based incidence of myopericarditis after COVID-19 vaccination in Danish adolescents. Pediatr Infect Dis J. 1(1):e25-e28. doi:10.1097/INF.0000000000003389

[325] Witberg, G., Magen, O., Hoss, S., Talmor-Barkan, Y., Richter, I., *et al.* (2022) Myocarditis after BNT162b2 vaccination in Israeli adolescents. N Engl J Med. 387(19):1816–1817. doi:10.1056/NEJMc2207270

[326] Mevorach, D., Anis, E., Cedar, N., Bromberg, M., Haas, E.J., *et al.* (2021) Myocarditis after BNT162b2 mRNA vaccine against COVID-19 in Israel. N Engl J Med. 385(23):2140–2149. doi:10.1056/NEJMoa2109730

Vaccine	Disease	Incidence per 100,000	Incidence/ Vaccinated Study Participants	Demo-graphic	Country	Study Period	Reference
Pfizer/ BioNTech - BNT162b2	Myocarditis	20.94	38/181,392	Males, 12-17 years	Hong Kong	March 10 to October 18, 2021	Li *et al.* (2022) [327]
		2.82	5/177,405	Females, 12-17 years			
Pfizer/ BioNTech - BNT162b2	Myocarditis and myopericarditis	4.3	19/442,025	Mixed, 16-18 years	South Korea	July 19 to October 2021	June Choe *et al.* (2022) [328]

*Exact numbers of military personnel vaccinated with the Moderna and Pfizer/BioNTech vaccines were not provided. However, it was reported that the US Army initially procured 5.9 million doses from Moderna and 2.1 million doses from Pfizer.[329] This ratio was applied to the total numbers of males (436,000) and females (108,000) that were vaccinated to calculate the myocarditis rates.

265. A small study by Levi *et al.* (2023) with 324 healthcare workers (59% female, median age of 52 years) in Israel with a fourth dose of BNT162b2 was undertaken to evaluate whether there was an increased risk of myocarditis with further vaccine boosting.[329a] The authors reported that two of the participants had acute vaccine-related myocardial injury, a female who had mild symptoms and the other a male who was asymptomatic. Despite high cardiac troponin levels in their blood, myocarditis was ruled out in both cases. About 41% of the participants had some sort of vaccine-adverse reaction, most commonly injection-site local pain, muscle aches and pains, and fatigue. A particularly interesting observation in this study was the elevated levels of troponin in 6.5% of the subjects just prior to receiving their fourth vaccine dose, which might be evidence of prior heart damage.

[327] Li, X., Lai, F.T.T., Chua, G.T., Kwan, M.Y.W., Lau, Y.L., *et al.* (2022) Myocarditis following COVID-19 BNT162b2 vaccination among adolescents in Hong Kong. JAMA Pediatr. 2022 Jun 1;176(6):612–614. doi:10.1001/jamapediatrics.2022.0101

[328] June Choe, Y., Yi, S., Hwang, I., Kim, J., Park, Y.J., *et al.* (2022) Safety and effectiveness of BNT162b2 mRNA COVID-19 vaccine in adolescents. Vaccine. 40(5):691–694. doi:10.1016/j.vaccine.2021.12.044

[329] Cronk, T.M. (2020) Pfizer, Moderna produce COVID-19 vaccine. U.S. Department of Defence. Retrieved from https://www.defense.gov/News/News-Stories/Article/Article/2453288/pfizer-moderna-produce-covid-19-vaccine/

[329a] Levi, N., Moravsky, G., Weitsman, T., Amsalem, I., Bar-Sheshet Itach, S., *et al.* (2023) A prospective study on myocardial injury after BNT162b2 mRNA COVID-19 fourth dose vaccination in healthy persons. Eur J Heart Fail. 25(2):313–318. doi:10.1002/ejhf.2687

266. As discussed in the previous subsection, the risk of myocarditis from a SARS-CoV-2 infection by age is much higher in elderly people who are known to also have more severe COVID-19 than in younger people. Consequently, the risk to benefit ratio with COVID-19 vaccination versus SARS-CoV-2 infection when it comes to myocarditis and myopericarditis is very different when based on age, sex and pre-existing morbidities. Yet, almost categorically in these aforementioned studies, the authors still advocated that everyone should be vaccinated against COVID-19 due to higher risks associated with a SARS-CoV-2 infection.

267. As seen with SARS-CoV-2-induced myocarditis, it should be appreciated that risks of undiagnosed asymptomatic myocarditis or myopericarditis would be expected to be much higher in adolescent and younger males, especially since they would normally have a long life before them. The prevalence of asymptomatic myocarditis or myopericarditis was never assessed in any of the clinical studies with COVID-19 vaccines, and not quantified in any of the aforementioned studies. However, it was carefully investigated by Mansanguan *et al.* (2022) in a study of 301 teenagers of 13 to 18 years of age in Thailand following their receipt of a second dose of the Pfizer/BioNtech BNT162b2 vaccine.[329b] **Cardiovascular effects were found in 29.24% of the teenagers, ranging from tachycardia, palpitation, and myopericarditis. Of the 201 males, four had evidence of asymptomatic myocarditis, one had myopericarditis, and two had pericarditis for a rate of 1 in 29**. This involved active monitoring of heart abnormalities, including presence of heart proteins such as troponin in the blood, cardiac MRI, electrocardiogram measurements and physical examinations.

268. In light of the relatively high frequency of risk for myocarditis and myopericarditis among younger males following COVID-19 vaccination, the question arises whether or not this is serious and potentially lethal. Kracalik *et al.* (2022) analyzed 519 US individuals (88% male) aged 12- to 19- years-old (median was 17 years) three months after the onset of COVID-19 vaccine-induced myocarditis.[330] They noted

[329b] Mansanguan, S., Charunwatthana, P., Piyaphanee, W., Dechkhajorn, W., Poolcharoen, A., Mansanguan, C. (2022) Cardiovascular manifestation of the BNT162b2 mRNA COVID-19 vaccine in adolescents. Trop. Med. Infect. Dis. 7(8):196. doi:10.3390/tropicalmed7080196

[330] Kracalik, I., Oster, M.E., Broder, K.R., Cortese, M.M., Glover, M., *et al.* (2022) Myocarditis outcomes after mRNA COVID-19 vaccination investigators and the CDC COVID-19 Response Team. Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: A follow-up surveillance study. Lancet Child Adolesc Health. 6(11):788–798. doi:10.1016/S2352-4642(22)00244-9

that while most patients showed marked improvements in cardiac diagnostic markers (*e.g.,* troponin) and testing (echocardiograms, electrocardiograms, exercise stress), 54% still showed abnormalities by cardiac MRI.

269. Barmada *et al.* (2023) found that 80% of those with vaccine-induced symptomatic myocarditis in their US study still had lasting effects on their hearts as revealed by MRI scans over 6 months after diagnosis.[331] Patone *et al*. reported in their analysis of 2,861 hospitalized English patients that got symptomatic myocarditis following COVID-19 vaccination, 345 (12%) died within 28 days of hospital admission with myocarditis or with myocarditis as the cause of death recorded in the death certificate.[322] Cho *et al.* (2023) in their study of 480 Koreans that got COVID-19 vaccine-induced symptomatic myocarditis observed 21 had died (4.4%) after a year.[332] Within a week of their COVID-19 mRNA vaccination, eight of these individuals, six males and two females all under 45 years of age, died from sudden cardiac death. These rates of death are consistent with the rates of death observed with viral-induced myocarditis.[298]

270. In a meta-analysis of 14 publications that described the autopsy results of 28 people who died mostly within a week following their COVID-19 vaccination, Hulscher *et al.* (2023) noted that 26 of them involved exclusively the cardiovascular system.[333] The authors established that all of these 28 deaths were causally linked to COVID-19 vaccination by independent adjudication and stated:

> ***"****The temporal relationship, internal and external consistency seen among cases in this review with known COVID-19 vaccine-induced myocarditis, its pathobiological mechanisms and related excess death, complemented with autopsy confirmation, independent adjudication, and application of the Bradford Hill criteria to the overall epidemiology of vaccine myocarditis, suggests there is a high likelihood of a causal link between COVID-19 vaccines and death from*

[331] Barmada, A., Klein, J., Ramaswamy, A., Brodsky, N.N., Jaycox, J.R., *et al.* (2023) Cytokinopathy with aberrant cytotoxic lymphocytes and profibrotic myeloid response in SARS-CoV-2 mRNA vaccine-associated myocarditis. Sci Immunol. 8(83):eadh3455. doi:10.1126/sciimmunol.adh3455

[332] Cho, J.Y., Kim, K.H., Lee, N., Cho, S.H., Kim, S.Y., *et al.* (2023) COVID-19 vaccination-related myocarditis: A Korean nationwide study. Eur Heart J. 44(24):2234–2243. doi:10.1093/eurheartj/ehad339

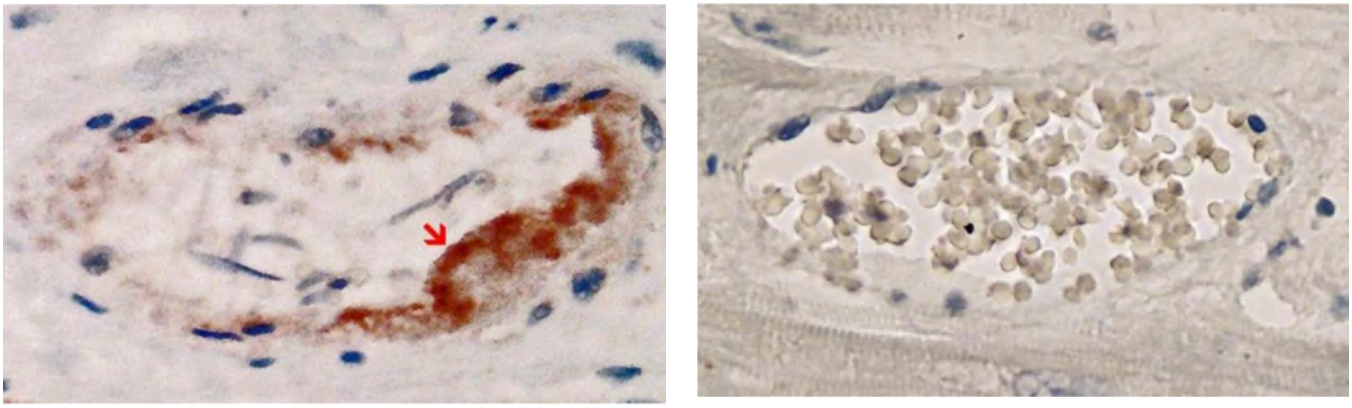
[333] Hulscher, N., Hodkinson, R., Makis, W., McCullough, P. (2023) Autopsy proven fatal COVID-19 vaccine-induced myocarditis. *Preprints.* 2023071198. doi:10.20944/preprints202307.1198.v1

suspected myocarditis in cases where sudden, unexpected death has occurred in a vaccinated person." [333]

2.12. Mechanism of COVID-19 Vaccine-Induced Pathology from Autopsy

271. The mechanism by which COVID-19 genetic vaccines induce myocarditis has been revealed from careful autopsy studies. This became first apparent in the scientific literature from immunohistochemistry studies performed by German pathologist Dr. Michael Mörz on a deceased male, 76-years-old Parkinson's patient who died within 3 weeks of receiving his third inoculation with the BNT162b2 mRNA.[334] Using specific antibodies to detect either the Spike or Nucleocapsid proteins in tissue slices, only the Spike protein was detected within the foci of inflammation in both the brain and the heart, particularly in the endothelial cells of small blood vessels (Figure 13). No Nucleocapsid protein could be detected at these sites, which ruled out an actual SARS-CoV-2 infection to account for the Spike protein detection. From inspection of the foci of Spike protein detected in the brain and heart slices, it was evident that the Spike protein had been locally produced, almost certainly from the spread of the lipid nanoparticles in the COVID-19 vaccine.

Figure 13. Immunohistochemistry of Spike (left panel with anti-Spike antibody) and Nucleocapsid protein (right panel with anti-Nucleocapsid antibody) expression in the heart left ventricle in a 76-year-old patient with Parkinson's disease that died 3 weeks after his third COVID-19 vaccination. The lack of brown stain indicates that Nucleocapsid protein from the SARS-CoV-2 virus was not in the heart tissue. The prevalence of blue-stained, mononuclear immune cells in image on the left was also associated with prominent endothelial swelling from the inflammation. Retrieved from Mörz (2022).[334]



[334] Mörz, M. (2022) Case report: Multifocal necrotizing encephalitis and myocarditis after BNT162b2 mRNA vaccination against COVID-19. Vaccines (Basel). 10(10):1651. doi:10.3390/vaccines10101651

272. Even more extensive analyses of 75 people in the Reutlingen area that had died following COVID-19 vaccinations were performed by another German pathologist Professor Arne Burkhardt and his international team of nine other pathologists, coroners, biologists and chemists. These deceased individuals (40 men and 35 women with a median age at death of 65.7 years) had died one day to ten months after their last COVID-19 vaccination, most commonly with the BNT162b2 vaccine. The cause of death for 68 of them was previously ruled as "natural" or "uncertain" by pathologists or coroners at the time of death (only 7 were possibly linked to COVID-19 vaccination), and 19 of these cases were examples of unexpected Sudden Adult Death Syndrome. Dr. Burkhardt's team subsequently determined that 77% of these deaths (21 beyond reasonable doubt and 37 probable) were caused by their COVID-19 vaccination. The CCCA Scientific and Medical Advisory Committee was privileged to review many of Professor Burkhardt's findings with him, and a video copy of his presentation is posted on the CCCA website.[335] In the immunohistochemistry images of the various tissues retrieved from the deceased individuals that Dr. Burkardt's team analyzed, it was apparent that the Spike protein was widely and highly expressed in many of the tissue samples, whereas the Nucleocapsid protein was absent, ruling out active SARS-CoV-2 infections. Furthermore, in these images it was clear that there was infiltration of immune cells and clear tissue pathology. This included, as observed by Dr. Matthew Mörz with the deceased Parkinson's patient, Spike protein expression, immune cell presence and cellular damage in the heart muscle. These findings are in line with the expected inflammatory responses that would arise from the expression of Spike protein on the surface of cells. Significantly, the detection of Spike protein was evident in the deceased who died even 10 months after their last vaccination, and the Spike protein production was concentrated in the tissue images at the sites of destruction. This means that the detected Spike protein was not simply produced at the site of injection in the muscle and released from the muscle cells into the circulation, but rather the lipid nanoparticles or adenoviruses in the vaccines traveled throughout the body and produced the Spike protein locally.

273. With respect to the type of immune cells that could be responsible for the inflammatory attack on Spike-producing cells in the heart with myocarditis and myopericarditis, the work of Barmada *et al.* (2023) provides some insight.[331] These investigators ruled out the production of cross-reactive

[335] Burkhardt, A. (2023) The underlying pathology of spike protein biodistribution in people that died post COVID-19 vaccination. Canadian Covid Care Alliance. Retrieved from https://www.canadiancovidcarealliance.org/all/professor-arne-burkhardt-video/

antibodies that recognized normal cardiac proteins or expansion of the T- and B-lymphocytes. They also noted that there was not an overproduction of Spike-recognizing antibodies especially in these patients compared to other people vaccinated for COVID-19. However, there were many immune changes, including more production of interleukins (*e.g.,* IL-1β, IL-1RA (actually a receptor for IL-1) and IL-15) and chemokines (*e.g.,* CCL4, CXCL1 and CXCL10), and activation of cytotoxic T-lymphocytes and natural killer (NK) cells, and inflammatory monocytes. These responses are consistent with the Spike protein-induced changes illustrated in Figure 3, which result in damage and potentially death to Spike protein-producing cells by immune cell attack and the activation of the complement-cascade. Other causes may include the dsRNA contamination which act as an intrinsic adjuvant and may induce uncontrolled immune-inflammatory reactions. Vaccine lipid nanoparticles have been proposed to preferentially transfect macrophages and dendritic cells residing in peripheral tissue such as myocardium, and may induce autoimmunity.[336] Initiatives to reduce dsRNA contamination in the vaccines have been noted by Moderna who have designed a T7 RNA polymerase that produces very little dsRNA.[337]

274. In view of the potential mechanisms of how myocarditis and myopericarditis can come about from COVID-19 genetic vaccines, there is no compelling reason to believe that these adverse effects at the cellular and tissue level are not also produced at high levels in many females and the elderly. The symptoms of vaccine-induced myocarditis and myopericarditis may be simply more manifested in young males, due to their tendency to be much more physically active, which could exacerbate the condition.

2.13. Increased Sudden Cardiac Arrest in Athletes

275. Prior to the COVID-19 pandemic, the incidences of sudden cardiac arrest (SCA) and sudden cardiac death (SCD) were relatively low in students and professional athletes under 30 years of age. Peterson *et al*. (2023) collected data in this regard from the US National Center for Catastrophic Sports Injury Research, the University of Washington Medicine Center for Sports Cardiology, searches of student-

[336] Milano, G., Gal, J., Creisson, A., Chamorey, E. (2021) Myocarditis and COVID-19 mRNA vaccines: A mechanistic hypothesis involving dsRNA. Future Virol. 10.2217/fvl-2021-0280. doi:10.2217/fvl-2021-0280

[337] Dousis, A., Ravichandran, K., Hobert, E.M., Moore, M.J., Rabideau, A.E. (2023) An engineered T7 RNA polymerase that produces mRNA free of immunostimulatory byproducts. Nat Biotechnol. 41(4):560–568. doi:10.1038/s41587-022-01525-6

athlete deaths on the National Collegiate Athletic Association's Resolutions List, the National Federation of State High School Associations, and the Parent Heart Watch.[338] From July 2014 through to June 2018, the authors identified 331 cases, of which 173 were fatal. The majority of these cases occurred in males (83.7%), high school athletes (61.6%), and during exercise (74%), with cardiomyopathies accounting for nearly half (47%) of the cases with college and professional athletes. Ice-hockey (1 in 23,550) followed by basketball (1 in 39,811) and then football (1 in 82,587) had the highest incidence rates of SCD for males. From their data, it can be calculated that there was an average of 43 SCD per year in the US student athletes.

276. An earlier study by Bille *et al.* (2006) on SCD in sport in the scientific literature for athletes under 35 years of age noted that between 1966 to 2004, there were 1,101 reported cases.[339] Of these about 50% had congenital anatomical heart disease and cardiomyopathies. The expected rate of SCD in young athletes averaged to about 29 per year.

277. And yet in recent times, there has been a surge in the number of news and social media reports of collapses and sudden deaths of athletes world-wide since the availability of COVID-19 vaccines. The most comprehensive list of athletes that have lost consciousness or died since January 2021 is available on the social media website www.goodsciencing.com.[340] Most of these reports arise out of US news sources. While the authors of the website are anonymous, they provide direct url links to news sources for most of the 2,024 athletes identified by name up to September 30, 2023, who have collapsed or died (69.4%), and who were confirmed or highly suspected to have been vaccinated against COVID-19. This list includes those over 40 years of age, but none apparently with reported congenital heart abnormalities. For the entries where the age of the person was provided (1,894), 1,293 (68%) were under 40 years of age and of these 625 (48%) had died. Some of the deaths were also identified as from

[338] Peterson, D.F., Kucera, K., Thomas, L.C., Maleszewski, J., Siebert, D., *et al.* (2021) Aetiology and incidence of sudden cardiac arrest and death in young competitive athletes in the USA: A 4-year prospective study. Br J Sports Med. 55(21):1196–1203. doi:10.1136/bjsports-2020-102666

[339] Bille, K., Figueiras, D., Schamasch, P., Kappenberger, L., Brenner, J.I., *et al.* (2006) Sudden cardiac death in athletes: The Lausanne Recommendations. Eur J Cardiovasc Prev Rehabil. 13(6):859–875. doi:10.1097/01.hjr.0000238397.50341

[340] (2023) 2024 athlete cardiac arrests or serious issues, 1417 of them dead, since COVID injection. Real Science. Retrieved from https://goodsciencing.com/covid/athletes-suffer-cardiac-arrest-die-after-covid-shot/

comorbidities such as cancer. From the 1,417 deaths over the 2.75-years period, this corresponds to a rate of 515 deaths per year on average since the introduction of COVID-19 vaccine.

278. Binkhorst and Goldstein (2023) analyzed the incidence of SCA and SCD in US athletes under 40 years of age from January 2021 to December 2022, using highly filtered data from the www.goodsciencing.com website.[341] They recognized that COVID-19 vaccination status of those that experienced SCA or SDA was unverified, and so they tried to apply the strict criteria indicated in the study by Peterson *et al.* (2021).[338] They noted that the deaths primarily occurred at rest (32.5%) (some died in their sleep) or under unknown circumstances (38.6%). Binkhorst and Goldstein concluded that the "*SCD rate among young US athletes in 2021-2022 was comparable to pre-pandemic estimates*." And, that there was at that time, "*no evidence to substantiate a link between (mRNA) COVID-19 vaccination and SCD in (young) athletes*." Most the www.goodsciencing.com website data were omitted from this analysis, because there was insufficient information about COVID-19 vaccination status of the affected people in most of the news reports. However, it is significant that during the time period of the COVID-19 vaccinations, there was a strong correlation between the rates of COVID-19 vaccination and the frequency of news reports of SDA and SCD. As vaccine uptake declined in 2023, so did the number of news reports in the www.goodsciencing.com website for the same period. It is also important to recognize that there was a strong push for COVID-19 vaccination of athletes in universities and professional sports, so it is highly likely that the vast majority of the cases captured in the www.goodsciencing.com website were vaccinated individuals. What is needed is the participation of the sporting organizations that supported the Peterson *et al*. (2023) study to provide equivalent data for their athletes after the release of COVID-19 vaccines.

2.14. Neurological Disorders Linked to COVID-19 Vaccines

279. A wide range of neurological disorders that affect the central or peripheral nervous systems (CNS, PNS) have also been linked to COVID-19 vaccination. This has been reviewed extensively in the recent

[341] Binkhorst, M., Goldstein, D.J. (2023) Athlete deaths during the COVID-19 vaccination campaign: Contextualization of online information. medRxiv (preprint). doi:10.1101/2023.02.13.232855851

scientific literature.[342, 343] In particular, headache, intracerebral hemorrhage, venous sinus thrombosis (VST), Guillain–Barré syndrome (GBS), and facial palsy (*e.g.,* Bell's Palsy) are the most commonly described adverse events. As pointed out by Finsterer (2023), other neurological conditions that appear to be induced by COVID-19 vaccines in the CNS include cerebro-vascular disorders (in addition to VST and intracerebral bleeding, ischemic stroke, subarachnoid bleeding, reversible, cerebral vasoconstriction syndrome, vasculitis, pituitary apoplexy, Susac syndrome), inflammatory diseases (encephalitis, meningitis, demyelinating disorders, transverse myelitis), epilepsy, and a number of other rarely reported CNS conditions. PNS disorders related to SARS-CoV-2 vaccines include neuropathy of cranial nerves, mono-/polyradiculitis (*e.g.,* GBS), Parsonage–Turner syndrome (plexitis), small fiber neuropathy, myasthenia, myositis/dermatomyositis, rhabdomyolysis, and a number of other conditions. CNS diseases can also indirectly arise from adverse effects of COVID-19 vaccines in extra-neural tissues such as myocarditis or vaccine-induce immune thrombotic thromocytopenia (VITT). VITT is a condition characterized by acute blood clots, and then a deficiency of platelets, which can lead to easy or excessive bruising and internal bleeding.

280. Headache has been reported in about 30 to 51% of COVID-19 vaccinees with neurological disorders.[342, 344] It was also amongst the most common side-effects of COVID-19 vaccines in Phase 3 clinical studies.

281. In the Italian NEURO-COVAX study conducted by Salsone *et al*. (2023), the investigators aimed to evaluate the neurological complications after the first and/or second dose of different COVID-19 vaccines and identify factors potentially associated with these adverse effects.[345] Adults aged 18 years and older in Novegro (Milan, Lombardy) who received two vaccine doses of Pfizer/BioNTech's BNT162b2 (15,368 participants), Moderna's mRNA-1273 (2,077 participants) and AstraZeneca's

[342] Alonso Castillo, R., Martínez Castrillo, J.C. (2022) Neurological manifestations associated with COVID-19 vaccine. Neurologia (Engl Ed). 23:S2173–5808(22)00141-9. doi:10.1016/j.nrleng.2022.09.007

[343] Finsterer, J. (2023) Neurological adverse reactions to SARS-CoV-2 vaccines. Clin Psychopharmacol Neurosci. 21(2):222–239. doi:10.9758/cpn.2023.21.2.222

[344] Undugodage, C., Dissanayake, U., Kumara, H., Samarasekera, B., Yapa, L., *et al.* (2021) Reactogenicity to ChAdOx1 nCoV-19 vaccine in health care workers: A multicenter observational study in Sri Lanka. Ceylon Med J. 66:177–184. doi:10.4038/cmj.v66i4.9508

[345] Salsone, M., Signorelli, C., Oldani, A., Alberti, V.F., Castronovo, *et al.* (2023) NEURO-COVAX: An Italian population-based study of neurological complications after COVID-19 vaccinations. Vaccines. (Basel) 11(10):1621. doi:10.3390/vaccines11101621

ChAdOx1nCov-19 vaccine (1,651 participants) described any neurological complications from their vaccination between July 7 and 16, 2021. Approximately 31.2% of the participants developed post-vaccination neurological complications, particularly with ChAdOx1nCov-19, and about 40% of these symptomatic individuals had comorbidities in their clinical histories. ChAdOx1nCov-19 was associated with increased risks of headaches, tremors, muscle spasms and insomnia. For Moderna's mRNA-1273 vaccine, there were increased risks of paresthesia (burning or prickling sensation on skin), vertigo (dizziness associated with sensation of motion or spinning), diplopia (double vision), and sleepiness. However, in the period that ranged from March to August 2021, none of the participants were hospitalized and/or died of severe complications related to COVID-19 vaccinations.

282. Of recent concern is the apparent increased risk of seizures/convulsions after BNT162b2 to 2- to 4-year-olds) and mRNA-1273 to 2- to 5-year olds from an analysis by Hu *et al.* (2023) of COVID-19 vaccine administered to 4,102,106 US children aged 6 months to 17-years-old.[346] In this report in which the corresponding author is from the FDA, 21 pre-specified outcomes were tracked from administrative claims data provided by Optum, Carelon Research, and CVS Health as well as pharmacy claims and data from participating local and state Immunization Information Systems. There were 65 observed COVID-19-vaccine-related seizures/convulsions cases amongst 752,415 doses (8.64 in 100,000 risk) given to aged 2- to 4/5-year-olds across a 7-day risk window following vaccination. Seizures/convulsions were also observed in 6-months to one-year-olds with an incidence of 5.32 in 100,000 doses, and in 5/6- to 17-year-olds with an incidence of 3.14 in 100,000 doses. In the same analysis, myocarditis/myopericarditis in ages 12- to 17-years-old was the other outcome that met the statistical threshold for a warning signal with 107 cases out of 3,083,412 doses with BNT192b2 for a 3.47 in 100,000 risk. The risk of Bell's Palsy for those aged 5/6- to 17-years-old was 1.97 in 100,000 based on 115 cases in 5,837,942 doses.

283. In the next subsections, the discussion focuses on GBS and Bell's Palsy, as these are neuropathies that have been more commonly associated with COVID-19 vaccine adverse effects in previous studies. However, it is important to appreciate that the full spectrum of neurological side-effects of these vaccines is broad, ranging in severity from initially asymptomatic to mild to severe, and outcomes that

[346] Hu, M., Shoaibi, A., Feng, Y., Lloyd, P.C., Wong, H.L., *et al.* (2023) Safety of monovalent BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and NVX-CoV2373 (Novavax) COVID-19 vaccines in US children aged 6 months to 17 years. medRxiv (preprint). doi:10.1101/2023.10.13.23296903

range from full recovery to death. A wide range of hypotheses have been proposed to account for these side-effects, including effects of the Spike protein directly on cellular targets such as Angiotensin 2 and Neuropilin, to the inflammatory responses that the vaccines evoke from their components (*e.g.,* pegylated lipids in the lipid nanoparticles) as they spread through the circulation, or Spike protein on the surface of cells that take up the lipid nanoparticles or adenoviruses used for delivery of Spike mRNA.

2.14.1. Guillain-Barré Disease

284. Guillain-Barré syndrome (GBS) is a neurological disorder in which one's immune system attacks the myelin coating of long axons, primarily of peripheral nerves. Incidence is approximately 1-2 in 100,000 people, and lower in children.[347, 348] While GBS can occur at any age, the incidence rate markedly increases after 50 years of age, by about 20% for each additional decade.[349]

285. GBS typically causes weakness and tingling in the arms and legs that can spread throughout the body. The typical presentation is bilateral. GBS can lead to paralysis and death by respiratory failure. The cause of GBS is unknown,[350] but is typically triggered by an infection with a wide range of bacteria and viruses or even by surgery.[351] A more controversial risk factor is that of vaccination, which may trigger an autoimmune response by a process known as molecular mimicry.[352] In 1976, those that were

[347] Mayo Clinic Staff. (2023) Guillain-Barré syndrome. Mayo Clinic. Retrieved from https://www.mayoclinic.org/diseases-conditions/guillain-barre-syndrome/symptoms-causes/syc-20362793

[348] Yale Medicine. (2023) Guillain-Barré syndrome. Retrieved from https://www.yalemedicine.org/conditions/guillain-barre-syndrome

[349] Sejvar, J.J., Baughman, A.L., Wise, M., Morgan, O.W. (2011) Population incidence of Guillain-Barré syndrome: A systematic review and meta-analysis. Neuroepidemiology. 36(2):123–133. doi:10.1159/000324710

[350] Cafasso, J., Reed-Guy, L. (2021) Guillain-Barré syndrome (GBS). Healthline. Retrieved from https://www.healthline.com/health/guillain-barre-syndrome

[351] (2023) Guillain-Barré syndrome. Wikipedia. Retrieved from https://en.wikipedia.org/wiki/Guillain%E2%80%93Barr%C3%A9_syndrome

[352] Ang, C.W., Jacobs, B.C., Laman, J.D. (2004) The Guillain–Barré syndrome: A true case of molecular mimicry. Trends Immunol. 25(2):61–66. https://www.sciencedirect.com/science/article/abs/pii/S1471490603003855

inoculated with the Swine Flu vaccine had an increased risk of about 1-2 per 100,000 doses for developing GBS.[353]

286. Diagnosis with GBS is usually based on the signs and symptoms with tests such as nerve conduction studies and examination of the cerebrospinal fluid. There are several GBS subtypes known to exist.[351]

287. Treatment for GBS includes supportive care, intravenous immunoglobulin, plasmapheresis, the latter replacing the patient's blood through transfusion to remove anti-myelin antibodies. Recovery from GBS may take years; some 30% of patients may retain some longer-term weakness.[347,351]

288. From a meta-analysis of 18 studies published in 2020 investigating GBS incidence in 136,746 hospitalized and non-hospitalized COVID-19 patients, Palaiodimou *et al.* (2021) estimated an incidence of 15 GBS cases per 100,000 COVID-19 cases.[354] Considering that a relatively low percentage of the population was expected to have been infected with SARS-CoV-2 in 2020, this indicates that the overall incidence of GBS would unlikely change appreciably during the first year of the COVID-19 pandemic. Keddie *et al.* (2021) observed a slight decrease in GBS cases in UK hospitals during the early stages of the COVID-19 pandemic between March and May of 2020.[355]

289. Ogunjimi *et al.* (2023) in their meta-analysis of 71 publications regarding GBS with COVID-19 vaccination established a rate of 0.8 cases per 100,000 doses, with a higher prevalence in males (59.4%) and in people between 40 and 60 years of age.[356] They found the onset of GBS typically occurred within two weeks of vaccination. The highest rates of GBS were associated with the AstraZeneca vaccine (56% of cases), which was 1.4- to 10-fold higher than expected depending on the studies analyzed. About

[353] Babazadeh, A., Mohseni Afshar, Z., Javanian, M., Mohammadnia-Afrouzi, M., Karkhah, A., *et al.* (2019) Influenza vaccination and Guillain-Barré Syndrome: Reality or fear. J Transl Int Med. 7(4):137–142. doi:10.2478/jtim-2019-0028

[354] Palaiodimou, L., Stefanou, M.I., Katsanos, A.H., Fragkou, P.C., Papadopoulou, M., *et al.* (2021) Prevalence, clinical characteristics and outcomes of Guillain-Barré syndrome spectrum associated with COVID-19: A systematic review and meta-analysis. Eur J Neurol. 28(10):3517–3529. doi:10.1111/ene.14860

[355] Keddie, S., Pakpoor, J., Mousele, C., Pipis, M., Machado, P.M., *et al.* (2021) Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain. 144(2):682–693. doi:10.1093/brain/awaa433

[356] Ogunjimi, O.B., Tsalamandris, G., Paladini, A., Varrassi, G., Zis, P. (2023) Guillain-Barré Syndrome induced by vaccination against COVID-19: A systematic review and meta-analysis. Cureus. 15(4):e37578

20% of the GBS cases were associated with the Pfizer/BioNTech COVID-19 vaccine and 5% with the Moderna product.

290. An outstanding question is whether prior infection with SARS-CoV-2 and subsequent COVID-19 vaccination may increase the rate of incidence of GBS. Zheng *et al.* (2023) tried to answer this question, but obtained inconclusive results, and this is worthy of further investigation.[357]

2.14.2. Bell's Palsy

291. Bell's palsy (BP) is a condition in which damage to the facial nerve (cranial nerve (CN)7) causes weakness in the muscles on one side of the face, leading that side of the face to droop. It can occur at any age.

292. Symptoms include lopsided smiles and an impact on eye closure on the affected side of the face. It can result from various forms of inflammation that may affect CN7. It is listed as one of the outcomes of pregnancy and from various infections causing inflammation. The face droop feature of BP is often temporary, but may be longer lasting, sometimes for life.[358]

293. The incidence of Bell's palsy prior to COVID-19 was 15-50 per 100,000 people.[359] Tamaki *et al.* (2021) from an analysis of data from 41 health organizations collected in 2020, identified 284 BP patients from 348,088 COVID-19 patients for an incidence rate of 81.6 BP cases per 100,000 COVID-19 cases.[360] About 46.1% of these BP patients had a previous history of Bell's palsy. Considering that most people in 2020 were not COVID-19 vaccinated, the rate of BP in the general population was not appreciably different with SARS-CoV-2.

[357] Zheng, X., Fang, Y., Song, Y., Liu, S., Li, K., *et al.* (2023) Is there a causal nexus between COVID-19 vaccination and Guillan-Barre syndrome? Eur J Med Res. 28(1):98. doi:10.1186/s40001-023-01055-0

[358] Mayo Clinic Staff. (2022) Bell's palsy. Mayo Clinic. Retrieved from https://www.mayoclinic.org/diseases-conditions/bells-palsy/symptoms-causes/syc-20370028

[359] Tiemstra, J.D., Khathate, N. (2007) Bell's palsy: Diagnosis and management. Am Fam Physician. 76(7): 997–1002.

[360] Tamaki, A., Cabrera, C.J., Li, S., Rabbani, C., Thuener, J.E., *et al.* (2021) Incidence of Bell's palsy in patients with COVID-19. JAMA Otolaryngol Head Neck Surg. 147(8):767–768. doi:10.1001/jamaoto.2021.1266

294. In another meta-analysis, Rafati *et al.* (2023) picked 17 published studies to calculate the rate of BP in COVID-19 vaccine recipients and following SARS-CoV-2 infection.[361] By pooling data from four randomized Phase 3 studies with COVID-19 vaccines, it can be calculated that there was a 221% increase in BP incidence with vaccination compared to placebo controls, with a rate of 19.3 cases of BP per 100,000 participants in the COVID-19 vaccinated, and 6.0 cases of BP per 100,000 unvaccinated participants. The authors claimed that no significant increase was evident when the data from observational studies were also considered, which included a study by Klein *et al.* (2021) that provided an incident rate that was 20.1 BP cases per 100,000 unvaccinated participants, but only 4.58 BP cases per 100,000 vaccinated participants.[362] Apart from having an opposite trend from most of the other studies cited, this data accounted for 88% of the people tracked in all the studies combined. However, by excluding the data from Klein *et al.* (2021) and aggregating the remaining data from the 12 studies presented, it can be calculated that there was a 13% decrease in BP incidence with vaccination compared to the unvaccinated, with a rate of 9.0 BP cases per 100,000 participants in the COVID-19 vaccinated, and 10.3 BP cases per 100,000 unvaccinated participants. An important caveat for consideration in this type of comparison is the time sampling period for quantifying COVID-19 vaccine-induced cases of BP, which are usually within a few weeks of receipt of the vaccine, whereas in the unvaccinated population, this is based on the duration of the study, which may be over a year. This is why the findings from controlled random clinical studies are much more insightful. The authors did not detect any differences between the rates of BP between the Pfizer/BioNTech and AstraZeneca vaccines.

295. In the meta-analysis of 86 articles on neurological disorders associated with COVID-19 vaccination by Castillo and Castrillo (2022), they calculated that 4,936 of 13,809 (35.7%) of these patients experienced BP, and it was more prevalent in women (60%) than men.[342]

296. Collectively, these studies indicate that incidence levels for Bell's palsy likely were not appreciably increased by SARS-CoV-2 infection and may not be by the COVID-19 vaccines. However, the diverse

[361] Rafati, A., Pasebani, Y., Jameie, M., Yang, Y., Ilkhani, S., *et al.* (2023) Association of SARS-CoV-2 vaccination or infection with Bell's Palsy: A systematic review and meta-analysis. JAMA Otolarygology Head Neck Surg. 149(6):493–504. doi:10.1001/jamaoto.2023.0160

[362] Klein, N.P., Lewis, N., Goddard, K., Fireman, B., Zerbo, O., *et al.* (2021) Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. 326(14):1390–1399. doi:10.1001/jama.2021.15072

findings across the quoted studies justify further investigations as to the relationships between BP, COVID-19, and its vaccines.

2.15. Excess Deaths and All-Cause Mortality Statistics

297. Since the introduction of the COVID-19 genetic vaccines, there has been at least an 8-fold surge in news reports of collapses and unexpected deaths in otherwise young healthy people, pilots, musicians and athletes.[340, 363] Sudden Adult Death Syndrome of "unknown" cause became amongst the top category of deaths in Alberta in 2021 since the rollout of the COVID-19 vaccines.[364] It is hard to ignore the rise of these unusual deaths with the timing of the launch of the COVID-19 genetic vaccines. The question is whether there has in fact been an increase in the total numbers of deaths since the advent of COVID-19 and with the introduction of the COVID-19 vaccines. This is best revealed by examining the available data on excess all-cause mortality.

298. With respect to deaths with COVID-19, the average age of a person that died of COVID-19 in Canada was about 84 years compared to about 82 years for all-cause mortality. There was no major increase in all-cause mortality in the first year of the COVID-19 pandemic, when the virus was more virulent, and there were no specific medications for its treatment or vaccination for its prevention. The total number of deaths from all causes in 2019 in Canada was 285,270, and 307,205 in 2020.[365] Infectious diseases accounted for only 8.6% of these deaths in 2019 and 12.6% of deaths in 2020 in Canada. By comparison, in 2020, cancer, and heart and stoke disease accounted for 27.0% and 23.2% of all deaths, respectively. The total number of deaths with COVID-19 in 2020, which was 16,151 (of which about half was due to a co-morbidity), accounted for 5.25% of the total number of deaths. Accidents and suicides killed more people in Canada in 2020 than COVID-19. Figure 14, show measurements of all-

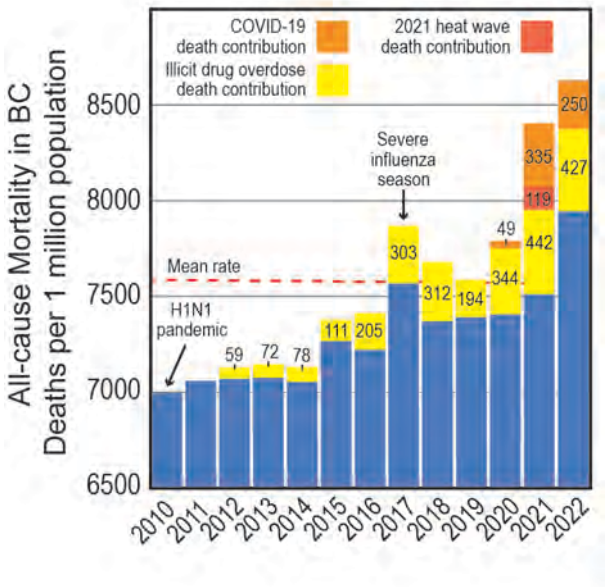
[363] Makis, W. (2023) Collapsed suddenly – 21 videos of collapses on stage and live on air: Greek South African rapper Costa Titch, age 27, collapsed & died; TV reporters collapsing or having strokes live on air. Substack. https://makismd.substack.com/p/18-videos-of-collapses-on-stage-and?utm_source=substack&utm_medium=email#play

[364] Donato, N.D. (2022) Deaths with unknown causes now Alberta's top killer: Province. Calgary CTV News. Retrieved from https://calgary.ctvnews.ca/deaths-with-unknown-causes-now-alberta-s-top-killer-province-1.5975536

[365] (2023) Statistics Canada. Table 13-10-0394-01 Leading causes of death, total population, by age group. doi:10.25318/1310039401-eng Retrieved from https://www150.statcan.gc.ca/n1/en/catalogue/13100394

cause mortality increases in British Columbia. Most of the excess all-cause mortality in 2022 in BC cannot be attributed to COVID-19.

Figure 14. British Columbia annual all-cause and COVID-19 mortality rates from October 1 to September 31 and illicit drug deaths rates from January 1 to December 31.[366]



299. It is also important to understand that there were fewer deaths from other infectious diseases such as influenza and RSV during the first two and a half years of the COVID-19 pandemic, and about half of the deaths ascribed to COVID-19 were in people that died with COVID-19, but actually may have been due to their co-morbidities. Rancourt *et al.* (2023) have concluded that there was no increase in all-cause mortality in the US in 2020, especially when compared to 2017.[367] Although there was virtually no increase in overall excess all-cause mortality in the 2020, the first year of the COVID-19 pandemic in Canada and elsewhere, it has increased significantly in 2021 and 2022, since the introduction of the

[366] Sourced data from https://bccdc.shinyapps.io/Mortality_Context_ShinyApp/ sourced February 24, 2023; https://www2.gov.bc.ca/gov/content/lifeevents/death/coroners-service/statistical-reports sourced February 24, 2023

[367] Rancourt, D. (2023) 2020-06-02: All-cause mortality during COVID-19 – No plague and a likely signature of mass homicide by government response. Ontario Civil Liberties Association. Retrieved from https://denisrancourt.ca/entries.php?id=9&name=2020_06_02_all_cause_mortality_during_covid_19_no_plague_and_a_likely_signature_of_mass_homicide_by_government_response

COVID-19 vaccines.[368, 369, 370] In a recent study of all-cause mortality in 31 European countries, this was positively correlated with increased COVID-19 vaccination.[371] A one percent increase in COVID-19 vaccine uptake in 2021 between the countries was associated with a statistically significant monthly increase in mortality in the first nine months of 2022 by 0.105%.

300. The United Kingdom is one of the few jurisdictions where all-cause and COVID-19 linked mortality has been correlated with COVID-19 vaccination status, age and sex, and this data is available for public scrutiny.[362] Graphic representation of some of the findings provided by the UK Office for National Statistics for England are shown in Figure 15. The data indicate that with the emergence of Omicron variants, there has been no real benefit of single or double COVID-19 vaccination for preventing COVID-19 deaths compared to not being vaccinated against SARS-CoV-2. There is evidence that triple vaccination might have reduced COVID-19 deaths prior to September 2022, but not significantly afterwards. This might be due to a temporary protection afforded by the booster vaccination in vulnerable groups and that many who were particularly susceptible to dying from COVID-19 may have already succumbed by the time a third vaccine dose was available. However, with all-cause mortality, especially with the first dose of the COVID-19 vaccines early in the vaccination program, and the second dose subsequently after September 2021, the inoculations are associated with higher rates of death. After May 2022, there is little support that even a third shot of COVID-19 vaccines provided any significant benefit in reducing all-cause mortality. Interpretation of the data in Figure 15 is complicated,

[368] Rancourt, D.G. (2022) Probable causal association between India's extraordinary April–July 2021 excess-mortality event and the vaccine rollout. Correlation Research in the Public Interest. Retrieved from https://correlation-canada.org/report-probable-causal-association-between-indias-extraordinary-april-july-2021-excess-mortality-event-and-the-vaccine-rollout/

[369] Rancourt, D.G., Baudin, M., Mercier, J. (2022) Probable causal association between Australia's new regime of high all-cause mortality and its COVID-19 vaccine rollout. Correlation Research in the Public Interest. Retrieved from https://correlation-canada.org/report-probable-causal-association-between-australias-newregime-of-high-all-cause-mortality-and-its-covid-19-vaccine-rollout/

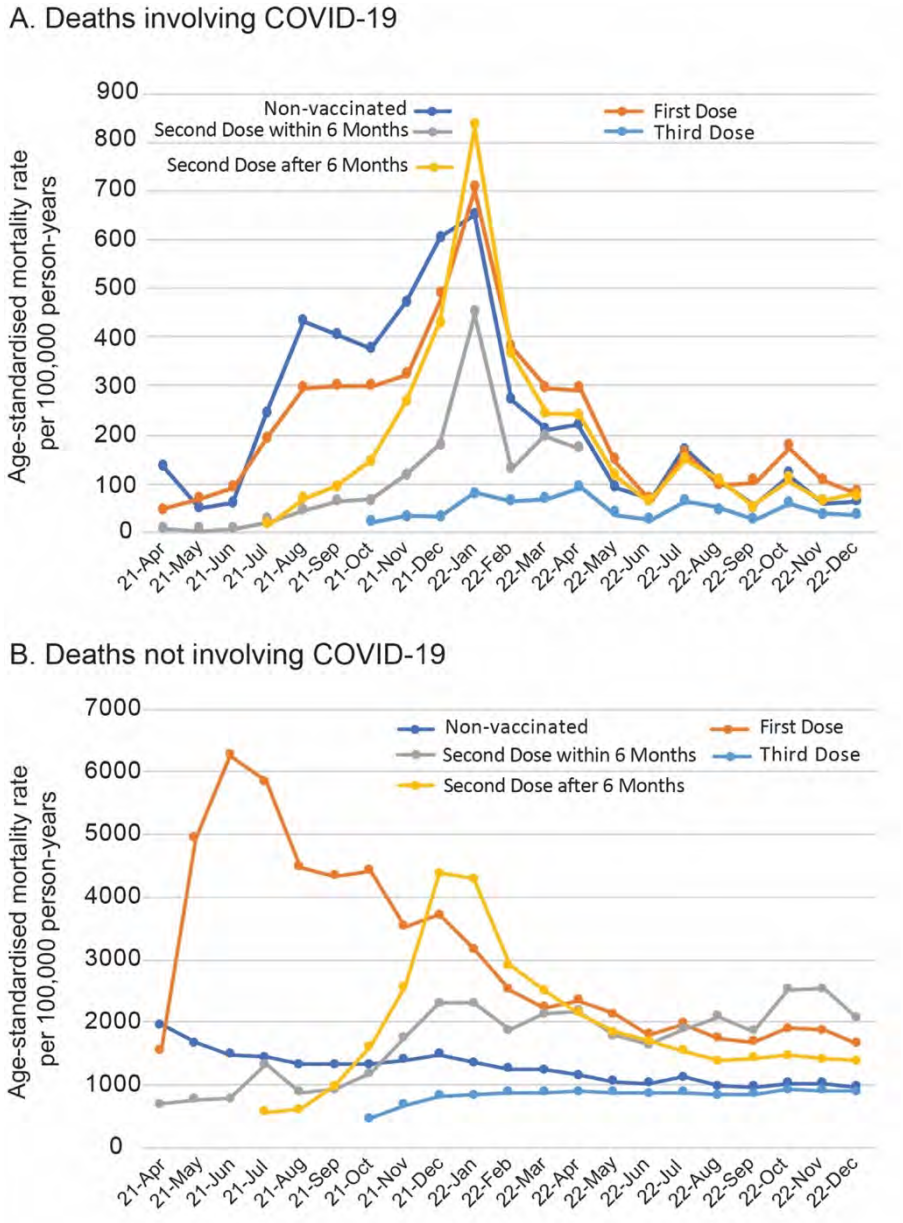
[370] Rancourt, D.G., Baudin, M., Hickey, J., Mercier, J. (2023) Age-stratified COVID-19 vaccine-dose fatality rate for Israel and Australia. Correlation Research in the Public Interest. Retrieved from https://correlation-canada.org/report-age-stratified-covid-19-vaccine-dose-fatality-rate-for-israel-and-australia/

[371] Aarstad, J., Kvitastein, O.A. (2023) Is there a link between the 2021 COVID-19 vaccine uptake in Europe and 2022 excess all-cause mortality? Asian Pacific J Health Sci. 10(1):25–31. doi.10.21276/apjhs.2023.10.1.6

[362] (2023) Deaths by vaccination status, England. Deaths occurring between 1 April 2021 and 31 December 2022 edition. UK Office for National Statistics. Retrieved from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsbyvaccinationstatusengland

since the virulence of the SARS-CoV-2 was steadily reduced with the evolution of new variants and the extent of natural immunity in the UK population also increased. However, it is evident by comparison of the top and bottom panels of Figure 15 that COVID-19 associated deaths only accounted for a small portion of the excess deaths in England.

Figure 15. England monthly all-cause and COVID-19 mortality rates from April 1, 2021 to December 31, 2022 as a function of COVID-19 vaccine status.[372]



[372] (2023) Deaths by vaccination status, England. Deaths occurring between 1 April 2021 and 31 December 2022 edition. UK Office for National Statistics. Retrieved from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsbyvaccinationstatusengland

301. While such a temporal link in these increased deaths with COVID-19 vaccination exists, it does not necessarily have to be a causal. However, in considering the proposed mechanisms of action of the COVID-19 genetic vaccines, their inadequate testing prior to wide-spread dissemination, and the unacceptably high risks for these vaccines for adverse reactions, it is not surprising that they do correlate.

2.16. The Changing Response of Public Health Abroad to COVID-19 Vaccination

302. While most Canadian public health authorities still zealously embrace COVID-19 vaccines, public health authorities in Quebec[373] and many other countries are much less enthusiastic. In fact, the COVID-19 adenovirus vaccines and Medicago, while initially approved by Health Canada, have all since been discontinued by the Fall of 2023.

303. In view of the mounting and disturbing data about the limited efficacy and serious safety issues associated with the COVID-19 genetic vaccines, health regulatory agencies around the world have begun to discourage or ban the use of these vaccines, especially in younger people. Denmark was the first nation in Europe to invoke this step by halting vaccination invitations on May 14, 2022.[374] By autumn 2022, Denmark recommended vaccination only to those over 50 years old and some vulnerable populations.[375]

304. Many European countries as well as Australia and some US states such as Florida have stopped recommending vaccinations for COVID-19 to anyone under 40, 50 or 60 years of age and especially children. Even in 2021, France and Scandinavian countries did not recommend the Moderna vaccine

[373] Rigs, A. (2023) COVID-19: Quebec drops recommendation that all should get booster vaccine. Montreal Gazette. Retrieved from https://montrealgazette.com/news/local-news/quebec-covid-vaccine-recommendation-hybrid-immunity

[374] Ellyatt, H. (2022) Denmark becomes the first country to halt its COVID vaccination program. CNBC News. Retrieved from https://www.cnbc.com/2022/04/28/denmark-the-first-country-to-halt-its-covid-vaccination-program.html

[375] Goldenberg, J. (2022) Denmark halts COVID vaccinations for low-risk people under 50. The Suburban. Retrieved from https:/www.thesuburban.com/news/city_news/denmark-halts-covid-vaccinations-for-low-risk-people-under-50/article_1e0264ec-dea3-59e0-bf3e-db59eee4378d.html

for people under 30 years of age.[376, 377] The United Kingdom Joint Committee on Vaccination and Immunisation (JCVI) no longer recommends vaccination of healthy individuals under 50 years of age in the UK except for those in clinical risk groups or those attending to such individuals.[378] The Federal Office of Public Health in Switzerland also no longer recommends COVID-19 vaccination for healthy people in all age groups, and will not pay for COVID-19 vaccination for anyone, unless medically indicated by a physician for a patient with a clear risk-benefit analysis.[379] The Australian government has advised that as of February 2023 a booster dose is **not recommended** for children and adolescents up to 18 years who do not have any risk factors for severe COVID-19, and only for those 18-64 years of age who have undergone a risk-benefit analysis with their healthcare provider.[380] The German Federation of Hospitals (DKG) had called for the mandatory vaccination obligation of healthcare personnel to be revoked after the German Ministry of Health admitted that 1 in 5,000 COVID-19 vaccination shots led to serious side-effects.[381]

305. In April 2023, the European Medicine Agency and the European Parliament finally recognized that at least 11,448 deaths in the EU occurred following COVID-19 vaccination, and that there were 50,648 deaths attributed to these vaccines in the EudraVigilance database as of April 10, 2023.[382] It would

[376] (2021) France advices against Moderna for under-30s over rare heart risk. France 24. Retrieved from https://www.france24.com/en/live-news/20211109-france-advises-against-moderna-for-under-30s-over-rare-heart-risk

[377] Lehto, E. (2021) Finland joins Sweden and Denmark in limiting Moderna's COVID-19 vaccine. Retrieved from https://www.reuters.com/world/europe/finland-pauses-use-moderna-covid-19-vaccine-young-men2021-10-07/

[378] (2023) JCVI statement on the COVID-19 vaccination programme for 2023: 8 November 2022. Updated 27 January 2023. UK Department of Health and Social Care. Retrieved from https://www.gov.uk/government/publications/covid-19-vaccination-programme-for-2023-jcvi-interim-advice-8-november-2022/jcvi-statement-on-the-covid-19-vaccination-programme-for-2023-8-november-2022

[379] (2023) COVID-19: Vaccination. Federal Office of Public Health FOPH. Retrieved from https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/impfen.html#21889874

[380] (2023) COVID-19. Australian Immunisation Handbook. Australian Government Department of Health and Aged Care. Retrieved from https://www.health.gov.au/our-work/covid-19-vaccines/advice-for-providers/clinical-guidance/clinical-recommendations

[381] Mek, A. (2022) German Hospital Federation demands withdrawal of vaccination mandate after massive side effects revealed. RAIR Foundation USA. Retrieved from https://rairfoundation.com/german-hospital-federation-demands-withdrawal-of-vaccination-mandate-after-massive-side-effects-revealed/

[382] Joro, V. (2023) European Parliament: How many deaths have been caused by "COVID vaccines"? Question for written answer E-001201/2023. Retrieved from https://www.europarl.europa.eu/doceo/document/E-9-2023-001201_EN.html

appear that health regulatory agencies in Europe and elsewhere have come to realize the clear and present dangers of the COVID-19 genetic vaccines.

306. It seems that the populations of Canada and the US have also finally come to recognize the efficacy and safety issues of the COVID-19 vaccines, despite the heavy messaging from public health officials to the contrary. For example, only about 16% of those 6 months or older in Ontario within the past year had received a COVID-19 vaccination by September 14, 2023.[383] Canada-wide, only about 3.4% of Canadian chose to be vaccinated between March 10 and September 10, 2023.[384] In the US, only about 5.4% of children and 14.8% of adults 18 years and older received the updated XBB1.5 COVID-19 vaccines by November 17, 2023, whereas 35.1% of children and 36.3% of adults opted to be vaccinated against influenza.[385]

2.17. Therapeutic Treatment of COVID-19

2.17.1. Introduction to COVID-19 Therapeutic Options

307. Of all the topics that have kindled debate and acrimony during the COVID-19 pandemic, perhaps none has been as intense as those concerning non-vaccine treatment paradigms for the disease. Very soon after the WHO's declaration of the COVID-19 pandemic in March 2020, public health officers around the world, along with heads of government and the media, began their expensive campaigns to convince the public that the only way out of the pandemic was though the application of vaccines against the virus.

308. Non-vaccine alternatives were routinely described as ineffective at best and harmful at worst. Two well studied and incredibly safe well-known anti-viral compounds, ivermectin and hydroxychloroquine were declared to be unsafe, spurring a strong negative public reaction to both, with ivermectin routinely

[383] (2023) COVID-19 vaccine uptake in Ontario: December 14, 2020 to November 5, 2023. Public Health Ontario. Retrieved from https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-vaccine-uptake-ontario-epi-summary.pdf?la=en

[384] Merkowsky, C.M. (2023) Only 3% of Canadians have taken most recent COVID booster: gov't data. LifeSite. Retrieved from https://www.lifesitenews.com/news/only-3-of-canadians-have-taken-most-recent-covid-booster-govt-data/

[385] (2023) Respiratory viruses. Vaccination trends – Adults. Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/respiratory-viruses/data-research/dashboard/vaccination-trends-adults.html

labeled as “horse paste”, simply because in veterinary practice as in humans, it had been successfully used to treat various parasitic infections. The fact that several research papers denying any benefit to the compounds were soon retracted as being fraudulent were overlooked in the rapid acceptance of mRNA and viral vector vaccines by regulatory agencies with Emergency Use Authorization (EUA) in the US or Interim Order status in Canada. It is worth noting that EUA status for drugs can only be attained normally if there is no alternative treatment. Hence, in brief, the steps were to convince the public that vaccines, and only vaccines, would allow a return to “normal.”

309. Three years after the rollout of the vaccines, with much of the population vaccinated with the initial two doses, followed by boosters, much more is known about the disease and the problems with the efficacy and safety of the COVID-19 vaccines. As discussed in the preceding sections, much of the official narrative in BC and Canada about COVID-19 has become highly questionable, and out of sync with many other countries with respect to vaccination policies and certain treatments such as ivermection.

2.17.2. Off-Label Medications

310. As the COVID-19 pandemic unfolded, the professional colleges regulating doctors, nurses and pharmacists instructed their members not to use treatments that lacked a college-approved imprimatur. If a patient tested positive for COVID-19 and had symptoms, what was the physician to do? The message from the professional colleges can be paraphrased as, tell the patient to “*Go home and isolate, take acetaminophen (Tylenol) for headaches and if/when your lips turn blue, go to the Emergency Department of your local hospital.”*

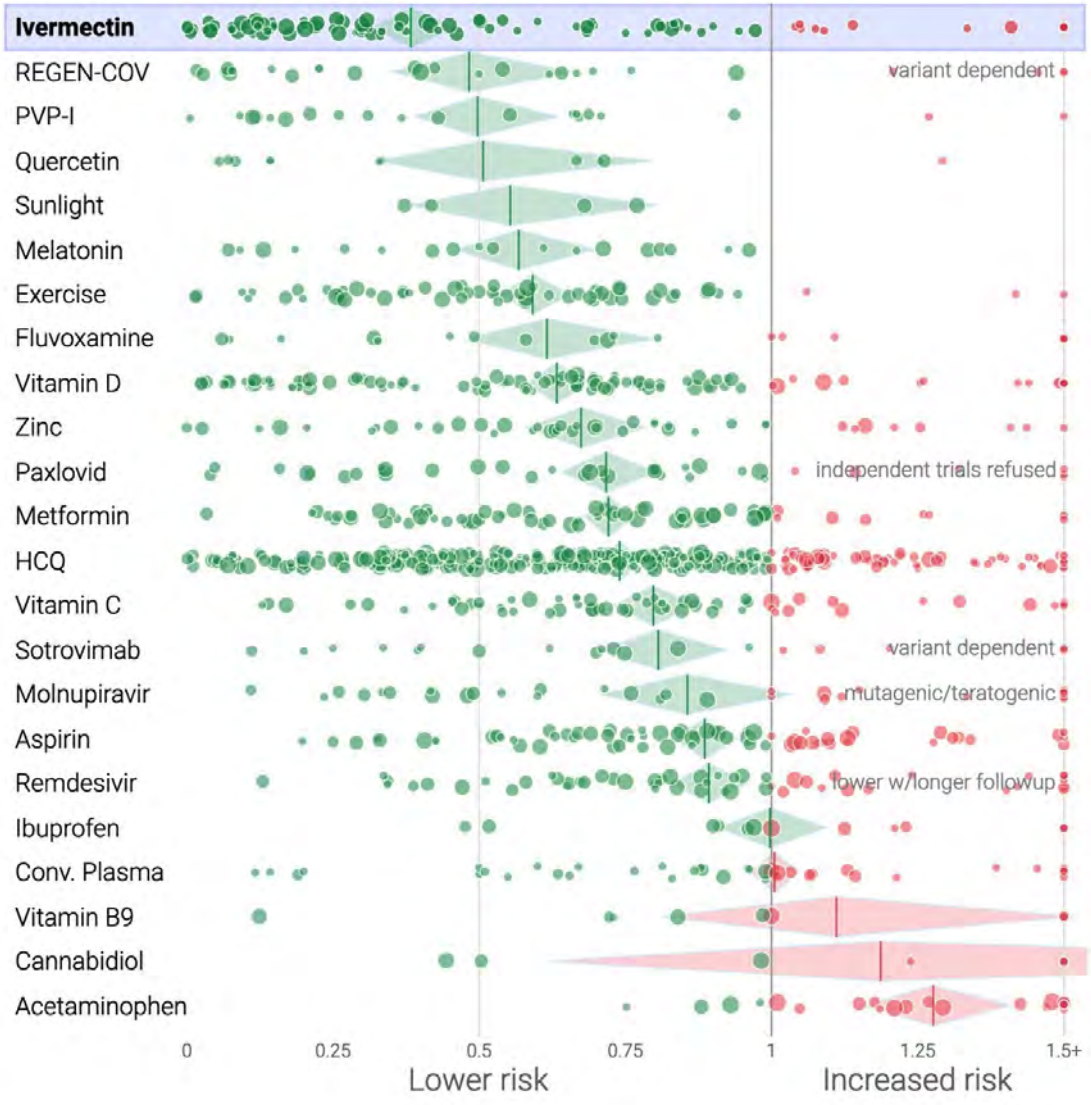
311. This directive to healthcare professionals was issued despite reports from around the world that COVID-19 could be treated effectively, especially if it was treated early, using existing, well-known generic drugs that had low to moderate risks if used at the correct dosages and times. It has been hypothesized that using these treatments could have saved most people who died from COVID-19 (perhaps 80% of the 6.99 million stated in WHO Coronavirus (COVID-19) Dashboard);[386] these treatments would have provided time for new therapies, such as novel antivirals and mRNA “vaccines”,

[386] (2023) WHO coronavirus (COVID-19) dashboard. World Health Organization. Retrieved from https://covid19.who.int/

to be subjected to the normal widely established safety evaluations. Significantly, using existing drugs would have removed the imperative for fast-tracking the new therapies, which was not in the fiscal interests of the manufacturers of these novel products. One outcome of this discordance was society-wide dismissal of many drugs such as ivermectin), as will be further detailed below.

312. What generic, cheap drugs were thought to be effective as early treatment for COVID-19? See a listing of these drugs in the Forest plot below in Figure 16.

Figure 16. Efficacy in COVID-19 studies (pooled effects). Scatter plot showing the most serious outcome in all studies in the context of multiple COVID-19 treatments. Diamonds show the results of random effects meta-analysis for each treatment.[387]



[387] (2023) COVID-19 early treatment: Real-time analysis of 3,363 studies. C19early.org. Retrieved August 18, 2023 from https://c19early.org/; reproduced under Creative Commons license.

313. Note that Paxlovid, molnupiravir, remdesivir and acetaminophen have been approved by most Canadian professional colleges for symptomatic treatment of COVID-19. Ironically, acetaminophen is one of the few drug treatments to show worsening of COVID-19 symptoms. An explanation for this may be its anti-febrile effect, since elevated body temperatures have an antiviral action as part of the immune response.

314. Many different protocols have been developed by many different doctors using many different drugs; most of the drugs used are from the Figure 16 above. Representative doctors, countries, approximate numbers treated and success (as mortality rate) are shown in Table 6.

Table 6. Representative doctors and success for treatment of COVID-19 patients. The numbers are based on personal communications that were provided to the Canadian Citizens Care Alliance.

Doctor(s)	Country	Number Patients	Mortality %
Dr. Ira Bernstein	Canada	>1,000	0
Dr. Flavio Cadegiani	Brazil	>3,450	0
Dr. Shankara Chetty	South Africa	>14,000	0
Drs. Bryan Tyson & George Fareed	USA	>20,000	0
Dr. Edward Leyton	Canada	>800	0
Dr. Abdulrahman Mohana	Saudi Arabia	2,733	0
Dr. Carlos Nigro	Brazil	5,000	0.5
Dr. Didier Raoult	France	8,315	0.1
Dr. Vladimir Zelenko	USA	2,200	0.1

315. Like Dr. Hoffe, several Canadian doctors have lost their positions/licenses or are under investigation by their professional college for treating COVID-19 patients with off-label drugs. Such medications are those that have already been approved for one purpose, but may have utility for treatment of other

illnesses based on new evidence in the scientific literature. As result of these threats of professional discipline, Canadian doctors and nurse practitioners have been reluctant to reveal their data. Unfortunately, many others have simply declined treating patients with COVID-19 and more recently with those with mRNA vaccine injuries.

Most doctors used combinations of re-purposed drugs shown in Figure 16. Ivermectin was used widely in virtually all nations, despite being censored (see subsequent section for full description). Ivermectin was most commonly used for early COVID-19 treatment followed closely by hydroxychloroquine, while vitamin D was the prime example of prophylaxis via its effects to boost the immune system.

2.17.3. Ivermectin

316. Ivermectin is a cheap medication used for over 30 years and has been given to billions of people as a generic drug, primarily for the treatment of parasitic infections like worms, lice and mites in humans and livestock. It has also been shown to have anti-viral activity against several RNA and DNA viruses, including alphaviruses chikungunya, Avian influenza A, BK polyomavirus, cow herpesvirus 1, dengue virus, Hendra, Human immunodeficiency virus type 1, mouse pseudorabies virus, pig circovirus 2, Semliki Forest and Sindbis virus, Venezuelan equine encephalitis, West Nile virus, yellow fever flavivirus, and Zika virus.[388, 389] Early on in 2020, it was reported that ivermectin also inhibited the replication of the SARS-CoV-2 virus in cultured cells.[390]

317. In view of the wide range of applications of ivermectin, it appears to have multiple mechanisms of action. For SARS-CoV-2, its proposed activities include: preventing entry of the virus into the cell, anti-inflammatory actions, and additional actions to prevent viral replication and prevention of the complications of the infection. In particular, the anti-inflammatory actions of ivermectin (notably its ability to dampen the activity of two major inflammatory cytokines, *i.e.,* Tumor necrosis factor-alpha

[388] Formiga, F.R., Leblanc, R., de Souza Rebouças, J., Farias, L.P., de Oliveira, R.N., Pena L. (2021) Ivermectin: An award-winning drug with expected antiviral activity against COVID-19. J Control Release. 329:758–761. doi:10.1016/j.jconrel.2020.10.009

[389] Heidary, F., Gharebaghi, R. (2020) Ivermectin: A systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot. 73:593–602. doi:10.1038/s41429-020-0336-z

[390] Caly, L., Druce, J.D., Catton, M.G., Jans, D.A., Wagstaff, K.M. (2020) The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. Antiviral Res. 178:104787. doi:10.1016/j.antiviral.2020.104787

(TNFα) and Interleukin-6 (IL-6)) are critical to reducing the destructive cytokine storm; the severity of which is a critical phase in determining overall disease severity and recovery.[391]

2.18.3.1. Ivermectin Efficacy for COVID-19 Treatment

318. Since the initial reports of ivermectin's inhibitory effects on SARS-CoV-2 replication, there have been over a hundred studies that support its use for the prevention and treatment of COVID-19. While there have been many individual reports that have been compelling for the effectiveness of ivermectin,[392] there have been several meta-analyses described by the most experienced and non-conflicted authors that document the effectiveness and safety of ivermectin for COVID-19 treatment.[393, 394, 395] For example, the second author in the Bryant *et al.* (2021) review, Dr. Theresa Lawrie, has over 50 Cochrane Collaboration reviews to her credit. These authors concluded that "*moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally*."

319. A smaller number of meta-analyses type studies of ivermectin have indicated that it is ineffective, including a Cochrane review by Popp *et al*. (2022),[396] which involved only 11 of the published studies on ivermectin use for treatment of COVID-19. These kinds of meta-analyses have been critically reviewed by Fordham *et al*. (2021), who identified at least 11 major issues with the Popp *et al.* Cochrane

[391] Wehbe, Z., Wehbe, M., Iratni, R., Pintus, G., Zaraket, H., *et al.* (2021) Repurposing ivermectin for COVID-19: Molecular aspects and therapeutic possibilities. Front Immunol. 12:2021. ISSN:1664-3224 doi:https://www.frontiersin.org/articles/10.3389/fimmu.2021.663586

[392] Bernigaud, C., Guillemot, D., Ahmed-Belkacem, A., Grimaldi-Bensouda, L., Lespine, A., *et al.* (2021) Oral ivermectin for a scabies outbreak in a long-term care facility: Potential value in preventing COVID-19 and associated mortality. Br J Dermatol. 184(6):1207–1209. doi:10.1111/bjd.19821

[393] (2023) Ivermectin for COVID-19: Real-time meta analysis of 95 studies. Retrieved from https://ivmmeta.com/

[394] Kory, P., Meduri, G.U., Varon, J., Iglesias, J., Marik, P.E. (2021) Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19. Am J Ther. 28(3):e299. doi:10.1097/MJT.0000000000001377

[395] Bryant, A., Lawrie, T.A., Dowswell, T., Fordham, E.J., Mitchell, S., *et al.* (2021) Ivermectin for prevention and treatment of COVID-19 infection: A systematic review, meta-analysis, and trial sequential analysis to inform clinical guidelines. Am J Ther. 28(4):e434–e460. doi:10.1097/MJT.0000000000001402

[396] Popp, M., Reis, S., Schieber, S., Hausinger, R.I., Stegemann, M., *et al.* (2022) Ivermectin for preventing and treating COVID-19. doi:10.1002/14651858.CD015017.pub3

review.[397] In virtually every study in which ivermectin did not perform well, deficiencies in experimental design protocols and conflicts of interest could be identified. Examples of the latter are: administration of ivermectin on an empty stomach to ensure that it stays in the gastrointestinal tract and is not absorbed; under-dosing ivermectin in obese people that are at higher risk of severe disease; conducting studies in environments in which ivermectin is freely available to the public resulting in both treated groups and controls taking ivermectin; and ignoring the status of natural immunity to COVID-19 in participants.

320. The ACTIV-6 (Accelerating COVID-19 Therapeutic Interventions and Vaccines) trial lower dose ivermectin arm has been published the *Journal of the American Medical Association* (*JAMA*) after peer-review.[398] Even only a cursory view of this paper reveals several shortcomings of methodology and statistical analysis that may invalidate the authors' interpretations. Some of these problems included:

    a. The treatment drug, ivermectin, was under-dosed.

        i. The doses were approximated on weight ranges to accommodate for dose per tablet. People at the upper end of the weight range would be under-dosed for the variants circulating at the time.

        ii. Maximum dose was capped, leaving patients over 88 kg (44% of participants) in receipt of inadequate dosing. This was even more problematic for obese patients, because ivermectin is lipophilic (fat attractive) and distributes into fat tissue leaving less drug available for therapeutic effect.

        iii. Authors instructed patients to take ivermectin on an empty stomach—*"Ivermectin should be taken on an empty stomach with water"* (original Protocol Section 16.3.3). Taking ivermectin on an empty stomach is suitable for treatment of intestinal parasites but not systemic

[397] ordham, E., Lawrie, T.A., MacGilchrist, K., Bryant, A. (2021) The uses and abuses of systematic reviews. doi:10.31219/osf.io/mp4f2

[398] Naggie, S., Boulware, D.R., Lindsell, C.J., Stewart, T.G., Gentile, N., *et al.* (2022) Effect of ivermectin vs placebo on time to sustained recovery in outpatients with mild to moderate COVID-19: A randomized clinical trial. JAMA. 328(16):1595–1603. doi:10.1001/jama.2022.18590

diseases, because ivermectin is lipophilic and administration with a fatty meal facilitates absorption.

iv. Ivermectin following a high-fat meal has resulted in ~2.5-fold higher bioavailability relative to administration in the fasted state.[399]

v. The lead author of the ACTIV-6 trial acknowledged that there was supporting evidence in the clinical literature for the use of higher doses of ivermectin as she stated in a video that, "*when we looked at the data, frankly we thought it justified a study with a higher dose.*"[400] As such, a second ivermectin arm was introduced in the study of 0.6 mg/kg/day for 6 days.

b. The ivermectin treatment was delayed or not provided.

Early treatment (ET) (5 days or less following symptom onset) is recognized as a key component for the successful management of COVID-19. Table 1 of the *JAMA* article showed that treatment was not started until a median time of 6 days following symptom onset.[398] Some patients did not receive their treatment for as long as two weeks after symptom onset, thereby negating the potential benefit of early treatment that could have prevented progression to the more severe inflammatory phase of the illness, which required a more aggressive treatment regime.

In her grand rounds presentation, Dr. Naggie acknowledged that the one patient who died in the treatment arm had not received their medication.[400] Of additional concern was that "*participants had already consented to participate but had not received* [the] *study drug, and these participants continued in their assigned study group.*"[398] Allocating patients to a treatment group when they in fact did not receive treatment skews the results in favor of the placebo group, that is with no ivermectin.

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[399] (2007) Stromectol (Ivermectin). NDA 50-742/S-022. U.S. Food and Drug Administration. United States Department of Health and Human Services. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050742s022lbl.pdf

[400] Naggie, S. (2022) NIH Pragmatic Trials Collaboratory. Grand Rounds July 22, 2022: ACTIV-6: 1-year later and trial results for ivermectin-400 and inhaled Fluticasone. Retrieved from https://rethinkingclinicaltrials.org/news/grand-rounds-july-22-2022-activ-6-1-year-later-and-trial-results-for-ivermectin-400-and-inhaled-fluticasone-susanna-naggie-md-mhs/ (see 47:57 minute mark).

c. Ivermectin was used as a monotherapy.

COVID-19 is a multifaceted disease with recognized treatment protocols using multi-drug regimens based on addressing the known underlying pathophysiologic disease mechanisms. However, in ACTIV-6, ivermectin was used as a monotherapy.

Participants in the treatment arm were sicker than those in the placebo arm.

The Supplemental Online Content eTable 1 indicates that a higher proportion of patients assigned to the treatment group experienced severe shortness of breath (dyspnea) compared to the patients assigned to the placebo group.[401]

d. Preprint results show benefit for the ivermectin treatment arm.

Despite these methodological concerns, a benefit for the treatment arm was evident in the study's preprint. Bayesian statistical analysis was used, and Table 2A in the preprint shows a treatment benefit of 97% and 98% probabilities on days 7 and 14, respectively.[402]

e. Conflict of Interest.

The study was funded by the US National Institutes of Health (NIH), which is involved in public-private partnerships with numerous pharmaceutical companies. The lead authors received funding from pharmaceutical companies, including those that make patented antiviral treatments for COVID-19. Interestingly, authors of most of the fewer trials and meta-analyses that concluded that ivermectin was ineffective had connections to large pharmaceutical companies. Moreover, critical aspects of many such trials rendered them "designed to fail", as described the leader of a small generic company that withdrew from one of the "failed" trials.[403]

[401] Supplemental Online Content. Naggie, S., Boulware, D.R., Lindsell, C.J., Stewart, T.G., Gentile, N., *et al.* (2022) Effect of ivermectin vs placebo on time to sustained recovery in outpatients with mild to moderate COVID-19: A randomized clinical trial. JAMA. 328(16):1595–1603. doi:10.1001/jama.2022.18590. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9587497/bin/jama-e2218590-s003.pdf

[402] Naggie, S. (2022) Ivermectin for treatment of mild-to-moderate COVID-19 in the outpatient setting: A decentralized, placebo-controlled, randomized, platform clinical trial. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 study group. medRxiv (preprint). doi:10.1101/2022.06.10.22276252

[403] Nakatsu, K., personal communication.

321. The TOGETHER trial, published in the *New England Journal of Medicine* in March 2022, was a large, randomized control trial whose ivermectin arm has been used by vested interests as conclusive evidence against the use of ivermectin in COVID-19.[404] Of the many shortcomings identified, the ivermectin dosage regimen was very problematic; 0.4 mg/kg/day for three days on an empty stomach is clearly inadequate for the reasons described above. Moreover, the trial was conducted in an area of Brazil where ivermectin was freely available to control subjects via over-the-counter sales. Even with these design flaws that would deter the detection of positive impacts of ivermectin treatment, the data nestled in the supplemental section still supported the validity of ivermectin use in COVID-19. A full and detailed critique of this ivermectin study has been written by Halgas (2022).[405]

322. The TOGETHER trial's lead authors also receive funding from pharmaceutic companies, including those that would financially gain from a preferential marketing and sale of patented antiviral treatments for COVID-19. Regretfully, the public pronouncement of the failure of the TOGETHER trial was made several months before the altered and flawed methodology of the study was finally revealed at the time of publication.[404]

323. Many examples of ivermectin distribution campaigns – in Mexico City, several states in India, and several Argentinian provinces – have demonstrated rapid population wide decreases in morbidity and mortality, indicating the safety and effectiveness of ivermectin in all phases of COVID-19.[406] In another recent study conducted with 159,561 subjects in Itajaí, Brazil, 113,845 (71.3%) were regular ivermectin users and 45,716 (23.3%) were non-users.[407] Of these, 4,311 ivermectin users were infected, among which 4,197 were from the city of Itajaí (3.7% infection rate), and 3,034 non-ivermectin users (from Itajaí) were infected (6.6% infection rate), with a 44% reduction in the COVID-19 infection rate. Non-

[404] Reis, G., Silva, E., Silva, D., Thabane, L., Milagres, A., *et al.* (2022) Effect of early treatment with ivermectin among patients with COVID-19. N Engl J Med.386:1721–1731. doi:10.1056/NEJMoa2115869

[405] Halgas, O. (2022) Analysis of the TOGETHER Trial's Ivermectin Arm Results. Canadian Covid Care Alliance. Retrieved from https://canadiancovidcarealliance.org/media-resources/analysis-together-ivermectin-trial/

[406] Chamie J. (2021) The latest results of ivermectin's success in treating outbreaks of COVID-19. Front Line COVID-19 Critical Care Alliance (FLCCC). Retrieved from https://COVID-19criticalcare.com/ivermectin-in-COVID-19/epidemiologic-analyses-on-COVID-19-and-ivermectin/

[407] Kerr, L., Baldi, F., Lobo, R., Assagra, W.L., Proenca, F.C., *et al.* (2022) Regular use of ivermectin as prophylaxis for COVID-19 led up to a 92% reduction in COVID-19 mortality rate in a dose-response manner: Results of a prospective observational study of a strictly controlled population of 88,012 Subjects. Cureus. 14(8): e28624. doi:10.7759/cureus.28624

use of ivermectin was associated with a 12.5-fold increase in mortality rate and a 7-fold increased risk of dying from COVID-19 compared to those with ivermectin treatment.

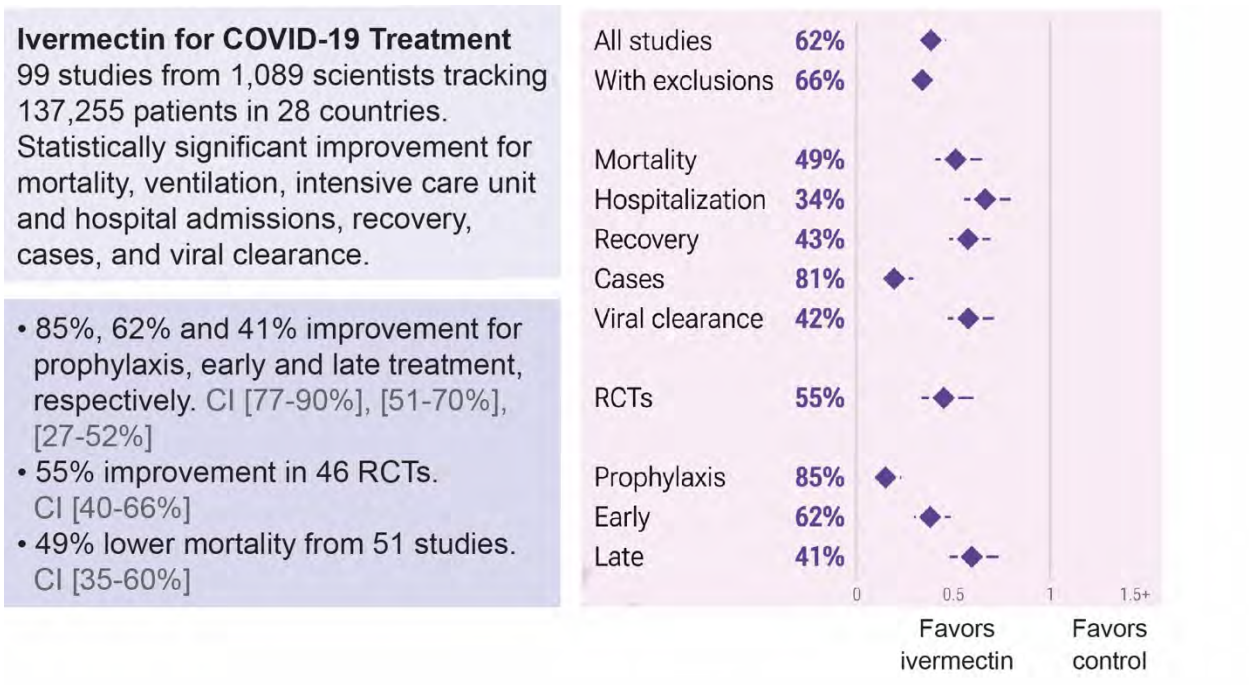
324. In early January 2023, MedinCell Pharmaceutical released the data from their SAIVE study (NCT 05305560) that was conducted from March to November 2022.[408] This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical study that evaluated the safety and efficacy of ivermectin tablets taken orally for 28 days (200 μg/kg on day 1 then 100 μg/kg daily until day 28). The study targeted unvaccinated adults who had been exposed to the virus within 5 days of screening after documented close contact with a person who had a PCR-confirmed SARS-CoV-2 infection. Participants in the ivermectin group showed no signs of drug safety concerns and experienced a significant 72% reduction in laboratory-confirmed infections (30/200) versus placebo (105/199), $p<0.0001$. This only added to the mounting evidence of ivermectin's significantly favorable level of protection against SARS-CoV-2 infection, especially during the highly transmissible Omicron-variant phase of the pandemic. At least 19 countries have officially or unofficially approved ivermectin usage for treatment of COVID-19.[409]

325. With respect to the effectiveness of ivermectin for COVID-19 treatment, the Front Line COVID-19 Critical Care (FLCCC) Alliance website has provided extensive documentation for its utility.[69] Figure 17 below is reproduced from the FLCCC website and provides a summary of a meta-analyses of 99 published studies. ivermectin clearly ranks well above Paxlovid, Molnupiravir and remdesivir, with respect to effectiveness against COVID-19 from analyses of over 99 studies by the C19early.org group as shown in Figure 16. Moreover, its cost is just pennies/day compared with thousands of dollars for the three newer drugs, which are all still protected by patents, and approved under Emergency Use Authorization in the US, and two of which are approved under Interim Order in Canada.

[408] (2023) MedinCell announces positive results for the SAIVE clinical study in prevention of COVID-19 infection in a contact-based population. Business Wire. https://www.businesswire.com/news/home/20230105005896/en/MedinCell-Announces-Positive-Results-for-the-SAIVE-Clinical-Study-in-Prevention-of-COVID-19-Infection-in-a-Contact-Based-Population

[409] (2023) Global adoption of COVID-19 early treatments. C19early.org group. Retrieved from https://c19early.org/adoption.html

Figure 17. Meta-analyses of ivermectin effectiveness for COVID-19. From https://c19ivm.org/; reproduced under Creative Commons license. Retrieved December 7, 2023.[410]



326. While there remains a lack of consensus on the utility of ivermectin for COVID-19 treatment amongst health regulatory agencies, there are nonetheless numerous advocates promoting its use for this indication as demonstrated in the above cited literature. Thousands of doctors world-wide have prescribed it for their patients. Multiple organizations including North American physicians highly experienced in treating COVID-19, *i.e.,* the FLCCC (led by Drs. Paul Marik and Pierre Kory), the British Ivermectin Recommendation Development (BIRD),[411] and the World Council of Health[412] are strong advocates for the use of ivermectin to treat COVID-19.

2.18.3.2. Ivermectin Safety for COVID-19 Treatment

327. Ivermectin has been used internationally for decades, affording the accumulation of a large amount of data related to its potential for toxicity in human use. While there has been controversy with respect

[410] (2023) Ivermectin for COVID-19. C19early.org group. Retrieved from https://c19ivm.org/
[411] (2023) BIRD International. British Ivermection Recommendation Development Group. Retrieved from https://bird-group.org/
[412] (2023) Early COVID-19 treatment guidelines: A practical approach to home-based care for healthy families. World Council for Health. Retrieved from https://worldcouncilforhealth.org/resources/early-covid-19-treatment-guide/

to the efficacy of ivermectin for COVID-19 treatment, there is no dispute about the safety of ivermectin. Occasionally, ivermectin side-effects have been noted to include skin rash, nausea, vomiting, diarrhea, hepatotoxicity, and neurologic adverse events (including seizures and confusion). These particular symptoms are more associated with the parasitic die off. They would be unlikely to occur with treatment of COVID-19 in the absence of a parasite. With over 4 billion ivermectin treatments administered, as of June 19, 2023, only 25 deaths have been recorded since 1992 according to the WHO.[413] All drugs, including those prescribed for the stated indications for which they are approved, can have side-effects. Ivermectin is clearly one of the best tolerated drugs known. There were no adverse effects in Merck's Phase 1 clinical trial when healthy human subjects were administered with ivermectin at a dosage appropriate for a horse.[414]

328. In March 2021, Dr. Jacques Descotes published an extensive analysis addressing the toxicity potential of this drug.[415, 416] In his overall summary, Dr. Descotes commented: ‘’*Safety analysis of >350 articles showing that ivermectin has an excellent safety profile*.” He noted that "*no severe adverse event has been reported in dozens of completed or ongoing studies involving thousands of participants worldwide to evaluate the efficacy of ivermectin against COVID-19*.“

Further key findings from the Descotes report included:

- Mild to moderate adverse effects of ivermectin usage have been infrequent and temporary;
- More severe neurological complications are possible with ivermectin, but rare, and affect susceptible individuals, especially those with severe parasitic disease;

[413] (2023) VigiAccess. World Health Organization. Retrieved from https://vigiaccess.org/

[414] Guzzo, C.A., Furtek, C.I., Porras, A.G., Chen, C., Tipping, R., *et al.* (2002) Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol. 42(10):1122–1133. doi:10.1177/009127002401382731

[415] (2021) MedinCell publishes an extensive Ivermectin safety expert analysis. Press release. Business Wire. Retrieved from https://www.businesswire.com/news/home/20210305005353/en/COVID-19-MedinCell-Publishes-an-

[416] Descotes, J. (2021) Expert review report: Medical safety of ivermectin. ImmunoSafe. Retrieved from https://www.covid-factuel.fr/wp-content/uploads/2022/01/Clinical_Safety_of_Ivermectin-March_2021.pdf

- Serious adverse events relate mainly to the body's efforts to rid itself of an overwhelming parasite load as a result of ivermectin's therapeutic effects—rather than any potential drug toxicity;

- Ivermectin safety has been confirmed with its long history of therapeutic use, spanning over 30 years.

329. Dr. Descotes added this statement of particular interest:

> "*The often-reiterated claim, even today, that ivermectin can be lethal in treated patients only rests on a one-page correspondence to the Lancet published in 1997. This claim is deemed to be unfounded as it has never been further substantiated until today and instead, subsequent publications repeatedly showed this claim was either incorrect or methodologically inaccurate. … No severe adverse reactions have seemingly so far been described in relation to off-label studies or clinical trials of ivermectin as a potential prophylactic or curative treatment of COVID-19."* [416]

330. There are many additional resources pointing to extensive ivermectin safety data:

- Ivermectin has been an approved medication internationally for human use for decades. It continues to be listed on the WHO list of essential medications.[417]

- Safety data of standard doses of ivermectin is widely established; safety of doses up to 10 times the highest FDA approved dose of 200 µg/kg have been well tolerated.[414]

- Adverse events, if they occur, are typically non-severe.[418, 419]

- The ACTIV-6 and TOGETHER trial data found no concerns with safety in their ivermectin treatment groups.[398, 404]

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[417] (2017) WHO model list of essential medicines, 20th List (April 2017). World Health Organization. Retrieved from https://www.who.int/publications/i/ item/eml-20

[418] De Sole, G., Remme, J., Awadzi, K., Accorsi, S., Alley, E.S., *et al.* (1989) Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: Combined results from eight community trials. Bulletin of the World Health Organization, 67(6):707–719. https://europepmc.org/article/PMC/PMC2491300

[419] Twum-Danso, N.A. (2003) Serious adverse events following treatment with ivermectin for onchocerciasis control: A review of reported cases. Filaria J. 2 Suppl 1(Suppl 1):S3. doi:10.1186/1475-2883-2-S1-S3

331. As documented in Figure 16, ivermectin is much safer to use than is acetaminophen/Tylenol, which the Colleges have recommended for management of pain in COVID-19 patients who have been advised to isolate at home. Acetaminophen, an over-the-counter medication, was associated with ~186,000 adverse events on the vigiaccess.org website over the same period (October 23, 2022 cumulative since 1992) in which ivermectin was associated with ~7,000 events. Moreover, there is some evidence that acetaminophen prolongs rather than shortens COVID-19. This would be expected since the virus is sensitive to raised temperatures, and acetaminophen lowers elevated temperatures, which would in turn reduce the effectiveness of the immune system to fight infectious diseases.

332. The use of ivermectin in some populations remains cautionary. This includes pregnancy, breastfeeding, pediatric patients less than 15 kg, and geriatric patients.[420]

333. Concerns had been expressed that the demand for ivermectin for COVID-19 could have resulted in a shortage of the drug available in Canada to treat parasitic infections. Any difficulty that patients may have had in Canada in obtaining ivermectin for any purpose is the fault of its main supplier Merck Canada, Inc. and the healthcare professional colleges, who worked to actively discourage its use for COVID-19 treatment. While ivermectin marketed by Merck as Stromectol was out of stock in many Canadian pharmacies, it was readily available in the US. Moreover, generic ivermectin was fully available in most other countries, such as in India in the state of Uttar Pradesh, where it was cheaply provided by the authorities in kits for prevention and treatment of COVID-19.[421] From consultation with many Canadian compounding pharmacies, the Canadian Citizens Care Alliance learned that such pharmacies possessed ample supplies of ivermectin. The pharmacists' main concern was the threats to their licenses issued by the provincial colleges of pharmacy if they filled prescriptions of ivermectin for COVID-19 treatment. Doctors that prescribed ivermectin for their patients were also at risk of disciplinary action from their provincial colleges of physicians and surgeons. The Canadian Citizens Care Alliance's position is that medical and pharmacy colleges should not be barring their members from considering the off-label use of ivermectin in a multifaceted COVID-19 prevention and early treatment

[420] Stromectal® Monograph. Last accessed October 23, 2022. Drug and Health Product Register – Canada. Retrieved from https://pdf.hres.ca/dpd_pm/00047237.pdf

[421] Staff at TrialSite (2022) Uttar Pradesh officials set the record straight: Ivermectin used. TrialSite News. Retrieved from https://www.trialsitenews.com/a/uttar-pradesh-officials-set-the-record-straight-ivermectin-used-successfully-to-combat-covid-19-in-the-northern-indian-state-a04783f3

protocol. Of note, the inability of Canadians to obtain ivermectin legally led to a robust black-market trade in the drug.

334. Global use of ivermectin has exploded, with more than half of the states in the US now recognizing ivermectin for early treatment of COVID-19,[422] as well as an array of regions around the world, including South America, Japan, India and the European countries of Germany, Portugal, Ukraine and Slovakia. As at August 2023, at least 44% of 50 sampled countries and 28% of the world population have used ivermectin for COVID-19 prevention and treatment.[419]

Part 3

Commentary on Dr. Trevor Corneil's September 26, 2023 Letter to Ms. Lisa Fong

335. I carefully read through Dr. Corneil's statements regarding the concerns that were expressed Dr. Charles Hoffe, and was rather surprised at the relatively poor scholarship to back up his comments. Part 2 of my report and Exhibit C provide a very detailed account how I came to my conclusions. I tried to review the extensive references that were provided by Dr. Corneil and his associate, Dr. Naomi Dove, a physician and assistant professor at UBC with a Master of Public Health Degree. I was shocked that more than a third of the urls (82 out 191 citations) that they provided for their references were non-functional and occasionally non-specific. The problematic citations were 3, 7, 8, 11, 17, 18, 21, 25, 30, 35, 41, 42, 43, 44, 45, 46, 47, 49, 50, 51, 52, 53, 54, 55, 56, 58, 62, 63, 64, 69, 70, 71, 72, 73, 74, 76, 77, 80, 81, 82, 83, 90, 91, 92, 93, 94, 95, 98, 99, 100, 104, 105, 111, 114, 117, 118, 121, 122, 123, 124, 125, 127, 128, 131, 134, 135, 145, 146, 147, 151, 152, 154, 155, 157, 160, 161, 164, 167, 175, 176, 181, and 182. In many of these cases, it appears that the urls were not properly transcribed with omissions or replacement of hyphen and underscores. Although 191 references were listed, in several instances the same reference was listed more than once with a different citation number. It also was disappointing that only about 57 of the citations were from primary sources such as peer-reviewed journals or pre-prints such as MedRxiv. The vast majority of references were guidelines and recommendations from

[422] Bean, M. (2022) 28 states have legislation to promote ivermectin access. Becker's Hospital Review. Retrieved from https://www.beckershospitalreview.com/pharmacy/28-states-have-legislation-to-promote-ivermectin-access.html

public health agencies (*e.g.,* Health Canada, BC Centre for Disease Control, Public Health Ontario, NACI), medical societies (*e.g*., Canadian Paediatrics Soc., Canadian Cardiovascular Soc., Society of Obstetricians and Gynecologists of Canada) and product monographs from vaccine manufacturers. In most of these websites or guidelines, primary references are not provided, and they tend to parrot each other. The data on the public websites is very useful, especially from Health Canada, since it is often downloadable and can be directly analyzed.

336. Dr. Corneil is a Public Health and Preventative Medicine specialist, trained in family medicine with an M.D. degree, and also hold a M.H.Sc. in Health Care and Epidemiology. He is presently a Medical Health Officer with Northern Health Authority and serve as both Associate Director of Clinical Faculty Affairs at UBC's School of Population and Public Health and Program Director of UBC's PHPM post-graduate residency program. He was a Senior Medical Advisor in 2020 to the integrated provincial COVID-19 health emergency command structure, BCCDC Senior Leadership Team, Office of the Provincial Health Officer, Ministry of Health Senior Executive Team. Later, he was a member, co-chair and chair of the BC COVID-19 Clinical Reference Group at the BCCDC until June 2022. His main research focus prior to COVID-19 was on transgender health and drug substance abuse. Although he has benefitted from a high degree of grant funding in group grants only as a co-investigator in the last decade, he only listed about 20 career publications in peer-reviewed journals, 9 as a first or senior author. I did not see any publications that he has authored that relate to immunology, virology, vaccinology, infectious diseases, or pharmacology in particular to cellular and molecular biology and mechanisms of actions. His work is more epidemiology-based, which involves collection of field data with surveys and analysis for correlations. Based on his *curriculum vitae*, and being on promotion and tenure committees for UBC for 7 years myself, I am bemused that he has Clinical Professor status. This usually requires international recognition for excellence in research or development of novel teaching practices. It is not usually awarded for administrative service.

337. In view of the weakness in Dr. Corneil's training and understanding of the mechanisms that underlie viral replication, natural immunity and vaccine-based immunity or the actions of drugs, I think might account for the many misconceptions that he has articulated in his report about the statements made by Dr. Hoffe that he feels are incorrect. It is ironic that he belies Dr. Hoffe's credentials as just a country doctor with inadequate understanding of COVID-19 vaccines and treatment. However, it would appear that both are trained as MD in family practice. I am somewhat concerned that Dr. Corneil has a played

a significant role in shaping the COVID-19 policies that have been mandated or recommended by the Ministry of Health in BC.

338. I have already provided over 600 citations in this report and Appendix C that helped me formulate my views on the COVID-19 vaccines and use of ivermectin. In this Part of my report, I will focus on specific statements made by Dr. Corneil (and Dr. Dove) in his September 26, 2023 letter by reference to the paragraph numbers in that letter. Where I have already addressed a debatable statement, I have referred to the subsections in Part 2 or in Exhibit C.

339. Dr. Corneil's expertise is apparently in epidemiology predictive modeling. In view of some of his statements with regard to such modeling by Dr. David Fisman and by Ogden *et al.* (2023),[423] I have also attached Exhibit D, entitled "Modeling Mischief and Other Data Crimes." This is an unpublished manuscript that is part of an upcoming book, which is based upon the published article "Counterfactuals of effects of vaccination and public health measures on COVID-19 cases in Canada: What could have happened?" in which I am the senior author.[424]

Comments in Reference to Contentious Statements by Dr. Corneil.

340. Para. [7] – Dr. Corneil states that he takes "*the case report forms, clinical investigations including phlebotomy reports, specialist consultations, any other records considered by the MHO, and their recommendations, as the professional opinion of all health care professionals involved, including but not limited to physicians, surgeons, and nurses*." This is a rather all encompassing statement that the records of the Medical Health Officer (MHO) reflects "*the professional opinions of all health care professionals involved*." As anyone involved in committees knows, there is always a diversity of opinions, and policies can be continuing to evolve. The ever-changing position of the MHO in BC, Dr. Bonnie Henry is a classic case of this when it comes to masking.

[423] Ogden, N.H., Turgeon, P., Fazil, A., Clark, J., Gabriele-Rivet, V., *et al.* (2022) Counterfactuals of effects of vaccination and public health measures on COVID-19 cases in Canada: What could have happened? Can Commun Dis Rep. 48(7-8):292–302. doi:10.14745/ccdr.v48i78a01

[424] Vickers, D.M., Hardie, J., Eberspaecher, S., Chaufan C., Pelech, S. (2023) Counterfactuals of effects of vaccination and public health measures on COVID-19 cases in Canada: What could have happened? Frontiers. 11:2023. doi:10.3389/fpubh.2023.1173673

341. I have written a detailed review of the literature on the effectiveness of masks to prevent COVID-19 and other infectious diseases that has been published previously.[425] The upshot of the 37-page review with 117 citation of the scientific literature, and government and news sources is that N95, surgical and cloth masks are essentially ineffective in preventing the spread of COVID-19 during an influenza or coronavirus pandemic. Here's Dr. Henry's position on this matter.

342. Dr. Henry initially argued against mandatory public masking for COVID-19, although on March 16th, 2020, she advocated health professions should use surgical masks.[426] Then on March 19, 2020, Dr. Henry claimed that if a person is not sick, wearing a mask is not effective. She also said wearing a mask in public does not protect a person in any way. On June 22, 2020, Dr. Henry said that people cannot rely on wearing a mask, because wearing a mask is not what keeps us safe. She reiterated this view on September 11, 2020.[427] Right up to November 18, 2020, she stated that "*Ordering universal mask use in all situations creates unnecessary challenges with enforcement and stigmatization*." A day later, in a Public Health Order, Dr. Henry proclaimed sweeping mandatory measures that included mandatory masking.[428] This Public Health Order was rescinded on March 11, 2022.[429] On November 17, 2022, Dr. Henry rejected calls for mask mandates for COVID-19 for the public.[430] The Public Health Order for mandatory masking in healthcare settings such as hospitals, long-term care and assisted living facilities in BC was finally lifted on April 6, 2023.[431] However, despite relative few COVID-19 cases in British

[425] Hardie, J., Pelech, S. (2023) The effectiveness and risks of masking for COVID-19. Canadian Covid Care Alliance. Retrieved from https://www.canadiancovidcarealliance.org/wp-content/uploads/2023/08/23AU28_PelechHardie_Effectiveness-of-Masks-for-COVID-19.pdf

[426] (2020) Message from Dr. Bonnie Henry provincial health officer. College of Optometrists of British Columbia. Retrieved from https://optometrybc.com/notices/news-stories/message-from-dr-bonnie-henry-provincial-health-officer/

[427] (2020) Dr. Bonnie Henry: Masks don't work. Rumble. Retrieved from https://rumble.com/vt4za6-dr-bonnie-henry-masks-dont-work.html

[428] McElroy, J. (2020) B.C.'s mask mandate an about-face in a province struggling to replicate its 1st wave success. Canadian Broadcasting Corporation News. Retrieved from https://www.cbc.ca/news/canada/british-columbia/covid-masks-bc-mandate-november-2020-1.5809260

[429] 2022) B.C. takes next step in balanced plan to lift COVID-19 restrictions. BC Gov News. Retrieved from https://news.gov.bc.ca/releases/2022HLTH0081-000324

[430] Chan (2022) "Heavy hand" of mask mandate not needed in B.C.: Dr. Bonnie Henry. Vancouver Sun. Retrieved from https://vancouversun.com/news/local-news/bc-health-officials-respiratory-illnesses-calls-mask-requirements

[431] Wyton, M. (2023) B.C. ends mask mandate in health-care facilities and proof of vaccination for long-term care visitors. Canadian Broadcasting Corporation News. Retrieved from https://www.cbc.ca/news/canada/british-columbia/henry-dix-respiratory-update-april-2023-1.6804003#

Columbia, she reimposed mandatory masking once again in health-care facilities on October 3, 2023.[432] However, this was only mandatory for healthcare workers, and not for their patients and visitors.

343. Para. [10] – Dr. Corneil states that "*Opinions are considered prudent if they are within the scope of a physician or surgeon's qualifications and are consistent with the current and widely accepted views of the profession (physician peers and Specialist organizations) when interpreting scientific knowledge to the public (Professional Responsibility 41, of this same Code)*." This stipulation is problematic as it may conflict with the practice of providing the best medical care to patients, since "*widely accepted views*" may be those that are spread by a limited number public health officials, and may be incorrect. Keeping up with the scientific literature is extremely important in this regard.

344. Para. [11f] – Dr. Corneil states that "*A Medical Opinion provided by a physician or surgeon is Incorrect if it is reasonably believed to be true by the persons seeking information or receiving information about their personal health or health care but is in fact not true when compared to the widely held knowledge of their physician peers or the relevant Clinical Practice Standards."* When it comes to a medical opinion, there are a lot of differences between doctors in the profession in this regard for treatment of the same patient depending on their specific training and experiences. This is why it is referred to as an "opinion." Widely held beliefs or the dictates of a governing body that is largely appointed by government are secondary to what the results of proper scientific inquiry actually shows. History is full of widely held dogma that has subsequently been shown to be wrong, such as the importance of washing hands between patients, avoiding the use of asbestos, polychlorinated biphenyls, diethylstilbestrol and thalidomide, retaining of tonsils, appendices and wisdom teeth in healthy people, and the use of antibiotics to treat stomach ulcers and treatment of colitis with "poop pills." I suspect this will prove to be the case with lipid nanoparticles with mRNA as ill-conceived for vaccine use.

345. Para. [11h] - The nature of epidemiology is such that it cannot easily establish causality, but is useful at finding correlations. Its methods can very effective, and with enough events tracked to establish correlations, it can guide future research into understanding mechanisms of pathology, and with that

[432] Lindsay, B., Pawson, C. (2023) New masking rules for health care settings in B.C. coming into force Oct. 3, officials confirm. Canadian Broadcasting Corporation News. Retrieved from https://www.cbc.ca/news/canada/british-columbia/bc-enhanced-masking-health-care-settings-1.6980600

information, effective prevention and treatment for diseases. Dr. Corneil mentions standard epidemiology terminology that provide for establishment of correlations that appear to be statistically significant or not. However, modeling is fraught with errors if the underlying assumptions are flawed or incomplete. Ultimately, causality requires understanding at the level of mechanism of action, which requires knowledge of the underlying processes, and further testing. For example, during the winter time in the Northern Hemisphere, more people have colds and flus. However, cold temperature itself does not cause a cold or a flu. This might arise in part from a vitamin D deficiency in the winter, with less available sunlight exposure of skin to produce this vitamin.

346. Para. [12] – Dr. Corneil states, "*As of September 16 2022, COVID-19 has caused over 190,000 hospitalizations and 44,000 deaths in Canada to date*." This is rather loose usage of the word "caused." These numbers reflect the hospitalizations and death with and not necessarily from COVID-19. About 60% of these numbers would be more accurate for COVID-19 caused hospitalizations. See Para. 159 above for further discussion.

347. Para. [12] – Dr. Corneil mentions a ~5% increase in deaths due to COVID-19. The actual Statistics Canada reference[433] that he cited states a 5.8% increase in excess deaths from March 2020 to mid-October 2021. It does not breakdown this number on the basis of vaccination status, but it clearly shows that for those 64 years and under, the vast majority of excess deaths were not linked to COVID-19 deaths. See Section 2.15, starting at Para. 298 for a discussion on excess deaths and all-cause mortality statistics. The BC data (Figure 14) shows that the increase in all-cause mortality in 2020 was not that appreciably different from pre-COVID, whereas it was substantially higher in 2021 and 2022 after the availability of COVID-19 vaccines.

348. Para. [12] – Dr. Corneil grossly misrepresents the rate of SARS-CoV-2 induced hospitalization with his statement "*Approximately 5% of COVID-19 cases in Canada overall have been hospitalized, with 15% of hospitalized cases admitted to the ICU*." The Public Health Agency of Canada data was provided up to September 4, 2022.[434] It does state that of 4,069,693 reported cases of COVID-19 in Canada up to this date, 191,631 (4.8%) were hospitalized. However, as mentioned in Para. 351 above, at least 40%

[433] (2022) COVID-19 in Canada: A Two-year Update on Social and Economic Impacts. Statistics Canada. https://www150.statcan.gc.ca/n1/pub/11-631-x/11-631-x2022001-eng.htm

[434] (2022) COVID-19 Epidemiology Update. Sept. 16, 2022. Public Health Agency of Canada. https://health-infobase.canada.ca/covid-19/

of people diagnosed in hospital with COVID-19 were admitted for other reasons. Moreover, by this date, serological studies in Canada testing for SARS-CoV-2 antibodies in various studies had shown that more than half of Canadians had recovered from a SARS-CoV2 infection by this time (see Section 4.7 starting on Page 75 of Exhibit C). Therefore, more than 20 million Canadians had COVID-19 or were asymptomatic for SARS-CoV-2 infection. This would indicate a hospitalization rate from SARS-CoV-2 that was less than 0.57% (=191,631 x 0.6 / 20,000,000 x 100%). I have provided more data in this regard by age in Table 1, although this table is based on reported cases to September 6, 2023.

349. Para. [12] – Dr. Corneil mentions a highly flawed publication, on which Dr. Teresa Tam is a coauthor, that "estimates that hospitalizations and deaths in Canada would have been up to 2 million and up to 800,000, respectively, in the absence of public health measures or vaccination, versus hospitalizations and deaths of 150,602 and 38,783, respectively, observed as of April 24, 2022 with public health measures and vaccines." This publication is rebuked in Appendix D and in a publication that I co-authored.[413] As an epidemiologist studying COVID-19, Dr. Corneil should have recognized that the assumption of an overall 1% lethality rate for SARS-CoV-2 infection in all age groups was ridiculous, even in the first year of the pandemic with no COVID-19 vaccines.

350. Para. [12] – Dr. Corneil states "*Delta variant, dominant during 2021, caused more severe disease (including greater risk of hospital and ICU admissions) and had a higher mortality rate than previous variants."* He cited two publications for this. This suggestion is actually not supported by the scientific literature and is incorrect. The first reference was from the BC Centre for Disease Control. COVID-19 Variants. July 15, 2022. http://www.bccdc.ca/health-info/diseasesconditions/covid-19/about-covid-19/variants. Accessed online September 4, 2022. The url link no longer works, and it was not archived in the Internet Archive WayBack Machine. The second citation was a publication from Dr. David Fisman, and is based on modeling studies.[435] The Fisman study involved dubious mixed-effect logistic regression models. He predicted a more deadly COVID-19 pandemic with new variants, which is something clearly not demonstrated so far with all of the other SARS-CoV-2 variants since the Wuhan strain. These main variants of concern successively displaced each other, because they evolved to be more infectious and less virulent. With less severe symptoms, infected people are more likely to go about their normal

[435] Fisman DN, Tuite AR. (2021) Evaluation of the relative virulence of novel SARS-CoV-2 variants: a retrospective cohort study in Ontario, Canada. CMAJ. 193(42):E1619-E1625. https://doi.org/10.1503/cmaj.211248

business and spread the virus. Dr. Fisman's track record when it comes to COVID-19 predictions has been very poor and far off the mark (see Exhibit D, starting on Page 5). In this study, the model, the parameters and the assumptions were not provided. There is no compelling reason to believe that the severity of Delta compared to earlier variants was higher, and increased hospitalization may well have reflected its increased infectivity and coincidence with seasonal flus. Like the Ogden *et al.* (2022) report that I critiqued,[423] as an epidemiologist, he should have quickly recognized the flaws in this Fisman analysis, although in fairness to Dr. Corneil, the methodology was not very transparent in the publication.[435]

351. Para. [13] – Dr. Corneil states *"In 2020 in Canada, almost 3 times more deaths occurred due to COVID-19 (16,151 deaths) than due to influenza and pneumonia combined (5,931 deaths, noting that not all deaths due to pneumonia are related to influenza, thus representing an overestimate of influenza deaths)."* This statement is highly deceiving, because the total number of deaths from influenza and RSV declined by 95% in 2020 compare to pre-COVID-19 pandemic estimates. About 40% of the COVID-19 deaths were with rather than from COVID-19 and due to a comorbidity and most COVID-19 deaths ultimately were due to pneumonia as a secondary infection. It is likely that many COVID-19 deaths were due to influenza, because it has very similar symptoms (see Exhibit C, Section 2.3 on Page 18) and when PCR testing for SARS-CoV-2 was performed, it was done at a cycle number greater than 35, which has a 90% false-positive rate (see Exhibit C, Section 4.2) on Page 62).

352. Para. [13] – Dr. Corneil notes "*A June 2020 article estimated the case fatality rate for COVID-19 to be 1.6% based on Canadian data*." Again, this estimate is based on a denominator that markedly underestimates how many people were infected by the SARS-CoV-2 virus.

353. Para. [13] – Dr. Cornell states that "*As of September 2022, the COVID-19 death rate in Canada is 117 per 100,000 population, compared to an estimated seasonal influenza mortality rate of 11 per 100,000, depending on the severity of strains each season*." This works out to a mortality rate from SARS-CoV2 of 0.12% and 0.011% for seasonal influenza. However, earlier in the same paragraph, he mentions that "*Global estimates of the case fatality rate for COVID-19, influenza A and influenza B are much higher at 6.5%, 6% and 3%, respectively*." It is obvious that these case fatality numbers vary by orders of magnitude, so it is hard to really say that "*COVID-19 is associated with a higher burden of serious illness*

and death than seasonal influenza." What is clear is that the risk of death for children under 15 years of age is about 10- to 100-times higher from influenza than from COVID-19.[436]

354. Para. [13] – Dr. Corneil notes that "*In a nation-wide retrospective analysis in France, in hospital mortality was almost three times higher for patients with COVID-19 than for patients with influenza (relative risk of death of 2.9; age standardized mortality ratio of 2.82).*" This mortality rate is based on patients and not all those that were infected with SARS-CoV-2.

355. Para. [13] – Dr. Corneil cites a US study where "*COVID-19 was associated with significantly more weekly hospitalizations, more use of mechanical ventilation and higher mortality rates than influenza.*" Very early on in the COVID-19 pandemic, mechanical ventilation was overused, and may have exacerbated deaths from COVID-19. Excess use of mechanical ventilator may cause direct lung damage by either delivering too much volume of air (volutrauma) or too much pressure (barotrauma), which can damage the lining of the alveoli.[437] Mechanical ventilation has other associated risks including prolonged immobilization, issues with fluid management, nutritional needs, neurological issues, and the potentially significant risk of additional infections, particularly when used long-term.[438, 439] One consequence of the prolonged use of ventilators is that patients may suffer secondary respiratory infections, such as bacterial pneumonia. This is termed ventilator-associated pneumonia (VAP). It can also cause lung damage, lead to a pneumothorax (collapsed lung), and alter heart function. It is noteworthy that most COVID-19 deaths were ultimately due to pneumonia,[440, 441] The early and premature adoption of mechanical ventilation in the US likely reflected a tendency to want to isolate

[436] Dattani, S. Spooner, F. (2022) How many people die from the flu? OurWorldInData.org. Retrieved from https://ourworldindata.org/influenza-deaths

[437] Beitler, J.R., Malhotra, A., Thompson, B.T. (2016) Ventilator-induced lung injury. Clin Chest Med. 37(4):633–646. doi:10.1016/j.ccm.2016.07.004

[438] ibhai, S., Mahboobi, S.K. (2022) Ventilator complications. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK560535/

[439] Maslove, D.M., Sibley, S., Boyd, J.G., Goligher, E.C., Munshi, L., *et al.* (2022) Complications of critical COVID-19: Diagnostic and therapeutic considerations for the mechanically ventilated patient. Chest. 161(4):989–998. doi:10.1016/j.chest.2021.10.011

[440] Gao, C.A., Markov, N.S., Stoeger, T., Pawlowski, A., Kang, M., *et al.*; NU SCRIPT Study Investigators (2023) Machine learning links unresolving secondary pneumonia to mortality in patients with severe pneumonia, including COVID-19. J Clin Invest. 133(12):e170682. doi:10.1172/JCI170682

[441] Nolley, E.P., Sahetya, S.K., Hochberg, C.H. Hossen, S., Hager, D.N., *et al.* (2023) Outcomes among mechanically ventilated patients with severe pneumonia and acute hypoxemic respiratory failure from SARS-CoV-2 and other etiologies. *JAMA Netw Open.* 6(1):e2250401. doi:10.1001/jamanetworkopen.2022.50401

the exhaled air coming from COVID-19 patients so as not to potentially infect hospital staff and other patients.

356. Para. [23] and Figure 1 - A big problem with this table is exactly defining the periods under comparison. It is unclear if this included all of 2020 and 2021, in which most people were unvaccinated. This seems to be implied in the figure legend. Again, at least 40% of the COVID-19 cases were probably not hospitalized in the first place due to COVID-19, and assessment was based largely on PCR tests at 35 cycles or higher. Figure 1 was published in a pre-print, but not subsequently in a peer-reviewed journal.

357. Para. [14] - Dr. Corneil stated "*During the Delta dominant wave in BC, two doses of any COVID-19 vaccine provided substantial protection against hospitalization (90%) and against SARS-CoV-2 infection (80%) that persisted 8 months post-vaccination. 43,44, During the Omicron dominant wave in BC, two dose VE estimates declined but remained substantial against serious illness (65-75% vs. hospitalization, 40-50% vs. ER visits), while protection against SARS-CoV-2 infection lessened to 10-15% due to a combination of waning immunity and immune evasion of novel variants.*[45]" These estimates are highly flawed, and are relative risk reduction rather than absolute risk reduction numbers. The URL for reference 43 does not work. It seems that the correct URL = http://www.bccdc.ca/about/news-stories/stories/2021/covid-19-vaccine-effectiveness-results. This is a press release that refers to a poster that was not published. This data is misleading, because the reductions in serious COVID-19 and deaths can also be easily attributed to more Omicron benign variations of concern and increasing natural immunity in the population. Cited references 44 and 45 are identical, and in both cases the stated URLs do not work. I think the correct URL is http://www.bccdc.ca/health-info/diseases-conditions/covid-19/covid-19-vaccine/measuring-vaccination-impact-coverage. The statistics are cited from a BCCDC poster that is not published and the source of the data is unclear.

358. Para. [14] – Dr. Corneil noted "*a 3rd booster dose in the Omicron wave increased protection against hospitalization (>90%) and bumped up protection against any SARS-CoV-2 infection (to ~50-60%).*" If this is true, then Dr. Corneil needs to explain why the vaccine based on the Wuhan strain is working against Omicron if it is not supposed to be recognizing Omicron variants. Also, the URL for cited reference 47 does not work.

359. Para. [14] – Dr. Corneil cited another "*scientific peer reviewed modelling paper [that] estimates that COVID-19 vaccines averted over 19.8 million deaths in the first year of the pandemic, reducing total deaths due to COVID-19 by 63%."* Again, this is another modeling study with a lot of problematic assumptions, depending on the scenario, including vaccine immunity was 100% effective, previous infection did not confer any immunity; those that were vaccinated did not transmit the disease or were 50% less like to transmit SARS-CoV-2; and was based on RRR rather than ARR values.

360. Para. [14] – Dr. Corneil noted "*as of August 28, 2022, of deaths occurring in Canada, 49% were unvaccinated, 17% had a primary series completed and 3% had a primary series completed with at least 2 booster doses*." This is a misleading statement, since it included deaths from the first year of the pandemic, before the availability of COVID-19 vaccines, the rate of vaccination in the first half of 2021 was slow due to inadequate supply of the vaccines, and the SARS-CoV-2 Wuhan strain was more virulent and lethal than subsequent variants of concern. This kind of statement has been previously used to suggest that the COVID-19 vaccines prevent deaths from COVID-19 (see Para. 141 above).

361. Para. [14] – Dr. Corneil inferred that "*Evidence accumulated during the Omicron wave suggests that booster vaccine doses and hybrid immunity may provide additional protection against serious COVID-19 illness and SARS-CoV-2 infection*." However, there are no controlled studies that actually demonstrate this. Reduce COVID-19 illness and death during the Omicron waves can just as easily be attributed to increased natural immunity in the population and reduced virulence of later SARS-CoV-2 variants. In fact, the Cleveland Clinic study shows that increased COVID-19 vaccination progressively increased the chances of getting COVID-19 (see Para. 56 and Figure 10 above).

362. Para. [17] – Dr. Corneil stated "I*t is important to note that COVID-19 vaccines approved for use in Canada underwent the same risk assessment process and thresholds for regulatory approval by Health Canada as all vaccines marketed in Canada, with expedited approval timelines due to the urgency of the COVID-19 pandemic… While approval timelines were expedited, no steps in the vaccine regulatory process were skipped, and efficacy, safety, manufacturing standards, and risk assessments were not compromised."* This is complete nonsense. Regulatory approvals were provided within 2 months of the submission of results from Phase 3 trials that were only conducted for two months. It would have been impossible to identify safety concerns that are evident after a couple of months (see Para. 124, 129, 131, 168, 177 and Exhibit C, Chapter 5.1 for more fulsome discussion). The fact of the matter is that

the COVID-19 vaccines were approved with Interim Order by Health Canada. However, it is not necessary to prove efficacy or safety with an Interim Order (see Para. 118).

363. Para. [18] – Dr. Corneil's account of the mechanism by which COVID-19 RNA vaccines induce immunity is very incomplete and typical of most deficient descriptions of the cellular and molecular details involved. He states "*When the mRNA vaccine is injected, it is taken up by antigen presenting cells (macrophages and dendritic cells) near the injection site. Inside these cells, the mRNA uses the host cell's ribosomes to produce the SARS-CoV-2 spike protein, which is then expressed on the surface of the cell, stimulating humoral and cellular immune responses*." The actual process is much more complicated and more fully explained in Para. 25-28, Figure 3 and Exhibit C, Chapter 3. Very few of the antigen-presenting cells would actually be directly taking up the lipid nanoparticles. The majority would end up in muscle and other cells of the body, where they would produce the full Spike protein on their outer surfaces, and evoke an immune attack by antigen-presenting cells. The antigen-presenting immune cells damage and may kill those cells that express the Spike protein, and the debris vesicles (called exosomes) with Spike protein is then gobbled up by the antigen-presenting cells, and the Spike fragments are displayed with major histocompatibility (MHC) antigens to elicit activation of selective B- and T-cells of the immune system.

364. Para. [18] – Dr. Corneil stated "*Importantly SARS-CoV-2 mRNA does not enter the cell nucleus, nor does it affect host DNA or RNA… There is no biologically plausible mechanism for COVID-19 mRNA vaccination to alter or modify cellular DNA and therefore is Incorrect to label as gene therapy."* This is incorrect. Not only is the modified Spike mRNA very stable, but it can be reverse transcribed back to DNA by the LINE-1 reverse transcriptase enzyme, and it has been found in the nucleus of liver cells.[91,92] This is discussed in Para. 27, 36, 51, and 79, and Figure 4. Short, linear pieces of DNA can integrate into the human genome and disrupt gene regulation. If the integration events are upstream of oncogenes or tumour-suppressor genes, this can lead to the development of cancer. While this may be a relatively rare event, since ten of trillions of lipid nanoparticles are injected with a COVID-19 RNA vaccine dose, and the human body typically has 50 trillion cells, the opportunity for such a successful oncogenic event is plausible. It only takes one cancer cell to give rise to a tumour full of descendent daughter cells.

365. Para. [18] – Dr. Corneil suggested that "*there is no evidence that COVID-19 vaccines or the spike-like proteins they produce cause adverse effects on the brain*." Immunohistochemistry studies conducted

by Drs. Michael Mörz,[334] Arne Burkhardt[335] and other have clearly documented the expression of Spike protein in the brain from COVID-19 vaccination, inflammatory cell accumulation and tissue damage in the brain where the Spike protein is detected (see Para. 272 and 273).

366. Para. [18] – Dr. Corneil noted that "*While the development of mRNA vaccines for COVID-19 was rapid by standard vaccine development timelines, mRNA vaccines have been studied for decades and used in humans in the context of numerous clinical trials in humans as described in a summative peer reviewed article by Wadhwa, et al., in January 2020*." I carefully read through this review, and nowhere did it state that mRNA vaccines have been in studies for decades. While I was PhD graduate student over 44 years ago, my supervisor's lab had close interactions with Dr. Pieter Cullis (our labs were right next to each), whose team has been associated with the development of the COVID-19 mRNA vaccine lipid nanoparticles, which were originally referred to as liposomes. These lipid nanoparticles were first developed for delivery of drugs and toxins, usually to kill cancer cells. There has been over three decades of research on anti-sense RNA, which is used to prevent the production of proteins by mRNA, again for primarily oncology purposes. However, only about a dozen anti-sense RNA drugs have been approved to date.[442] The successful use of mRNA in vaccines for humans is completely novel prior to COVID-19 (see Para. 109-111 for further discussion). To suggest otherwise, gives a false sense of the stage of development of this technology.

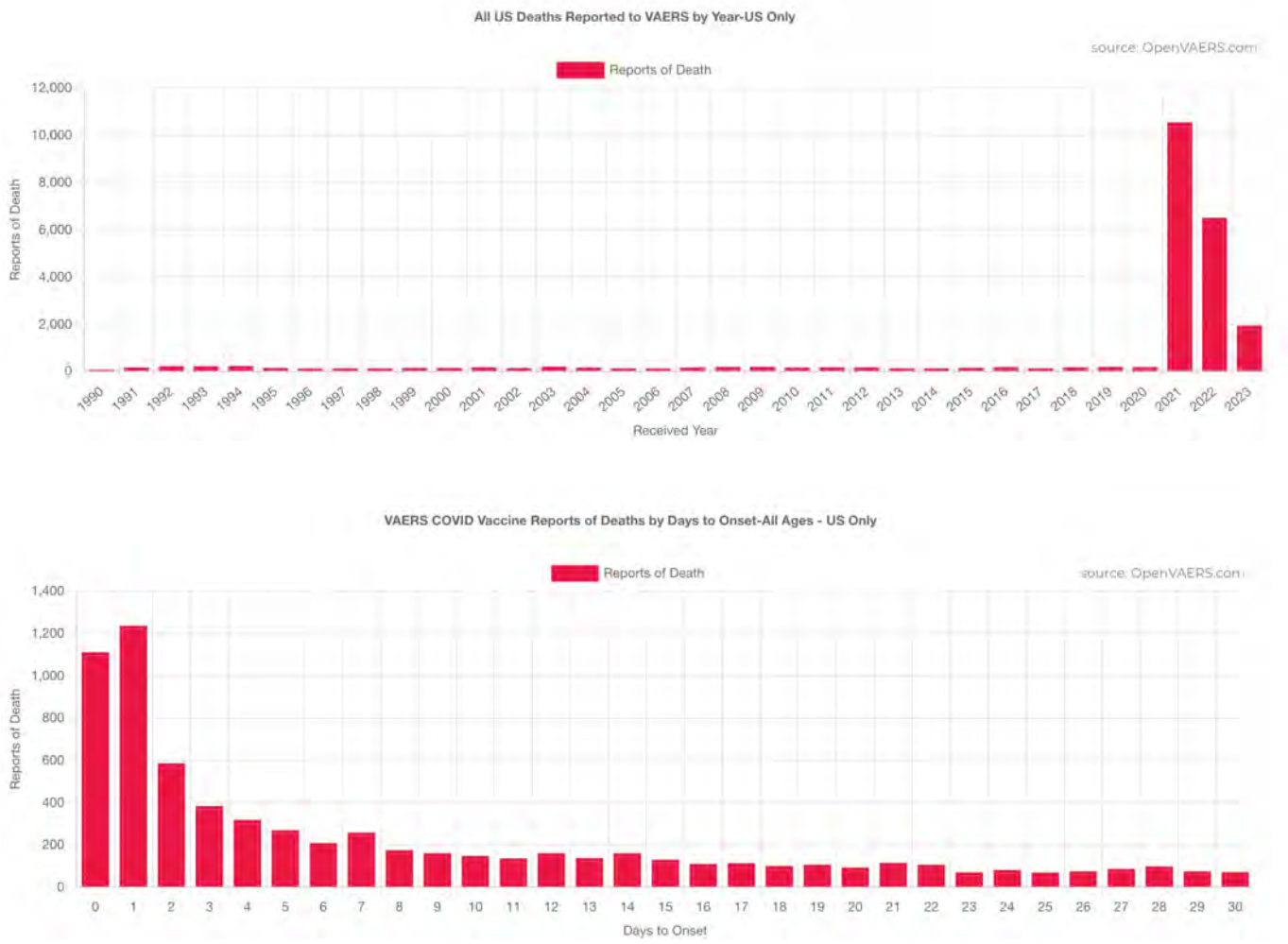
367. Para. [18] – Dr. Corneil stated *""… mRNA vaccines are only targeted for cytoplasmic delivery, circumventing the risk of genomic integration. The relatively short half-life results in transient and more controlled expression of the encoded antigen." That is, they do not change or influence human genes and break down very quickly (within a few days."* As mentioned earlier, the modified Spike RNA appears to be stable from weeks to months, and it can be reversed transcribed into a DNA anti-sense copy, which can enter in the nucleus of cells and theoretically used to generate more Spike RNA (see Para. 36, 41, and 79, and Figure 4).

368. Para. [20] – Dr. Corneil noted "*CAEFISS is designed to be sensitive to capture AEFIs and includes a Causality assessment applying clinical information to standardized tools and comparing events against background rates*." However, CAEFISS clearly rejects many adverse events following immunization

[442] Crooke, S.T., Liang, X.H., Baker, B.F., Crooke, R.M. (2021) Antisense technology: A review. J Biol Chem. 296:100416. doi:10.1016/j.jbc.2021.100416

(AEFI) as exemplified in the cases of Dr. Hoffe and Dr. Patrick Phillips[221] (Para. 182) amongst others. As CAEFISS does not record adverse events in the absence of immunization, it is not clear how comparable estimates to background rates could be properly calculated. However, larger vaccine reporting databases such as VAERS and VigiAccess can permit comparison of the adverse events numbers with COVID-19 vaccines to other vaccines. The number of COVID-19 vaccine injury and death reports in VAERS account for 63% and 78%, respectively, of the total number of all injury and all death reports from all vaccines combined together for the last 31 years. This is extensively discussed in Section 2.7.4 in Para. 79-185. The number of deaths recorded in VAERS as associated with all vaccines is shown in Figure 18.

Figure 18. Annual reported deaths in US VAERS from all vaccines (Top panel) and days to onset for COVID-19 vaccine reports up to November 23, 2023.[443]



[443] https://www.openvaers.com/covid-data (Sourced on January 11, 2024)

369. Para. [20] – Dr. Corneil suggested "*A peer reviewed pre-pandemic evaluation of CAEFISS in 2014 determined that Canada's overall annual AEFI reporting rate (10.1 per 10,000 population administered vaccines) is high relative to other countries with similar immunization schedules, including the United States (AEFI reporting rate of 4.4 per 10,000 population between 1991-2001*)." However, this is not the case with respect to COVID-19 vaccine injury reports. When adjusted for population size, there were nearly double the number of adverse events per capita with COVID-19 vaccines reported in Americans in VAERS than Canadians in CAEFISS, and 4.5-times more deaths per capita (Para. 184).

370. Para. [21] – Dr. Corneil described how in BC, the BCCDC used strict criteria (*e.g.,* the Brighton Collaboration Case Definitions) and then submitted the final vetted reports to CAEFISS contributing to the national surveillance system in Canada. While this all sounds good in theory, in practice, there is a clear underreporting of COVID-19 vaccine injury in CAEFISS and the other vaccine injury recording systems. The fact of the matter is that the actual Phase 3 clinical trials with mRNA vaccines demonstrate severe reactions (required hospitalization or medical attention) in about 5% of people that were vaccinated (see Para. 169), which would be 5000 in 100,000,[202] which is very different from the calculated CAEFISS rate of serious AEFI's of 0.012% (12 in 100,000).

371. Para. [24 and 40] – Dr. Corneil noted that "*The Society of Obstetricians and Gynecologists of Canada ("SOGC") released a statement regarding COVID-19 vaccination and fertility on March 18, 2021 stating 'there is absolutely no evidence, and no theoretic reason to suspect that the COVID-19 vaccine could impair male or female fertility*." I have extensively described theoretical reasons why the COVID-19 genetic vaccines might be expected to cause fertility problems in women (*i.e*., vaccine lipid nanoparticles concentrate in the ovaries, and with Spike protein expression could evoke inflammatory reactions that damage this organ and its oocytes) and evidence of altered ovarian function with COVID-19 effects on menstrual cycles, which is controlled by the ovaries. This is extensive discussed in Sections 2.9.3 (Para. 192-201), Part of my own research program over 40 years is related to the control of oocyte meiotic maturation into a fertilizable egg. There is in fact a fairly high degree of amino acid sequence identity between the Spike protein and the human protein Syncytin-1 as shown in Figure 19. This raised speculation that some of the antibodies generated against Spike from vaccination could cross-react and interfere with the function of Syncytin-1, which is necessary for placental implantation of the fertilized egg. My lab actually investigated this using blood samples from participants in the Kinexus SARS-CoV-2 antibody clinical testing study who were already demonstrated to have antibodies in the

regions of overlap between the Spike protein and Syncytin-1 shown in Figure 19. While anti-Syncytin-1 antibodies could be detected, these were not enriched in the participants that demonstrated Spike antibodies against the overlapping region as compared to participants that do not. Thus, while it possible such anti-Syncytin-1 antibodies could be produced, with the infrequency of fertilization coupled with the highly variable antibody responses of individuals to the Spike protein, this would be very difficult to detect.

Figure 19. Amino acid sequence overlap between SARS-CoV-2 Spike protein and human Syncytin-1. Conservative substitutions of similar amino acids are highlighted in orange.

SARS-CoV-2: NGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQDVVNQNAQALNTLVKQ
Syncytin-1: GIGGITTSTQFYYKLS-QELNGDMERVADSLVTLQDQLNSLAAVVLQNRRALDLLTAE

372. Para. [24] – Dr. Corneil mentioned "*a recent Canadian study led out of BC of close to 200,000 women between the ages of 15 to 49 up to November 2021 determined that COVID-19 vaccines have a good safety profile in pregnancy with low risk of serious adverse effects*." It is noteworthy in this study that "*pregnant vaccinated females had an increased odds of a significant health event within 7 days of the vaccine after dose two of mRNA-1273 (adjusted odds ratio [aOR] 4·4 [95% CI 2·4–8·3]) compared with pregnant unvaccinated controls within the past 7 days*."[286] This study is critiqued in Para. 234.

373. Para. [25] – Dr. Corneil describes the child Phase 3 clinical studies with the Pfizer/BioNTech COVID-19 mRNA vaccine, and notes high efficacy in preventing symptomatic COVID-19 using relative risk reduction numbers. However, the actual rate of symptomatic COVID-19 was also low in the unvaccinated participants, and the trial groups were too small to identify vaccine-induced that occurred with a frequency of less than 1 in 1000. These clinical studies are discussed in Para. 133-137, 150, 151.

374. Para. [25] – Dr. Corneil mentions the risk of symptomatic myocarditis and myopericarditis suggests that it is rare (1,114/88,237,534 or 1.26/100,000) and "*characterized by mild illness which responds well to conservative treatment and rest, with rapid resolution of symptoms*." For males between 12 and 29 years of age, the rate of myocarditis and/or myopericarditis is much closer to 25/100,000 and can be fatal in around 4.4% of cases in the first year.[332] The risk of myocarditis in this age and sex demographic is 10- to 100-times lower from COVID-19. This is extensively discussed in Section 2.11 (Para. 248-275).

375. Para. [27] – Dr. Corneil notes that Dr. Hoffe has stated with respect to the COVID-19 vaccines and safety "*no animal trials were done."* Limited, preclinical animal studies were performed with the COVID-19 vaccines. However, many safety studies in animals were never performed, such as pharmacokinetic, toxicology and distribution studies of the encoded Spike protein. When they were done, it was in laboratory rats and mice, which do not express an ACE2 protein that binds the Spike protein. This is discussed in Para. 166, and 235.

376. Para. [28] – Dr. Corneil concluded that "*concerns expressed by Dr. Charles Hoffe regarding the use of an experimental vaccine which included gene therapy on humans were unfounded*." As thoroughly discussed earlier in this report, the COVID-19 genetic vaccines remain experimental as the technology has proven to not to meet the previous standards as to what constitutes a safe and effective vaccine. It is not normal to expect people to receive five or more shots of a vaccine due to waning and even negative efficacy. The safety record of COVID-19 mRNA and adenovirus vaccines are the worst by far according to vaccine adverse event reports in all of the vaccine injury collecting data bases. While the FDA and Health Canada did not consider RNA vaccines as a gene therapy (since it is not used in treatment) (see Section 2.5.1, Para. 42-47), it is clear that DNA plasmid contaminants (billions in a vaccine dose) with the RNA in the lipid nanoparticles in both the Pfizer/BioNTech and Moderna vaccines[74-78] as well as documented reverse transcription of Spike RNA into Spike DNA[91,92] provides for potential alteration of the human genome of vaccine recipients. Since cancer can arise from DNA integration events upstream of proto-oncogenes and tumour-suppressor genes in a single cell, there remains the opportunity for increased cancer from RNA vaccines.

377. Para. [29i] – Dr. Corneil remarked that Dr. Hoffe's "*Medical Opinion differs significantly from Clinical Practice Standards for the prevention of COVID-19*." The "Clinical Practice Standards" were usually recommendations put forth by individuals who often had conflicts of interest with the manufacturers of COVID-19 vaccines and treatment. Specialist physicians are not particularly appropriate to ascertain the risks and benefits of vaccines and treatment, although they may play an important role in the conductance of Phase 1, 2 and 3 clinical studies and post-marketing in monitoring the effects on patients. The development and assessment of such products usually reveals involves Ph.D. scientists in

academia and industry. Dr. Corneil is ignoring a large part of the scientific literature that is at odds with the narrative that he and others in health regulatory agencies have espoused.

378. Para. [29iii] – The crux of this matter is whether Dr. Hoffe's statement are incorrect and misleading. This is obviously debatable, since many professional physicians and scientists think otherwise. This is clearly evident from the beginning of the COVID-19 pandemic in 2020 and since then by the signatories of the Great Barrington Declaration, which includes 16,109 medical and public health scientists and 47,658 medical practitioners, with 938,866 total signatories to January 10, 2024.[444] In this Declaration, the signatories expressed "*expressed grave concerns about the damaging physical and mental health impacts of the prevailing COVID-19 policies*." The Declaration was drafted before the availability of COVID-19 vaccines, but it does reflect a recognition that natural immunity is robust and the COVID-19 virus was not particularly lethal in children and working adults, and the document advocated for focused protection for those that were elderly, obese and/or with comorbidities such diabetes. Interestingly "medical misinformation" is a relatively new term that was not commonly used prior to COVID-19.

379. Para. [31] – Dr. Corneil acknowledged that "*temporary short-term changes in menstrual cycle length may be associated with COVID-19 vaccination, however effects are not persistent*." However, he does not seem to recognize that such disruptions are likely a consequence of disruptions of the hormonal regulation of the menstrual cycle by the pituitary, hypothalamus and ovary." Since the ovaries are known to concentrate lipid nanoparticles, this is a "red-flag" for potential damage at the site. Immunohistochemistry studies on autopsied tissues have shown the expression of Spike protein and infiltration of immune monocytes to the ovaries.[335] While the effects of vaccines on menstrual cycles appear to be reversible, it is still unclear if the oocytes in the ovaries are undamaged. There are underlying mechanisms for selection of one of the healthiest oocytes from thousands for each ovulation cycle. However, the total number of oocytes do not change from birth, and menopause does not commence until all of the healthy oocytes are fully depleted. It may take decades before the consequences of the COVID-19 genetic vaccines on fertility are clear.

[444] (2024) Great Barrington Declaration. Retrieved from https://gbdeclaration.org/view-signatures/

380. Para. [34] – Dr. Corneil pointed out that *"There is no evidence that the mechanism for myocarditis is related to "micro-clotting", rather Inflammatory mechanisms are more plausible*." I completely agree that inflammatory reactions are most likely to account for the initiation of myocarditis and myopericarditis. I did not get the sense at all in the quoted statement that Dr. Hoffe was suggesting that abnormal blood clotting was underlying myocarditis and myopericarditis. Rather, I think he was advocating the D-dimer test for evidence of thrombosis. Troponin would be the test that he mentioned for detection of heart damage, which would be evident with myocarditis and myopericarditis.

381. Para. [34, 35ib] – Dr. Corneil suggested that "while serious AEFI such as myocarditis can occur, cases were known to be rare, mild, and treatable with no evidence of permanent myocardial damage." In a Nordic study, when the risks of either symptomatic myocarditis or myopericarditis are considered together, the chances of acquiring one of these diseases becomes even greater, as high at 1 in 704 with BNT162b2 and 1 in 264 for 16- to 24-years-old males following a second dose.[317] This is in consideration of strictly symptomatic disease. When it comes to asymptomatic myocarditis or myopericarditis, the risks are likely 3-times high, if this is similar to situation with symptomatic versus asymptomatic viral-induced myocarditis.[309] In a Thailand study of 301 teenagers of 13 to 18 years of age following their receipt of a second dose of the Pfizer/BioNtech BNT162b2 vaccine, cardiovascular effects were found in 29.24% of the teenagers.[329b] Of the 201 males in the study, four had evidence of asymptomatic myocarditis, one had myopericarditis, and two had pericarditis for a rate of 1 in 29. In a study of 519 US individuals (88% male) aged 12- to 19-year-olds, three months after the onset of COVID-19 vaccine-induced myocarditis that while most patients showed marked improvements in cardiac diagnostic markers (e.g., troponin) and testing (echocardiograms, electrocardiograms, exercise stress), 54% still showed abnormalities by cardiac MRI.[330] In a Korean study with around 480 people with vaccine-induce myocarditis, 4.4% died within the first year.[332] A more fulsome discussion of this is presented in Section 2.11 (Para. 248-250, 261-275), but it is a gross misrepresentation to suggest that the myocarditis and myopericarditis from the COVID-19 vaccines is rare, mild and treatable. Once heart muscle cells die, they cannot be renewed. The dead myocytes are replaced by scar tissue and the damage is permanent.

382. Para. [37] – Dr. Corneil stated that "*Prior and current evidence strongly suggest that Ivermectin is neither a safe nor effective treatment or prophylaxis for COVID-19 illness*." The weight of the published data in the scientific literature strongly supports the utility of ivermectin to both prevent and treat early stages of COVID-19. This is clearly shown in Figures 16 and 17, and Dr. Corneil's pronouncement

is fully rebutted in Section 2.17.3 (para. 317-340). Apart from being efficacious for COVID-19, it is also clearly one of the safest drugs known according the World Health Organization.[417] Billions of people have taken ivermectin over the last 30 years, with 96% fewer reports of adverse effects than acetaminophen/Tylenol in VigiAccess (see Para. 337).

383. Para. [37 and 40] – Dr. Corneil stated "reports of ivermectin poisoning causing harm were reported in several jurisdictions including BC." Considering how many people took ivermectin, the actual numbers of reports were low, and calling poison centre does not mean that a person necessarily. took the medication, but may be seeking information. None of the report were fatal or required hospitalization. In cited reference [149], it is written: "*the BC Drug and Poison Information centre received 50 calls concerning exposure to ivermectin and related compounds during the period we studied. Prior to the COVID-19 pandemic, 23 calls were made, and all but one were unintentional exposures. The first ivermectin call referencing COVID-19 was received in March 2021, after which call frequency increased, leading to 27 more calls, of which 19 were intentional exposures to ivermectin referencing COVID-19. Of these calls, 11 concerned veterinary-grade ivermectin…Three exposures were asymptomatic, 11 were considered to have minor effects, 1 was moderate, 4 were symptomatic but considered unrelated to ivermectin, and in 1 case symptoms were not recorded*." It needs to be emphasized that the stance taken by the College of Physicians and Surgeons in BC to discipline doctors from prescribing ivermectin compelled many people to turn instead to alternatives such as ivermectin for livestock, which increased the prospects for toxic doses of ivermectin being used (since dosage may not be properly adjusted to body weight). Health Canada did not approve COVID-19 as an indication for ivermectin as it was not requested by a pharmaceutical company to review drug submission for such as purpose. In a statement issued to the House of Commons in Parliament in response to a petition (e-3588) for its use for COVID-19 treatment, the Minister of Health responded back "*Healthcare practitioners may prescribe drugs, including ivermectin, outside of their authorized indications (also known as "off-label use"), based on other sources of information, such as medical literature. Off-label use falls under the practice of medicine and is regulated at the provincial and territorial level. Heath Canada has no jurisdiction over how health care professionals prescribe drugs once authorized. Given the potential risks outlined above, it would be*

more appropriate for off-label use of ivermectin to be done under the care and supervision of a physician. Maintaining ivermectin's prescription status helps to ensure professional oversight."[445]

384. Para. [46] - Dr. Corneil noted "Thrombosis occurs when a blood clot forms that block veins or arteries." All blood cells eventually pass through capillaries. Consequently, microclots collected from capillaries could be expected to form larger clots that could ultimately block veins and arteries. I do not understand Dr. Cornell's lack of concern in this regard. Capillaries are particularly important for providing nourishment and oxygen and removal of CO_2 and other breakdown products and toxins from the brain. Blockage of capillaries in the brain could results in ministrokes from death of specific neurons.

385. Para. [46] – While the D-dimer test is non-specific, it is nonetheless alarming that about 62% of Dr. Hoffe's patients tested positive soon after their COVID-19 vaccination. This would support a causative role of COVID-19 vaccines in the development of thrombosis.

386. Para. [49] – Dr. Corneil stated "*VAERS is a post-market vaccine safety reporting system in the United States, therefore is not applicable to Canada*." It is the same COVID-19 vaccine products (except AstraZeneca vaccine was not approved in the US (so there should be fewer vaccine injuries), and Americans and Canadians had the same physiology. Self reporting is also available with CAEFISS, and the vast majority of vaccine injury report in VAERS are made by health professionals.[190]

387. Para. [49] – Dr. Hoffe in his cited comments stated "Harvard" not "Harvard University." This might be reasonably inferred. While Dr. Corneil is inclined to dismiss the Harvard Pilgram Health Centre as not peer-reviewed, that does not negate its legitimacy.[215] In any event, other studies have independently indicated that the underreporting factor for vaccine-induced adverse effects in VAERS indicated by the Harvard Pilgram study is realistic.[216] The Harvard Pilgram study was originally prepared for the Agency of Healthcare Research and Quality section of the US Department of Health and Human Services, and indicated that less than 2% of actual injuries that may be produced from a vaccine are reported in VAERS. As pointed out earlier in Para. 169 and 369, when the percentage of severe adverse events (~5% of vaccinated participants) associated with the Pfizer/BioNTech COVID-19 vaccine reported in the

[445] (2022) Petition e-3588 to House of Commons Canada. Response by the Minister of Health. Signed by Minister or Parliamentary Secretary): Adam van Koeverden. https://www.ourcommons.ca/petitions/en/Petition/Details?Petition=e-3588

Phase 3 trial is compared to VAERS reports, it is clearly evident that the underreporting value for the data in VAERS is greater than 100. VAERS lists about 197,326 reports of doctor office visits in VAERS by November 3, 2023,[443] and some 984,444,295 COVID-19 vaccine doses given in the US as on May 10, 2023.[446] Assuming that the number of vaccine doses given is about 1 trillion in the US by November 3, 2023, this indicates a severe COVID-19 vaccine injury rate of 0.02% by passive reporting, which is 250-times lower than 5% expect based on the Pfizer Phase III clinical results in random controlled trial.[133]

388. Para. [51] – Dr. Corneil stated that CHD is an "*organization that questions the safety of vaccines and their regulatory bodies offering statements and articles exaggerating or overemphasizing vaccine risks that are not referenced or peer reviewed*." The CHD indicates that it maintains a database on their website which "*contains hundreds of peer-reviewed, published articles on environmental contaminants that are implicated in the rise of the childhood epidemics we are currently experiencing in the U.S. and other industrialized nations*."[447] When I visited the CHD website, such publications in peer-reviewed journals were easily visible and retrievable.

389. Para. [55] – Dr. Corneil completely ignored the biodistribution studies performed with COVID-19 vaccine lipid nanoparticles in rodents, which demonstrated 76% of lipid nanoparticles have travelled away from the site of injection within 2 days of inoculation (Para. 165). The lipid nanoparticles could travel to salivary glands, for example, and be released from the mouth. It is also possible that shedding of Spike protein occurs with inflammatory immune cell attack of Spike-expressing cells and the release of exosomes with Spike protein. Another possibility is that immediately after vaccination in the first few days, vaccine recipients are more susceptible to infection and release of the SARS-CoV-2 virus as indicated in Figures 6 and 7.

[446] (2023) US Coronovirus vaccine tracker. USA Facts. Retrieved from https://usafacts.org/visualizations/covid-vaccine-tracker-states/

[447] (2023) Childens Health Defence. https://childrenshealthdefense.org/research-database/?section=Research+Articles

Respectfully submitted by

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Canadian Citizens Care Alliance

++++++++++++++++++++++++++
Dr. Steven Pelech
Dated this 25th day of January, 2024

This is Exhibit “A” referred to in the
Expert Report of Steven Pelech

Curriculum Vitae

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University of British Columbia

Curriculum Vitae for Faculty Members

Date: **January 24, 2024**

Initial: — S —

1. SURNAME: Pelech

FIRST NAME: Steven

MIDDLE NAME(S):

2. DEPARTMENT/SCHOOL: Medicine, Div. Neurology

3. FACULTY: Medicine

JOINT APPOINTMENTS:

4. PRESENT RANK: Professor **SINCE:** Juyl 1, 1998

5. POST-SECONDARY EDUCATION

(a)

University or Institution	Degree	Subject Area	Dates
University of British Columbia	B.Sc.	Biochemistry	1975-1979
University of British Columbia	Ph.D.	Biochemistry	1979-1982

(b) Title of Dissertation and Name of Supervisor

Regulation of Phosphatidylcholine Biosynthesis - with Dr. Dennis E. Vance

(c) Continuing Education or Training

(d) Continuing Medical Education

(e) Professional Qualifications

1 Biomedical Research Scientist

6. EMPLOYMENT RECORD

Prior

University, Company or Organization	Rank or title	Dates
University of British Columbia	Assistant Professor	July 1, 1988 - June 30, 1993
University of British Columbia	Associate Professor	July 1, 1993 - June 30, 1997
University of British Columbia	Postdoctoral Fellow (with Dr. Dennis Vance)	1983-1983
University of Dundee, Scotland	Postdoctoral Fellow (with Dr. Philip Cohen, knighted as Sir Philip Cohen)	1983-1984
University of Washington, Seattle	Postdoctoral Fellow (with Dr. Edwin Krebs, Nobel Prize recipient)	1984-1987
Biomedical Research Centre, Vancouver (Immunology Institute)	Senior Scientist	1987-1998
Kinetek Pharmaceuticals, Inc.	Founder, President & Chief Executive Officer	1992-1997

Present

University, Company or Organization	Rank or title	Dates
University of British Columbia	Professor	July 1, 1997 - present
Kinexus Bioinformatics Corporation	Founder, President & Chief Scientific Officer, Director	1999-present

c) Date of granting tenure at UBC:

July 1, 1993

7. LEAVES OF ABSENCE

University, Company Or Organization at which Leave was taken	Type of Leave	Dates

None taken since starting as a UBC faculty member. However, from November 3, 2004 through to April 15, 2005, I was summoned for 24 full days to appear in a B.C. Human Rights Hearing Case. I also had to appear in the BC Supreme Court for a judicial review of this case over a week's period in April 2009.

8. TEACHING

(a) Areas of special interest and accomplishments

1 Percentage of Overall Time Devoted to:

Non-clinical instruction:	20%
Clinical instruction:	0%
Research/publication:	55% (includes R&D at private biotechnology company)
Administration (UBC):	20%
Administration (Kinexus):	5%
Clinical practice:	0%

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2 For over 30 years, I was very active in the establishment of the Experimental Medicine Graduate Program and worked closely with its six directors (i.e. Drs. Rabkin, Quamme, Wong, Duronio, Sly and Tang). My goal was to develop courses that would provide practical, useful skills to graduate students. In particular, the students should acquire a solid knowledge base, be able to read the scientific literature and on-line websites critically, adapt to new lab environments and assimilate new techniques, deliver clear oral presentations, and write competitive grants for funding. I left this committee in the Spring of 2023.

3 To improve the knowledge-base of Experimental Medicine students, I became the course coordinator for MEDI 501, a lecture course that is required of all students in the program and focuses on the molecular basis of disease. I originally presented the opening four lectures for this course, which is taught by several faculty members. I am convinced that future improvements in the treatment of diseases will depend upon a firm understanding of the molecular mechanisms underlying the diseases. Imparting this knowledge to graduate students will better prepare them for disease-related research. In 2023, I taught one 90 minutes lecture in the Fall term. I also provide an examination question for the mid-term exam and graded 24 answers.

4 To improve the laboratory skills of Experimental Medicine students, I became the course coordinator for MEDI 502, which is the second course that is required of all students in the program. Previously, the students went on mass together to a different lab each week to see a technique taught by a faculty member. I altered the course so that each student could select two host labs out of two dozen possible labs in which they would spend half a day per week for two months in each lab learning about the research area and various techniques in use in that lab. This improved research interactions among various members of the Department of Medicine. Half way through this course, the student has to give to the other students in the course a 20 minutes

oral presentation that outines the nature of the research in the first host lab and a technique that is being used to approach a biological problem in that lab. At the conclusion of the rotation in the second host lab, the student has to write an MRC grant application that combines aspects of his experience in the host laboratories. The oral presentation and the grant application account for the majority of the final grade for this course. This is the only course of this kind that is offered through the U.B.C. Currently, I am willing to take on one to two students per term in my laboratory for this course.

5 I have also provided the opportunity for many undergraduate students to obtain research experience in my laboratory through the BIOL 448A, E2P PharmD & BPSc and MEDI 548 Directed Studies courses and the cooperative education programs at the Department of Microbiology and Immunology at U.B.C. and the Simon Fraser University Science Coop. From these coop programs, over 200 undergraduate students have work full-time in my laboratory under my supervision for 4 to 12 month terms.

6 My area of research expertise is signal transduction, and there is growing appreciation that defective cell signalling is at the root of cancer, Alzheimer's, diabetes, immune disfunction and many other chronic diseases of aging. As there was no advanced, graduate level course in signal transduction that was offered each year at U.B.C., I decided to create one. The majority of my teaching is in the MEDI 590 Cell Regulation course, which I coordinate and deliver all of the lectures. The course is very advanced and covers a lot of ground, but most students perform very well. The final mark for MEDI 590 course is now largely dependent upon an exercise to gather detailed information about various members of a family of cell signalling proteins. This exercise forces the students to read the scientific literature and collect data from relevant websites, and present their results organized in Excel tables. The collected information is made available to the scientific community after it is integrated into a database. In 2023, there were 7 registered graduate students that completed the course. All of the 52 hours of PowerPoint lectures and supporting materials are provided to all the students in pdf format in advance of each class. I devoted over 30 hours additional outside of the classroom in 2023 in MEDI 590 course preparation, including the development of new original content and marking midterms and final assignments. I have made much of these educational materials available to wider audiences on the Kinexus Bioinformatics website at www.kinexus.ca. My long term objective is to produce 10 minute teaching videos of portions of the lectures for the MEDI590 course that will be posted on-line with open-access.

7 Another course that I originally coordinated for five years is MEDI 535, which I designed to be a journal club in which the participants critically analyze recent scientific papers based on signal transduction research. In this course, the students received a scientific paper a week before the next class that they are expected to read and critically review. The following week, the student that originally selected the paper provided a brief synopsis of the paper and then led the round table discussion among myself and the other students of the paper's strengths and deficiencies. I believe that this course provides the students with strong analytical skills that are useful when the students prepare their own scientific manuscripts and for when they read the literature. I have not tutored in this course in recent years.

8 I have also provided 2 hours of lecture per year in the Neuroscience 500 course (1999-2001), I participated as a medical student PBL tutor in the Endocrinology Block for Second Year (1999, 2000) and Hyperplasia Block for First Year), gave a 1 hour lecture to First Year Medical Students (2002) and 2 hours of lecture per year in Pathology 500 (2001, 2002) and 2 hours of lecture to Pharmaceutical Sciences graduate students in PHAR 545 (2003).

(b) Recent Courses Taught at UBC:

Year	Session	Course Number	Scheduled Hours	Class Size	Hours Taught			
					Lecture	Tutorials	Labs	Other
2019 + 2020	Fall 2019 + Winter 2020	BIOL 448 – Directed Studies	60	1 – Kevin Wong	0	5	>250 h	1
2019 + 2020	Fall 2019 + Winter 2020	ISCI 448 – Directed Studies	60	1 – Abiel Kwok	0	5	>250 h	1
2020	Winter 2020	MEDI 502 - Molecular and Cellular Biology	30	1 – Jackie Ho	0	4	10	1
2020	Fall 2020	MEDI 590 - Molecular Regulation of Cell Growth	>100	9	56	0	0	>100 h (see Note 1)
2020	Fall 2020	MEDI 501 - Molecular and Cellular Biology	7	19	1.5	0	0	+5.5 h (see Note 2)
2021	Fall 2021	MEDI 590 - Molecular Regulation of Cell Growth	>100	4	52	0	0	>50 h (see Note 1)
2021	Fall 2021	MEDI 501 - Molecular and Cellular Biology	10	30	1.5	0	0	+5.5 h (see Note 2)
2022	Fall 2022	MEDI 590 - Molecular Regulation of Cell Growth	>100	6-12	52	0	0	>50 h (see Note 1)
2022	Fall 2022	MEDI 501 - Molecular and Cellular Biology	10	24	1.5	0	0	+5.5 h (see Note 2)
2023	Fall 2023	MEDI 590 - Molecular Regulation of Cell Growth	>100	7	52	0	0	>50 h (see Note 1)
2023	Fall 2023	MEDI 501 - Molecular and Cellular Biology	10	28	1.5	0	0	+8.5 h (see Note 2)

Note 1 - +50-150 h course preparation; +2 h for midterm; +2 h midterm marking; + >50 h final assignment marking

Note 2 - +4.5-10 h lecture preparation and mid-term or final exam marking

(c) Graduate Students directly supervised at UBC:

Student Name	Program Type	Year		Principal Supervisor	Co-Supervisors
		Start	Finish		
Palaty, Chrystal	Exp. Med. Ph.D.	1990	1995	Pelech	
Samiei, Mitra	Exp. Med. Ph.D.	1990	1994	Pelech	Devine
Mordred, Guy	Biochemistry Ph.D.	1991	1993	Paucellier	Pelech
Charest, David	Exp. Med. Ph.D.	1991	1998	Pelech	
Charlton, Lorin	Exp. Med. Ph.D.	1991	1998	Pelech	
Morrison, Donna	Exp. Med. Ph.D.	1992	1998	Pelech	
Kim, Sung	Pharm. Sci. Ph.D.	1992	1998	Katz	Pelech
Tudan, Christopher	Exp. Med. Ph.D.	1993	1999	Pelech	
Tao, Jingsong	Microbiol. Ph.D.	1995	1998	Levy	Pelech
Marotta, Anthony	Exp. Med. Ph.D.	1996	1999	Sahl	Pelech
Wagey, Ravenska	Exp. Med. Ph.D.	1996	2000	Krieger	Pelech
Sayed, Mohamed	Exp. Med. Ph.D.	1998	2002	Pelech	Sahl
Vilimek, Dino	Exp. Med. M.Sc.	1999	1999	Duronio	Pelech
Je-Hong Hu	Simon Fraser	2000	2004	Krieger	Pelech
Gobind Sun	Exp. Med. Ph.D.	2006	2008	Pelech	
Amy Lai	Exp. Med. Ph.D.	2007	2008	Pelech	
Shenshen Lai	Exp. Med. Ph.D.	2009	2015	Pelech	
Javad Safaei	Math. & Comp. Sci. Ph.D	2009	2015	Gupta	Pelech
Dominik Sommerfeld	Exp. Med. Ph.D.	2010	2012	Pelech	
S.M. Shabab Hossain	Comp. Sci. M.Sc.	2011	2011	Gupta	Pelech
Lambert Yue	Exp. Med. Ph.D.	2016	2020	Pelech	

Hamidreza Galavi	Exp. Med. Ph.D.	2020	2023	Pelech	
Andréa Bleret	M.Sc. Université catholique de Louvain	2022 Feb.	2022 May	Bernard Hallet	Pelech
Ghada Maged Ali	M.Sc.(Neuro-science) Alexandria Univ., Egypt	2022 Feb.	present	Ahmad Raafat Bassiouny	Pelech

(d) MEDI 502 Graduate Student Rotation Supervision

1	Julian Vasilescu	UBC , MEDI 502	January 27-31, 2003
2	Lisa Bradley	UBC , MEDI 502	January 13-17, 2003
3	Loutfig Demirjian	UBC , MEDI 502	March 23 – April 23, 2004
4	Edgar Lam	UBC , MEDI 502	February 28 – March 4, 2005
5	Philip Ly	UBC , MEDI 502	January 10, 2006 – February 28, 2006
6	Michael Butt	UBC , MEDI 502	April 12, 2007 – April 30, 2007
7	Alastair Davies	UBC , MEDI 502	January 15 – February 15, 2008
8	Chengcheng Zhang	UBC , MEDI 502	February 15, 2009 – March 15, 2009
9	Anthony Tam	UBC , MEDI 502	January 15 – February 15, 2010
10	Helen Chen	UBC , MEDI 502	February 15 – February 28, 2011
11	Jack Lui	UBC , MEDI 502	March 1 – March 16, 2011
12	Saeideh Davoodi	UBC , MEDI 502	January 10 – January 30, 2012
13	Soojin Kim	UBC , MEDI 502	January 11 – February 1, 2013
14	Sehyun Cho	UBC , MEDI 502	February 1 – February 28, 2013
15	Paul Toren	UBC , MEDI 502	January 11 – February 1, 2014
16	Franco Cavaleri	UBC , MEDI 502	February 1 – February 28, 2015
17	Ryan Yue	UBC, MEDI 502	January 14 – February 28, 2016
18	Alexandre Kadhim	UBC, MEDI 502	January 14 – February 28, 2016
19	Jian Gao	UBC, MEDI 502	January 14 – February 28, 2017
20	Muyan Cao	UBC, MEDI 502	January 29 – February 28, 2018
21	Jackie Ho	UBC, MEDI 502	January 29 – February 28, 2020

In 2012, I also marked mock grant reviews prepared by Mary Rose Pambid and Saeideh Davoodi as part of the MEDI-502 course.

(e) MBA Student Supervision (at my industrial lab at Kinexus)

1	Deborah Bender	SFU, MBA Student	May 1 - July 31, 2001
2	Darius Panaligan	SFU, MBA Student	June 5 - August 31, 2001

(f) Undergraduate Coop Student Research Supervision (at my industrial lab at Kinexus)

I have taken on over 175 undergraduate students from the Simon Fraser University, University of Victoria and University of B.C. Coop programs through my companies Kinetek Pharmaceuticals Inc. (1992-1998) and Kinexus Bioinformatics Corp. (1999-present). Most of these students worked on average for 8 months full work-terms. I have only listed my trainees at Kinexus below.

No.	Name of Student	Months	Start Date	End Date
1	Korine Ung	4	1-Sep-1999	30-Dec-1999
2	David Brewster	4	1-Jan-2000	30-Apr-2000
3	Michael Hsing	8	1-Jan-2000	31-Aug-2000
4	Pinky Chua	4	1-May-2000	31-Aug-2000
5	Bonnie Jones	8	1-May-2000	31-Dec-2000
6	Claire Hou	4	1-Sep-2000	31-Dec-2000
7	Tiffany Chen	8	2-Jan-2001	31-Aug-2001
8	Christopher Huang	8	2-Jan-2001	31-Aug-2001
9	Kevin Ma	8	1-May-2001	31-Dec-2001
10	Jason Sterne	8	7-May-2001	31-Dec-2001
11	Kristy Lynn Williams	8	27-Aug-2001	31-Dec-2001
12	Jeff Druce	8	27-Aug-2001	31-Dec-2001
13	Mark White	4	27-Aug-2001	31-Dec-2001
14	Jack Min	4	4-Sep-2001	31-Dec-2001
15	Jill Youds	8	1-Jan-2002	31-Aug-2002
16	Jackie To	8	1-Jan-2002	31-Aug-2002
17	Marina Kanjer	4	1-Jan-2002	30-Apr-2002
18	Andrea Ramalho	8	1-Jan-2002	30-Aug-2002
19	Leon Poznanski	8	1-May-2002	31-Dec-2002
20	Devon Yeoman	8	1-May-2002	31-Dec-2002
21	Kyla Hingwing	8	1-Sep-2002	30-Apr-2003
22	Gavin Lee	4	10-Sep-2002	31-Dec-2002
23	Richard Li	8	1-Jan-2003	30-Aug-2003
24	Anna Moorhouse	8	1-Jan-2003	30-Aug-2003
25	Beth Clendening	8	22-Apr-2003	31-Dec-2003
26	Shauna Murray	12	25-Aug-2003	31-Aug-2004
27	Heidi Cheung	8	1-Sep-2003	30-Apr-2004
28	Sharan Swarup	16	1-Sep-2004	31-Dec-2004
29	Nadia Brinkman	8	1-Jan-2004	31-Aug-2004
30	Elbert Chang	4	1-Jan-2004	30-Apr-2004
31	Wilson Luk	8	3-May-2004	31-Dec-2004
32	Tina Chen	8	26-Aug-2004	30-Apr-2005

33	Anar Dhallar	8	26-Aug-2004	30-Apr-2005
34	Sylive Bryant	8	4-Jan-2005	31-Aug-2005
35	Melissa Hogg	4	4-Jan-2005	30-Apr-2005
36	Benjamin Jong	8	4-Jan-2005	31-Aug-2005
37	Amanda Heiler	8	2-May-2005	31-Dec-2005
38	Poonam Jassi	8	2-May-2005	31-Dec-2005
39	Theresa Connor	8	1-Sep-2005	30-Apr-2006
40	Gavin Ha	8	1-Jan-2006	31-Aug-2006
41	Megan Kofoed	16	1-Jan-2006	30-Apr-2007
42	Iris Juan	8	1-May-2006	31-Dec-2006
43	Andrew Park	5	1-May-2006	1-Oct-2006
44	Ryan Whitehead	4	1-May-2006	25-Aug-2006
45	Bryanna Grace	4	1-Sep-2006	31-Dec-2006
46	Michael Peabody	8	1-Sep-2006	30-Apr-2007
47	Joanna Kam	8	19-Dec-2006	31-Aug-2007
48	Nova Do	8	1-Jan-2007	31-Aug-2007
49	Jason Wong	8	1-Jan-2007	31-Aug-2007
50	Charrise Pagarigan	4	1-Jan-2007	30-Apr-2007
51	Sabrina Rayworth	8	1-May-2007	31-Dec-2007
52	Fredrick Bantandos (SFU)	8	1-Sep-2007	30-Apr-2008
53	Pringle Comia (SFU)	8	1-Sep-2007	30-Apr-2008
54	Raymond Leung (SFU)	8	1-Sep-2007	30-Apr-2008
55	Adam Leigh (UBC)	8	1-Jan-2008	31-Aug-2008
56	Ellen Sung (UBC)	4	1-Jan-2008	30-Apr-2008
57	Angie Chu (UBC)	4	1-May-2008	31-Aug-2008
58	Stephanie Lam (SFU)	8	1-May-2008	31-Dec-2008
59	Amy Tam (UBC)	8	1-May-2008	31-Dec-2008
60	Ken Ng (SFU)	8	1-May-2008	31-Dec-2008
61	Ryan Saranchuk (UBC)	4	1-Sep-2008	31-Dec-2008
62	Sarah Zaidi (SFU)	3.5	1-Sep-2008	15-Dec-2008
63	Anna Chau (UBC)	8	1-Jan-2009	31-Aug-2009
64	Kerrie Law (UBC)	8	1-Jan-2009	31-Aug-2009
65	Jose Canas (SFU)	8	1-Jan-2009	31-Aug-2009
66	Steven Pham (UBC)	8	1-Jan-2009	31-Aug-2009
67	Connie Drewbrook (SFU)	4	1-May-2009	31-Aug-2009
68	Justin Yu (UBC)	4	1-May-2009	31-Aug-2009
69	Ryan Foyle (UBC)	8	1-May-2009	31-Dec-2009
70	Tak Poon (UBC)	8	1-May-2009	31-Dec-2009
71	Tammy Wang (UBC)	4	1-Sept-2009	31-Dec-2009
72	Yan Zhou (SFU)	4	1-Sept-2009	31-Dec-2009
73	Tommy Lee (UBC)	4	1-Sept-2009	31-Dec-2009
74	Kerrie Tian (SFU)	8	1-Sept-2009	30-Apr-2010
75	Christine Yu (UBC)	4	1-Jan-2010	30-Apr-2010
76	Vivienne Chan (UBC)	8	1-Jan-2010	31-Aug-2010

77	Katelyn Fines (UBC)	4	1-Jan-2010	30-Apr-2010
78	Katelyn Janzen (UBC)	8	1-Jan-2010	31-Aug-2010
79	Mandy Hu (UBC)	8	1-Jan-2010	31-Aug-2010
80	Mandy Chung (SFU)	4	1-May-2010	31-Aug-2010
81	Abby Yang (UBC)	8	1-May-2010	31-Dec-2010
82	Christopher Bond (SFU)	8	1-Sep-2010	31-Dec-2010
83	Jarrod Mackay (SFU)	4	1-Sep-2010	31-Dec-2010
84	Karyll Magtibay (UBC)	8	1-Sep-2010	30-Apr-2011
85	Kathryn Marshall (SFU)	4	1-Sep-2010	30-Apr-2011
86	Christopher Meschino (SFU)	4	1-Sep-2010	30-Apr-2011
87	Bonnie Cheung (UBC)	8	1-Jan-2011	31-Aug-2011
88	Lisa Luo (UBC)	8	1-Jan-2011	31-Aug-2011
89	Abhinav Sharma (UBC)	8	1-Jan-2011	31-Aug-2011
90	Cherie Tan (UBC)	8	1-Jan-2011	31-Aug-2011
91	Puneet Litt (SFU)	4	1-May-2011	31-Aug-2011
92	Kingsley Shih (UBC)	8	1-May-2011	31-Dec-2011
93	Sophie Tsai (SFU)	8	1-May-2011	31-Dec-2011
94	Sze Wing Wong (UBC)	4	1-May-2011	31-Aug-2011
95	J.C. Cheng (UBC)	4	1-Sep-2011	31-Dec-2011
96	Dennis Chau (SFU)	4	1-Sep-2011	31-Dec-2011
97	Jarrod Mackay (SFU)	8	1-Sep-2011	30-Apr-2012
98	Lisa Ying (UBC)	8	1-Jan-2012	31-Aug-2012
99	Krista Wong (UBC)	8	1-Jan-2012	31-Aug-2012
100	Gurjot Dhaliwal (UBC)	8	1-Jan-2012	31-Aug-2012
101	Michael Ni (UBC)	4	1-May-2012	31-Aug-2012
102	Chelsea Lee (Emily Carr)	3	20-May-2012	31-Aug-2012
103	Inderpal Gill (UBC)	4	1-Sep-2012	31-Dec-2012
104	Ryan Lee (SFU)	4	1-Sep-2012	31-Dec-2012
105	Ashley Steuck (UBC)	4	1-Sep-2012	31-Dec-2012
106	Kaitlin Hong Tai (SFU)	12	1-Sep-2012	31-August-2013
107	Roanette Postma (SFU)	8	1-Jan-2013	31-Aug-2013
108	Christine Chan (UBC)	8	1-Jan-2013	31-Aug-2013
109	James Hopkins (SFU)	8	1-Jan-2013	31-Aug-2013
110	Sally Maguet (SFU)	4	1-Sep-2013	31-Dec-2013
111	Martin Radvenis (UBC)	4	1-Sep-2013	31-Dec-2013
112	Katy Tan (UBC)	4	1-Sep-2013	31-Dec-2013
113	Alisa Too (UBC)	8	1-Jan-2014	31-Aug-2014
114	Lambert Yue (UBC)	8	1-Jan-2014	31-Aug-2014
115	Enoli de Silva (UBC)	8	1-Jan-2014	31-Aug-2014
116	Sonia Hessels (SFU)	8	1-Jan-2014	31-Aug-2014
117	Jeremy Nan (UBC)	8	1-Jan-2014	31-Aug-2014
118	Alexander Mann (UBC)	8	1-May-2014	31-Dec-2014
119	Alexa Creenan (UBC)	4	1-Sep-2014	31-Dec-2014
120	Maggie Fu (UBC)	4	1-Sep-2014	31-Dec-2014

121	Lisa Lee (UBC)	4	1-Sep-2014	31-Dec-2014
122	Colm Quirke (UBC)	8	1-Sep-2014	30-April-2015
123	Kristy Dever (UBC)	8	1-Sep-2014	30-April-2015
124	Jordan Chiu (UBC)	8	1-Jan-2015	31-August-2015
125	Tam Dang (UBC)	8	1-Jan-2015	31-August-2015
126	Minnie Huang (UBC)	8	1-Jan-2015	31-August-2015
127	Marti Hua (UBC)	8	1-Jan-2015	31-August-2015
128	Nimisha Arora (India)	6	1-Jan-2015	30-June-2015
129	Jeffrey White (UBC)	8	1- May-2015	31-December-2015
130	Alex Sweeten (SFU)	4	1- May-2015	30-August-2015
131	Lambert Yue (UBC)	8	1- May-2015	31-December-2015
	Lambert Yue (UBC)	8	1-May-2016	31-December-2016
132	Ryan Hounjet (UBC)	4	1-Sept-2015	31-December-2015
133	Andy Lam (UBC)	4	1-Sept-2015	31-December-2015
134	Tianna Sun (UBC)	4	1-Sept-2015	31-December-2015
135	Johnathan Wong (SFU)	4	1-Jan-2016	30-April-2016
136	Paula Tao (UBC)	8	1-Jan-2016	31-August-2016
137	Tony Han (UBC)	8	1-Jan-2016	31-August-2016
138	Desiree Pagulayan (UBC)	4	1-Jan-2016	30-April-2016
139	Jason Liu (UBC)	8	1-Jan-2016	31-August-2016
140	Jenny Chan (UBC)	8	1-Jan-2016	31-August-2016
141	Claire Doyon (UBC)	12	1-May-2016	30-April-2017
142	Christine Sam (UBC)	4	1-Sept-2016	31-December-2016
143	Yezen Dean (SFU)	8	1-Sept-2016	30-April-2017
144	Kevin Gonzalez (UBC)	12	1-Sept-2016	31-August-2017
145	Karin Parkeh (UBC)	4	1-Sept-2016	31-December-2016
146	Ayasha Brown (UBC)	8	1-Jan-2017	31-August-2017
147	Sarina Chen (UBC)	4	1-May-2017	31-August-2017
148	Jenna Grose (SFU)	8	1-May-2017	31-December-2017
149	Dhiraj Mannar (UBC)	8	1-May-2017	31-December-2017
150	Aster Fan (SFU)	8	1-Sept-2017	30-April-2018
151	Leo Escano (SFU)	4	1-Sept-2017	31-December-2017
152	Ashley Perron (UBC)	8	1-Jan-2018	31-August-2018
153	Eva Momchilova (SFU)	8	1-Jan-2018	31-August-2018
154	Iqbal Sarai (SFU)	8	1-May-2018	31-December-2018
156	Angela Wu (UBC)	8	1-May-2018	31-December-2018
157	Joanne Chan (UBC)	4	1-Sept-2018	31-December-2018
158	Abiel Kwok (UBC)	12	1-Sept-2018	31-August-2019
159	Jazica Chan (SFU)	12	1-Sept-2018	31-August-2019
160	Zhong Yuan Zhang (UBC)	4	1-Jan-2019	30-April-2019
161	Guravneet Gill (UBC)	4	1-May-2019	31-August-2019
162	Naiomi Khan (UBC)	4	1-May-2019	31-August-2019
163	Mona Golmohammadzadeh (UBC)	8	1-Sept-2019	30-April-2020

164	Avery Mak (SFU)	8	1-Sept-2019	30-April-2020
165	Mataya Lukas (SFU)	8	1-Jan-2020	31-August-2020
166	Sarah Agnew (UBC/BCIT)	8	1-May-2020	31-December-2020
167	Gage Fairlie (UBC)	8	1-May-2020	31-December-2020
168	Akshra Atrey (UBC)	12	1-Sept-2020	15-August-2021
169	Hallie Emory (UBC)	8	1-Sept-2020	30-April-2021
170	Tammy Yu (SFU)	8	1-Jan-2021	31-August-2021
171	Britney Yuen (UBC)	8	1-May-2021	31-December-2021
172	Jason Zhao (UBC)	10	1 July-2021	30-April-2022
172	Melody Lam (UBC)	8	1-Sept-2021	30-April-2022
173	Ekaterina Galysheva (UBC)	8	1-Jan-2022	31-August-2022
174	Trang Ngyen (UBC)	4	1-May-2022	31-August-2022
175	Trinity Truong (UBC)	8	1-May-2022	31-December-2022
176	Sierra Neff (UBC)	3.5	1-May-2022	15-August-2022
177	Samuel Bakteria (UBC)	>9	1-May-2023	present

(g) Undergraduate BC Institute of Technology Student Supervision (at my industrial lab at Kinexus)

I directly worked with each of these students in the development of the open-access, on-line databases and knowledgebases hosted Kinexus Bioinformatics Corporation. These usually involved bi-weekly interactions for 1 to 2 hours over a 5 to 6 week period.

1	Anchal Jain	BCIT Computer Sci. Prgm.	21-June-2005 to 10 –Sep-2005
2	Eric Chua	BCIT Computer Sci. Prgm.	21-June-2005 to 10 –Sep-2005
3	Ho Sand (Alex) Lee	BCIT Computer Sci. Prgm.	21-June-2005 to 10 –Sep-2005
4	Jimmy Chan	BCIT Computer Sci. Prgm.	12-Oct-2005 to 25 –Nov-2005
5	Kevin Rabang	BCIT Computer Sci. Prgm.	12-Oct-2005 to 25 –Nov-2005
6	Kannon Woo	BCIT Computer Sci. Prgm.	12-Oct-2005 to 25 –Nov-2005
7	Norma Wong	BCIT Computer Sci. Prgm.	12-Oct-2005 to 25 –Nov-2005
8	Kevin Odger	BCIT Computer Sci. Prgm.	1-Nov-2006 to 30-Jan-2007
9	Travis Nicholson	BCIT Computer Sci. Prgm.	21-Apr-2008 to 21-May-2008
10	Jonathan Jose	BCIT Computer Sci. Prgm.	21-Apr-2008 to 21-May-2008
11	Ryan Pattinson	BCIT Computer Sci. Prgm.	21-Apr-2008 to 21-May-2008
12	Hannah Rosellon	BCIT Computer Sci. Prgm.	21-Apr-2008 to 21-May-2008
13	John Liau	BCIT Computer Sci. Prgm.	1-Oct-2008 to 28-Feb-2009
14	Joe Hu	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
15	Ysabel Lago	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
16	David Liau	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
17	Christine Livingstone	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
18	Melissa Manalac	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
19	Nevin Petersen	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
20	Janice Sargent	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
21	Brandon Wang	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
22	Alvin Yip	BCIT Computer Sci. Prgm.	15-Apr-2010 to 21-May-2010
23	Nicholas Tagle	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
24	Igor Kozlov	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011

25	Fausto Faioli	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
26	Justin Ma	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
27	Simon Ho	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
28	Isan Chen	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
29	Keegan Kelly	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
30	Aly Jamani	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
31	Colin Nguyen	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
32	David Gannon	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
33	Lili Hao	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
34	Mila Khadarina	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
35	Andrii Skrynnyk	BCIT Computer Sci. Prgm.	26-Apr-2011 to 27-May-2011
36	Kyle Li	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
37	Theo Mutia	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
38	Travis Ryder	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
39	Clarence Sng	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
40	James Chen	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
41	Andy Chow	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
42	Sunju Christine Jeong	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
43	Dan Stephenson	BCIT Computer Sci. Prgm.	21-Apr-2013 to 24-May-2013
44	Nadezhda Dobrianskaia	BCIT Computer Sci. Prgm.	20-Apr-2015 to 18-May-2015
45	Guanyi Fang	BCIT Computer Sci. Prgm.	20-Apr-2015 to 18-May-2015
46	Calvin Truong	BCIT Computer Sci. Prgm.	20-Apr-2015 to 18-May-2015
47	Kevin Thet	BCIT Computer Sci. Prgm.	20-Apr-2015 to 18-May-2015
48	Haruna Kakinoki	BCIT Computer Sci. Prgm.	20-Apr-2018 to 18-May-2018
49	Matthew Lau	BCIT Computer Sci. Prgm.	20-Apr-2018 to 18-May-2018
50	Noah McMurchy	BCIT Computer Sci. Prgm.	20-Apr-2018 to 18-May-2018
51	Roberg Koeing	BCIT Computer Sci. Prgm.	20-Apr-2018 to 18-May-2018
52	Ryan Liang	BCIT Computer Sci. Prgm.	10-Sept-2018 to 30-Nov-2018
53	Garth Nelson	BCIT Computer Sci. Prgm.	10-Sept-2019 to 30-Nov-2018
54	Andy Tang	BCIT Computer Sci. Prgm.	10-Sept-2018 to 30-Nov-2018
55	Thomas Bui	BCIT Computer Sci. Prgm.	10-Sept-2019 to 25-May-2020
56	Saeed Naguib	BCIT Computer Sci. Prgm.	10-Sept-2019 to 25-May-2020
57	Daria Dimchuk	BCIT Computer Sci. Prgm.	10-Sept-2019 to 25-May-2020
58	Dawson Verboven	BCIT Computer Sci. Prgm.	10-Sept-2019 to 25-May-2020

I have also provided co-supervision for UBC Computer Science Ph.D. candidate Mr. Alireza Davoodi with Dr. Jan Manuch in a MITAC Project from April 1, 2013 for the KinATLAS website.

(h) Continuing Education Activities

1 February 9, 2005 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

2 November 9, 2005 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

3 November 30, 2005 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

4 February 15, 2006 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

5 March 15, 2006 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

6 November 8, 2006 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

7 April 11, 2007 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

8 November 14, 2007 – UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

9 November 21, 2007 - UBC TAG Workshop for Dept. of Urology – Preparation of Teaching Dossier for Promotion and Tenure

10 March 5, 2008 - UBC TAG Workshop – Preparation of Teaching Dossier for Promotion and Tenure

11 January 26, 2022 - UBC Ethics in the Arts Workshop

12 July 20, August 31, October 26, 2022 - UBC Racism Workshop - Decolonial and Anti-Racist Approaches to Wellbeing with Future Ancestors' Larissa Crawford

13 As part of my continuing education activities, I regularly attend the Neurosciences Grand Rounds on Wednesday mornings at 8:00 am, the Department of Medicine Grand Rounds on Thursdays at 12:00 noon and the DMCBH Lectures on Fridays at 11:00 am each week.

(i) Visiting Lecturer (indicate university/organization and dates)

This is included with my invited presentation list in Section 9(d).

(j) Mentor for Sabbatical

1	Dr. Byung Soon Moon – Professor and Head of Surgery, WONKWANG University Iksan Oriental Medical Center, Korea, February 1, 2007 - January 31, 2008

(k) Other

1 MRC Representative for Scholarships Day at U.B.C. - October 25, 1991; Sept. 24, 1992

2 Volunteer for Careers Presentation - Science World, Vancouver - March 9, 1993

3 Scientists & Innovators in the Schools, Kitsilano Secondary School, Vancouver -Feb. 14, 1993

4 Volunteer for Careers Presentation - Science World, Vancouver - March 1, 1996

5 Scientists & Innovators in the Schools, Gladstone Secondary School, Vancouver -January 24, 1997

6 Volunteer for B.C. Regional Science Fair, University of B.C. - April 5, 2001

High School Student Mentorship (1 day to 2 weeks) at my industrial lab at Kinexus

1 Davita Fuchs - Windermere Secondary School, Vancouver, 24-29-Jul-2001

2 Ariella Zbar – Eric Hamber High School, Vancouver, 26-30-Aug-2002

3 Tom Chan - Windermere Secondary School, Vancouver, 27-31-Jan-2003
4 Nga Wailau - Windermere Secondary School, Vancouver, 23-27-Jun-2003
5 Maggie Lau - Windermere Secondary School, Vancouver, 21-25-Jul-2003
6 Winnie Chen – Prince of Wales Secondary School, Vancouver, 18-22-Aug-2003
7 Peter Quon - Windermere Secondary School, Vancouver, 26-30-Jan-2004
8 Reginald Naidu - Windermere Secondary School, Vancouver, 17-30-Jun-2004
9 Anthony Leung - Windermere Secondary School, Vancouver, 24-28-Jan-2005
10 Ricky Quan - Windermere Secondary School, Vancouver, 20-25-Jun-2005
11 Dorothy Yeung - Windermere Secondary School, Vancouver, 23-27-Jan-2006
12 Sophia Guerrero - Windermere Secondary School, Vancouver, 19 – 30-Jun-2006
13 Alex Sutter- McMath Secondary School, Richmond, 26-30-Jun-2006
14 Yin Woo - Windermere Secondary School, Vancouver, 14-31-Dec-2007
15 Gail Ng - Windermere Secondary School, Vancouver, 26-30-Jan-2009
16 Fiona Leung - Windermere Secondary School, Vancouver, 25-29-Jan-2010
17 Leanne Huang - Windermere Secondary School, Vancouver, 21-Jun - 2-Jul-2010
18 Wilkin Chou - Windermere Secondary School, Vancouver, 21-Jun - 2-Jul-2010
19 Rebecca Hu – Templeton Secondary School, Vancouver, 24-25-Jun-2010
20 Angela Pinto – Windermere Secondary School, Vancouver, 22-Jun - 30-Jun-2011
21 Katie Piper – Windermere Secondary School, Vancouver, 22-Jun - 30-Jun-2011
22 Hailey Xi - Secondary School, Vancouver, 16-Dec-2022; July 16-31-2023

(l) Post-doctoral Fellows
1 Dr. Hong Zhang – 2000-2002
2 Dr. Y. J. Xu – 1998-1999
3 Dr. D. F. Liao – 1998 (3 months)
4 Dr. Ian Melhado – 1998 (6 months)
5 Dr. Sanjay Bhanot – 1995-1997
6 Dr. Baljinder Sahl – 1994-1998
7 Dr. Diana Lefebvre – 1994-1996
8 Dr. Brook Koide – 1993-1995
9 Dr. Yaw Loon Siow – 1992-1997
10 Dr. Jasbinder Sanghera – 1989-1995
11 Dr. Maleki Daya-Makin – 1989-1991

9. SCHOLARLY AND PROFESSIONAL ACTIVITIES

(a) Areas of special interest and accomplishments

Role of protein phosphorylation in cellular signal transduction.

1 My research focuses on the characterization of protein-serine kinases involved in mitogen- and stress-signalling and cell cycle control. Protein kinases are major intracellular transducers of information from extracellular stimuli. Their defective signalling, as a consequence of mutations in the genes that encode these enzymes, underlies many degenerative diseases of aging such as cancer, diabetes, immune cell dysfunction, heart disease and neurological disorders.

2 The main model systems that are under investigation in my laboratory are oocytes from sea stars and frogs, human solid tumours, insulin-target tissues such as skeletal muscle and heart from normal and diabetic rats, and human brain and spinal cord tissues from patients with neurological disorders. Many of the same protein kinases that are abnormally activated in cancer cells are stimulated in a controlled fashion during the meiotic maturation of oocytes or during activation of terminally differentiated immune cells of the blood, heart and brain.

3 As a postdoctoral fellow in the laboratory of Dr. Edwin Krebs, I was one of the co-discoverers of MAP kinase. Over the last 35 years, as a principal investigator, my research team and I have shown that MAP kinases such as Erk1 and Erk2 operate in the following mitogen-activated protein kinase cascade: Raf1-Mek-Erk1/2-Rsk1/2. My laboratory examined the role of this protein kinase cascade in platelets, T cells, B cells, macrophages, neutrophils, keratinocytes, cardiomyocytes, oligodendrocytes and neurons. These studies have been expanded for analysis of the related MAP kinase-dependent pathways that involve JNK and p38 MAP kinases.

4 Other protein kinases under scrutiny in my lab include cyclin-dependent kinases, p70 S6 kinase, protein kinase C, oncogene-encoded kinases (e.g. Pim1, Cot and PKB), and a novel protein-histidine kinase. Some of these kinases are activated by second messengers such as calcium, whereas others are regulated by small GTP-binding proteins such as Ras and Rac or via direct phosphorylation by upstream kinases. Anti-peptide antibodies developed in my laboratory have been produced for the specific detection of all of these kinases. Recombinant forms of mammalian versions of kinases are expressed in E. coli, COS cells and baculovirus-infected Sf9 cells. Site-directed mutagenesis is used to identify important regulatory phosphorylation sites in Erk1, Mek1, Mekk and Pim1. Synthetic peptide substrates are used to identify the critical amino acid residues that are required for kinase recognition. Specific roles for these kinases are being defined by identification of their target substrates and by establishing how the kinases are integrated into signaling networks.

5 Other technologies that are applied in my research program include antibody microarrays, multi-immunoblotting, protein sequencing, cDNA cloning, sequencing and site-directed mutagenesis, cell culture and microinjection, and immunocytochemical localization. We can now track over 600 protein kinases, phosphatases, stress, cell cycle and apoptosis proteins in addition to over 900 phosphorylation sites in many of these phosphoproteins. This technology has led to the spin-out of Kinexus Bioinformatics Corporation from my UBC lab. Kinexus produces the highest density commercial antibody microarrays in the world, which feature 2026 different antibodies printed in quadruplicate per slide.

6 Over the last 24 years, in collaboration with my company Kinexus, I have built a strong bioinformatics program to create databases and knowledgebases that are available online with free access for the scientific community. KiNET (http://www.kinet.ca) has the results from the analysis of over 10,000 multi-immunoblots performed in-house at Kinexus using the Kinetworks methodology that was development in my UBC lab. It is the largest repository of quantitative proteomics data on cell signalling proteins available. In 2010, we launched the PhosphoNET knowledgebase (www.phosphoNET.ca). It presently has detailed information on over 180,000 experimentally confirmed and 780,000 predicted human phosphorylation sites. PhosphoNET also provides evolutionary analysis and kinase prediction for all 967,000 phosphosites. In 2011, we launched the TranscriptoNET knowledgebase (www.transcriptonet.ca) with detailed mRNA expression data information on 21,000 genes in over 600 different human tissues, tumour types and cancer cell lines. We also released the KiNET-AM database (www.kinet-am.ca) which contains antibody microarray data on 650-800 proteins and phosphosites levels tracked in over 2000 cell and tissues lysates from diverse experimental model systems. In 2013, we launched the DrugKiNET knowledgebase (www.drugkinet.ca) with information on the sensitivities of over 400 protein kinases to more than 850 drugs and other kinase inhibitory compounds. In 2015, we produced beta-versions of the OncoNET knowledgebase (www.onconet.ca) with detailed information on over 3000 proteins related to cancer, and the KinaseNET knowledgebase (www.kinasenet.ca) with detailed information on 536 human protein kinases. Most of these knowledgebases were further updated in 2017 and 2018. In 2018, we also developed a website for drug-protein interactions with identification of the most critical amino acid residues in proteins for the binding of over 2000 approved and experimental drugs (www.drugpronet.ca). I am also working on online knowledgebases for protein phosphatases, adaptor proteins, stress protein and transcription factors. My ultimate goal is to create an atlas of cell signalling maps and the ability to track key proteins and phosphosites within these networks with protein microarrays. Towards this end, I have also been working on producing signalling maps online with Kinections Maps that detail experimentally verified interactions with protein kinases and KinATLAS (www.kinatlas.ca), which features customizable maps of kinase-drug, protein-protein interactions, and kinase-substrate interactions with KiNector (www.kinector.ca).

7 Ultimately, the research undertaken in my laboratory should help identify rational targets for the development of pharmacological agents for the treatment of cancer, neurological diseases, diabetes, autoimmune diseases, and other disorders that involve protein kinases. In addition, it is helping to identify biomarkers that may be useful for diagnosing diseases and defining the most appropriate therapeutic strategies to treat these diseases.

8 Since February of 2020, my lab has been extensively involved in the analysis of natural and COVID-19 vaccine induced immunity to the SARS-CoV-2 virus. This included leading a 4500-person clinical study to evaluate antibody levels against 10 of the SARS-CoV-2 proteins in blood, serum and saliva samples. This involved an extensive examination of hundreds of epitopes in SARS-CoV-2 proteins. My research also involved the development of rabbit polyclonal antibodies against at least 8 of the SARS-CoV-2 proteins, including several against the Spike protein. We also examined the role of the kinase GSK3-beta in the replication of the SARS-CoV-2 virus, and identified inhibitors of this kinase that blocked the reproduction of the virus in cultured cells. More recently, we have been optimizing a pentapeptide that binds to the SARS-CoV-2 NSP15 protein, which also has the potential to block the replication of the SARS-CoV-2 virus.

(b)+(c) Research or equivalent grants/contracts (indicate under COMP whether grants were obtained competitively (C) or non-competitively (NC))

Grants

Granting Agency	Subject	COMP	$ Per Year	Year	Principal Investigator	Co-Investigator(s)
Med. Res. Council of Canada	Role of Protein phosphorylation in viral action	C	54,000 -2 yr	1987-1989	Pelech	
B.C. Health Care Res. Foundation	Phosphatidylcholine turnover and protein phosphorylation in lymphokine action	C	12,000 -2 yr	1988-1990	Pelech	
B.C. Health Care Res. Foundation	TL-100 ultracentrifuge - Role of protein phosphorylation in cell cycle progression	C	17,000	1989	Pelech	
Med. Res. Council of Canada	Purification and characterization of cell cycle-regulated protein kinases	C	57,640 -2 yr	1989-1991	Pelech	
B.C. Health Care Res. Foundation	Role of protein phosphorylation in signal transduction by platelet agonists	C	22,000 -1 yr	1990		
B.C. Health Care Res. Foundation	Oocyte microinjection system & microscope	C	19,600	1990	Pelech	
B.C. Health Care Res. Foundation	Role of protein kinase C in signal transduction by platelet agonists	C	23,320 -1 yr	1991	Pelech	
Medical Research Council of Canada	Sorvall RC28S supraspeed centrifuge & F28/36 rotor	C	32,736	1991	Pelech	
B.C. Heart & Stroke Foundation	Protein kinase cascades in signal transduction by platelet agonists	C	60,000 -2 yr	1991-1993	Pelech	
Nat'l Cancer Inst. of Canada	Tyrosine-phosphorylated MBP/MAP-2 kinases in haemopoietic signal transduction	C	59,438 -3 yr	1991-1994	Pelech	
Nat'l Cancer Inst. of Canada	Characterization of oncogene-encoded protein-serine kinases	C	64,050 -3 yr	1991-1994	Pelech	

Med. Res. Council of Canada	Protein kinase cascades in cell cycle control	C	81,488 -3 yr	1991-1994	Pelech	
B.C. Health Care Res. Foundation	Elutriator Centrifuge	C	48,000	1992	Pelech	Berger, Weeks, Sadowski, Astell
B.C. Health Care Res. Foundation	HPLC system	C	29,000	1993	Pelech	
National Cancer Institute of Canada	HPLC system	C	29,000 (declined)	1993	Pelech	
B.C. Heart & Stroke Foundation	Role of protein kinase cascades in platelets	C	84,500 -2 yr	1993-1995	Pelech	
NRC of Canada IRAP	Protein kinase assay kit development	C	50,000	1994-1995	Pelech(Kinetek)	
Med. Res. Council of Canada	Protein kinase cascades in cell cycle control	C	84,748 -3 yr	1994-1997	Pelech	
Nat'l Cancer Inst. of Canada	MAP kinase pathways in haemopoietic signal transduction	C	77,825 -4 yr	1994-1998	Pelech	
Nat'l Cancer Inst. of Canada	Characterization of oncogene-encoded protein-serine kinases	C	99,063 -4 yr	1994-1998	Pelech	
B.C. Heart & Stroke Foundation	Role of protein kinase cascades in platelets	C	10,000 -1 yr	1995-1996	Pelech	
B.C. Science Council	Assay for activated Ras-related G proteins	C	50,000	1995-1996	Pelech (Kinetek)	Kalmar (Simon Fraser Univ.)
B.C. Heart & Stroke Foundation	Activation of protein kinases in heart	C	82,000 -3 yr	1996-1999	Katz	Pelech
Kinetek Pharmaceuticals, Inc.	Histidine kinase and tumour-activated protein kinases	NC	65,000 - 3 yr	1996 - 1999	Pelech	

Med. Res. Council of Canada	Characterization of insulin-inhibited serine kinases	C	82,000 -1 yr	1997-1998	Pelech	McNeill
Nat'l Cancer Inst. of Canada	MAP kinase pathways in seastar oocyte cell cycle control	C	10,000	1998-1999	Pelech	
Nat'l Cancer Inst. of Canada	Structure-function analysis of protein-serine kinase complexes	C	37,500	1998-1999	Pelech	
BC Heart & Stroke Foundation	Regulation of cardiomyocyte differentiation by protein kinases	C	58,450 - 2 yr	1999 - 2001	Pelech	
JDF/MRC NCE	Cell signalling in NOD mice	C	5,000 - 3 yr	1999 - 2001	Delovich Ochi et al.	Pelech
Nat'l Cancer Inst. of Canada	Identification of putative breast cancer-linked protein kinases	C	49,000 - 1 yr	1999 - 2001	Pelech	
BC Heart & Stroke Foundation	MAP kinase pathways in normal and disease heart	C	92,970 - 3 yr	1999 - 2002	Pelech	Katz
Can. Inst. Health Res.	MAP kinase pathways in seastar oocycte cell cycle control	C	82,000 - 3 year	2000-2003	Pelech	
National Research Council of Canada IRAP	Development of Relational Functional Proteomics Databases	C	48,000 - 9 months	2004-2005	Pelech	Kinexus Bioinformatics Corporation
National Research Council of Canada IRAP	Development of Protein Kinase-Based Arrays for Diagnostics and Drug Discovery	C	80,000 - 2 year	2004-2006	Pelech	Kinexus Bioinformatics Corporation
Can. Inst. Health Res.	Protein kinase pathways in seastar oocyte cell cycle control	C	107,000 - 5 year	2005-2007	Pelech	
Can. Foundation for Innovation	Brain Research Centre: A Platform for Basic and Translational Neuroscience.	C	$6.8 million	2007	Cynader	Pelech + 10 other co-investigators. I wrote approximately 30% of this successful

National Research Council of Canada IRAP	Building the On-line SigNET KnowledgeBank	C	50,000 – 1 year	2009-2010	Pelech	Kinexus Bioinformatics Corporation
Nati. Sci. & Eng. Res. Council of Canada	Mapping the human kineome and phosphoproteome	C	80,000 – 2 years	2009-2011	Stacho + Pelech	Simon Fraser Univ. + Kinexus Bioinformatics Corporation. I wrote 95% of this successful grant
National Research Council of Canada IRAP	Production of Epitope-mapped Phosphosite Antibodies	C	38,000 – 1 year	2011-2011	Pelech	Kinexus Bioinformatics Corporation
National Research Council of Canada IRAP	Development of Protein Kinase/Phosphatase Substrate Microarrays	C	178,000 – 2 years	2012-2014	Pelech	Kinexus Bioinformatics Corporation
National Research Council of Canada IRAP	Development of Protein Kinase/Phosphatase Assays (Salary support for Iqbal Sarai)	C	20,000 – 9 months	2020	Pelech	Kinexus Bioinformatics Corporation
Neurodegenerative Disease Research (NDR), Inc.	Development of Phosphosite Antibodies for ALS Target Proteins	C	US$140,000	2021	Pelech	Kinexus Bioinformatics Corporation
COVID-19 Immunity Task Force	Immmunogenicity of current SARS-CoV-2 vaccine schedules in BC and Ontario	C	$729,149	2021	Pascal Lavoie	Pelech
Neurodegenerative Disease Research (NDR), Inc.	Development of Phosphosite Antibodies for ALS Target Proteins (Salary support for Ghada Maged)	C	US$15,000	2022	Pelech	Kinexus Bioinformatics Corporation

(d) Invited Presentations

103 Local in B.C.; 37 in Canada outside B.C.; 66 in U.S.A.; 32 Internationally, outside of Canada and USA

1. July 1987 - Biochemistry Department, Univ. of B.C.
2. December 1988 - Biochemistry & Molecular Biology, Univ. of Manitoba, Winnipeg, Manitoba.
3. 14 December 1989 - Dept. of Obstetrics & Gynaecology, Univ. of B.C., Grace Hospital Site. Regulation of meiotic maturation and egg mitosis by protein phosphorylation.
4. 6 February 1989 - Vancouver Council of Woman, Unitarian Church, Vancouver. Present and future of human embryo and fetal research.
5. 12 March 1990 - Dept. of Paediatrics, Univ. of B.C., Shaughnessy Hospital Site.
   Protein phosphorylation in cell cycle control.
6. 21 March 1990 - Pharmacology Department, Univ. of B.C. Cell cycle-regulated protein kinase cascades.
7. July 1990 - Ludwig Cancer Institute, London, U.K.
8. July 1990 - Imperial Cancer Research Fund, London, U.K. Regulation of protein kinase C in haemopoietic cells.
9. July 1990 - Wellcome Biotech., Beckenham, U.K.
10. February 1991 - Biotechnology Building, Cornell University, Itheca, NY, USA. p44mpk - a paradigm for a family of mitogen-regulated, tyrosine-phosphorylated protein-serine kinases implicated in cell cycle control.
11. 4 October 1991 - Inst. Molecular Biol. & Biochem., Simon Fraser Univ., Burnaby. MAP kinases, a family of tyrosyl-phosphorylated and activated protein-seryl kinases.
12. 8 October 1991 - Dept. of Ophthalmology, Univ. of B.C., Eye Care Centre, V.G.H. MAP kinases, a family of tyrosine-phosphorylated & activated protein-serine kinases.
13. 7 November 1991 - Manitoba Inst. of Cell Biology, Univ. of Manitoba, Winnipeg, Manitoba.
14. 6 December 1991 - Dept. of Biochemistry, Queens University, Kingston, Ontario. MAP kinases, a family of tyrosyl-phosphorylated and activated protein-seryl kinases.
15. 15 January 1992 - Department of Physiology, Univ. of B.C. MAP kinases, God's gift to the Pelech lab.
16. 28 February 1992 - Dept. of Microbiology, University of Virginia, Charlottesville, VA, USA. Charting regulatory pathways with MAP kinase.
17. 11 March 1992 - Department of Microbiology, Univ. of B.C.
18. 9 April 1992 - Department of Anatomy & Cell Biology, University of Kansas, Kansas, USA.
19. 8 May 1992 - Department of Biochemistry, University of Calgary, Calgary, AB. Charting regulatory pathways with MAP kinase.
20. 17 September 1992 - Div. Endocrinology, Dept. Medicine, Univ. of B.C. Charting regulatory pathways with MAP kinase.
21. 11 July 1992 - D. Vance Honourary Symposium, Univ. of B.C.
22. 25 October 1992 – Keystone A.S.B.M.B. Symposium, Keystone, CO, USA Chairperson
23. 14 November 1992 - Frontiers in Science, Shrum Science Centre, Simon Fraser Univ., Burnaby. The power and promise of biomedical research.

24. 3 March 1993 - Dept. of Biochemistry, University of Alberta, Edmonton, AB
25. 26 October 1993 - Department of Medicine, Univ. of B.C. Abnormal insulin regulation of protein kinases during diabetes.
26. 28 October 1993 - Pharmaceutical Sciences, Univ. of B.C. Insulin-activated protein kinase cascades - A paradigm for mitogenic signalling.
27. 4 November 1993 - Department of Obstetrics & Gynaecology, Univ. of B.C. Networking with MAP kinases.
28. 8 December 1993 - Department of Biochemistry, McGill Univ., Montreal, QC. Charting regulatory pathways with MAP kinases.
29. 18 June 1993 - C.F.B.S. Meeting, Windsor, ON. Merck Frosst Canada Prize Award Lecture for C.S.B.M.B.
30. 21 June 1993 - Hotel Dieu Hospital, Montreal, QC. Regulation of insulin-activated protein kinases in diabetic rats.
31. 22 June 1993 - N.R.C. Biotechnology Research Institute, Montreal, QC. Networking with protein kinases.
32. 22 September 1993 - European Cell Cycle Conference, La Rochelle, France.
33. 1 October 1993 - Biological Regulatory Mechanisms, Rossiter Conference, Barrie, ON. Cell cycle-regulation of serine/threonine kinases
34. 18 April 1994 - Dept. Anatomy & Cell Biology, University of Toronto, Toronto, ON. At the cross-roads of diverse signal transduction pathways.
35. April 1994 - Department of Biochemistry, University of Minnosota, St. Paul, MN, USA. Networking with protein kinases.
36. November 1994 - N.R.C. Workshop-Biotechnology Research Institute, Montreal, QC. Signal transduction: Advances and applications.
37. 21 May 1994 - Schmitt Symposium: The Cytoskeleton in Alzheimer's Disease, Univ. of Rochester, Rochester, NY. Phosphorylation cascades.
38. 14 June 1994 - Dupont Symposium on Biological Signals, C.F.B.S. Meeting, Montreal, QC. Mitogen-activated protein kinases: at the cross-roads of diverse signal transduction pathways.
39. 21 June 1994 - XIIth Annual Workshop on Membrane Transport, University of Montreal, Montreal, QC. Protein kinase and phosphatase networks in cell signaling.
40. 21 July 1994 - XVI Annual Meeting Internatl. Society Heart Research Symposium, London, ON. Regulation of protein kinase circuitry by growth factors.
41. November 1994 - Onyx Pharmaceuticals, Richmond, CA. U.S.A. MEK'ing connections in MAP kinase-dependent signalling pathways.
42. 28 March 1995 - Dept. of Pathology, Univ. of B.C., St. Paul's Hospital. MAP kinase networks in cell proliferation and stress.
43. 16 May 1995 - Dept. of Pharmacology, Vanderbilt University, Nashville, TN, USA. Mitogenic and stress-activated protein kinase modules in cellular signalling.
44. 29 June 1995 - Internatl. Soc. Neurochemistry Workshop, Nagoya Japan.
45. 18 July 1995 - Cornell University, Ithaca, NY, USA.
46. 28 August 1995 - Virological and Immunological Mechanisms, Functional Outcomes and Possibilities for Therapy in Enteroviral Heart Disease: An International Workshop, St. Paul's

Hospital, Vancouver, Moderator, Ventricular function, myocyte biology, therapeutics.

47. 26 January 1995 - Pacific NorthWest Biotechnology Exposition, Westin Hotel, Vancouver.
48. 27 January 1995 - Aquatech'95 Conference, Westin Hotel, Vancouver.
49. 9 May 1995- John P. Robarts Research Institute, London, ON. MAP kinase pathways in hemopoietic cell activation.
50. 15 February 1995 - Merck Frosst - Growth Factor Meeting, Hyatt Regency, Vancouver.
51. 11 May 1995 - Weis Centre for Research, Geisinger Clinic, Dansville, PE, USA. Regulation of mitogenic and stress-activated protein kinases.
52. 19 May 1995 - ICOS Inc., Bothell, WA, USA.
53. 20 July 1995 - W. Alton Jones Science Centre, Lake Placid, NY, USA. Protein kinase circuitry in mitogenic and stress signalling.
54. 6 December 1995 - Upstate Biotechnology Inc., Lake Placid, NY, USA.
55. 3 May 1996 - Dept. of Surgery, Univ. of B.C., Jack Bell Research Centre. Malfunctions in cell signaling systems - the molecular basis of chronic diseases.
56. 9 May 1996 - Dept. of Pathology, Univ. of B.C., Eye Care Centre. Protein kinases and disease.
57. 22 January 1996 - Pierce Chemicals, Rockford, IL, USA.
58. 21 February 1996 - Hospital for Sick Children, Toronto, ON.
59. 4 March 1996 - Biochemistry, Pharmacology & Physiol. Club of Univ. of B.C.- Keynote Speaker. Your future in the basic medical sciences-bridging academia, government & industry.
60. 23 March 1996 - Fisher Winternational Conference, Banff, AB.
61. 26 March 1996 - Vancouver Enterprise Forum, Science World, Vancouver. Coaching the captain: the mentoring process.
62. October 1996 - Signal Transduction Conference, Lake Tahoe, Nevada, USA. Insulin signaling through protein kinase cascades.
63. October 1996 - Insulin Signaling & Diabetes, Washington, D.C. , USA Vanadium compounds for treatment of diabetes in rats.
64. November 1996 - Biochem. Pharma, Laval, QC. Insulin signal transduction through protein kinases.
65. November 1996 - Life Sciences Venture Forum, Toronto, ON. Kinetek Pharmaceuticals Inc.
66. 20 December 1996 - Biochemistry, Pharmacology & Physiol. Club of U.B.C.- Vancouver Keynote Speaker - Careers in Biotechnology.
67. 7 November 1997 - Dept. of Medicine, Univ. of B.C., St. Paul’s Diabetes Centre. Insulin signalling and organovanandium compounds.
68. 23 July 1997 -1997 International Society for Heart Research International Conference, Vancouver. Protein kinase workshop.
69. 22 September 1997 - IBC Signal Transduction Therapy, San Diego, CA, USA. Insulin signalling and vanadium compounds for treatment of diabetes in rats.
70. 23 June 1997 - University of Calgary, Dept. of Pharmacology, Calgary, AB. Insulin signalling through kinase cascades.
71. 18 December 1997 - Dept. of Medicine, University of B.C., St. Paul's Diabetes Centre. Insulin signalling and organovandandium compounds.

72. 29 November 1997 - Brain and Spinal Cord Research Centre Symposium. UBC, Vancouver. Signal transduction research.
73. 6 June 1998 - Bridging the Straight of Georgia Cancer Conference, Cowichan Bay, BC. Protein kinases for cancer diagnosis and therapeutic targets for chemotherapy.
74. 11 June 1998 - Dept. of Pharmacology, University of Virginia, Charlottesville, Virginia, USA. MAP kinases in sea star oocyte cell cycle control.
75. 5 March 1998 - Biochemistry, Pharmacology & Physiol. Club of University of BC, Vancouver. Keynote speaker - Career opportunities in the biotechnology industry.
76. 7 May 1998 - Association of University Anaethesists Annual General Meeting, San Francisco, CA, USA. Pursuit of scientific excellence in industry.
77. 11 March 1999 - Dept. of Physiology, Univ. of B.C. Introduction to protein kinases.
78. 8 April 1999 - Dept. of Pharmacology, Univ. of B.C. Introduction to protein kinases.
79. 25 June 1999 - American Society for Microbiology Conference, Vancouver. Analysis of protein kinase networks.
80. 24 August 1999 - Pacific Institute for the Mathematical Sciences Symposium, Univ. of B.C. Mathematical analysis of protein kinase networks.
81. 14 October 1999 - Simon Fraser University - Harbour Centre, Vancouver. Canadian Brain drain to United States.
82. 3 February 2000 - Dept. of Pharmacology, University of South Alabama, Mobile, Alabama, USA. MAP kinases in cardiovascular disease.
83. 21 February 2000 - UBC Signal Transduction Network, Univ. of B.C. Mapping kineomes - protein kinase network analysis.
84. 28 April 2000 - Dept. of Biochemistry, University of Alberta, Edmonton, AB. p38 MAP kinase pathways.
85. 6 October 2000 - Montreal Heart Institute, Montreal, QC. Analysis of protein kinase networks in muscle models.
86. 14 March 2000 - BC Biotechnology Alliance, Hyatt Regency, Vancouver. Genomics, proteomics and bioinformatics.
87. 8 June 2000 - Canadian Society Pharmaceutical Sciences, Crowne Plaza Hotel, Vancouver. Spinning out companies from university research.
88. 21 August 2000 - Univ. of B.C. Dept. of Medicine Jubilee CME, Galaxy Cruise, Alaska. What you need to know about molecular biology.
89. 30 September 2000 - Foresight Capital Corporation, Delta Resort, Whistler, BC. Human genome project benefits for disease diagnosis and treatment.
90. 13 November 2000 - Pacific Rim biotechnology Conference, Hotel Vancouver, Vancouver. The Midas Touch.
91. 30 November 2000 - Eldercollege/Capilano College, North Vancouver. How to invest in biotechnology with dollars and sense.
92. 30 November 2000 - Biofuture Fund conference, Vancouver. Human genome and personalized medicine.
93. 25 January 2001 - PENCE Group, University of Toronto, Toronto, ON. Proteomic analysis of signal transduction pathways.

94. 24 April 2001 - Vancouver Enterprise Forum - Proteomics, bioinformatics and personalized medicine.
95. 26 April 2001 - Aventis Biotechnology Fair - BCIT, Burnaby - Genomics, proteomics and bioinformatics.
96. 27 April 2001 - UBC Department of Pharmacology and Therapeutics - Proteomics analyses of protein kinase networks.
97. 28 May 2001 - UBC Department of Biochemistry and Molecular Biology. MAP kinase networks in cell signaling.
98. 11 June 2001 - University of Calgary, Calgary, AB. Kinetworks mapping of cell signaling pathways.
99. 28 June 2001 - BC Canacer Agency - Advanced Therapeutics Group. Analysis of protein kinase networks.
100. 4 October 2001 - UBC Faulty of Medicine Distinguished Lecture. MAP kinase signalling pathways in human cancer.
101. 3 July 2001 Institute of Molecular and Cell Biology, National University of Singapore - Proteomic analyses of cell signalling networks: Mapping protein kinase networks.
102. 27 February 2002 - Children's Hospital Eastern Ontario, Univ. of Ottawa, Ottawa, ON. Kinetworks proteomics analyses: Mapping protein kinase networks in neural disorders.
103. 5 March 2002 - Scripps Institute, San Diego, CA, USA. Kineome analysis: Mapping cell signalling networks.
104. 6 March 2002 - International Business Communications - Protein Kinase Drug Discovery Conference, San Diego, CA, USA. Kineome analysis: Mapping protein kinase networks.
105. 21 March 2002 - Cambridge Health Institute- Protein to Profits Conference, Munich, Germany. Kinetworks analysis: Mapping cell signalling networks.
106. 4 April 2002 - First Forward Network/BC Biotech, Vancouver Terminal City Club. Bioinformatics for Biotech Executives - Keynote talk - A history of Bioinformatics: The past and beyond.
107. 12 April 2002 - The Prostate Centre at Vancouver General Hospital Seminar. Mapping cell signalling systems by Kinetworks analysis.
108. 26 April 2002 -BC Institute of Technology, Aventis Student Biotech Challenge Talk. Biotechnology in your future.
109. 3 June 2002 - 85th Meeting of the Canadian Chemical Society, Vancouver. Drug profiling by Kinetworks analysis.
110. 9 September 2002 - IBC 2nd Annual Protein Kinase Conference, Boston, MA, USA Mapping protein kinase pathways by Kinetworks.
111. 19 September 2002 - The First Pacific North-West Cell Signalling Conference, Vancouver. Charting protein kinase pathways involved in mitotic checkpoint control.
112. 20 September 2002 - The 4th Annual Pacific Northwest Venture Forum- Monte Jade, Vancouver. Kinexus Bioinformatics.
113. 9 October 2002 - Laval University, Quebec City, QC. Mapping protein kinase networks.
114. 21 November 2002 - BioFuture 2002 Conference and Exhibition, Vancouver. Stress Molecules - Listening to cells to silence disease.
115. 29 November 2002 - University of Calgary, Calgary, AB. Promise of proteomics in the post-genomic era.

116. 29 November 2002 - University of Calgary, Calgary, AB. Challenge to the entrepreneur scientist in the pursuit of academic excellence and success in the biotechnology industry.
117. 3 March 2003 - Strategic Health Institute's Protein Kinase Meeting, San Diego, CA, USA. Kinetworks analysis: Elucidating the cell specific architecture of protein kinase networks.
118. 6 March 2003 - Bioinformatics Training Initiative - BC Institute of Technology. Drug discovery in the post-genomics era: The Bioinformatics challenge and opportunity.
119. 10 March 2003 - Invest NorthWest Conference, Seattle, WA, USA. Drug target discovery by Kinetworks analysis.
120. 19 March 2003 - Cambridge Health Institutes, Molecular Market Place Meeting, Santa Clara, CA, USA. Tracking protein kinase pathways for identification and validation of drug targets.
121. 21 March 2003 - Cambridge Health Institute's TriGenome Conference - Santa Clara, CA, USA. Kinetworks analysis: Elucidating the cell-specific architecture of protein kinase networks.
122. 29 March 2003 - BC Pharmacy Assoc. Continuing Education Association - Richmond, BC. The promise of proteomics in the post-genomics era of personalized medicine.
123. 4 April 2003 - Eric Hamber Secondary School, Vancouver, BC. Careers in biotechnology.
124. 25 April 2003 - British Columbia Institute of Technology - Burnaby, BC. Genomics and proteomics and the future of medicine.
125. 29 April 2003 - Pt. Grey Secondary School, Vancouver BC. Careers in biotechnology.
126. 29 May 2003 - International Council of Electrophoresis Society on Proteomics: Present perspectives and future challenges. Glasgow, Scotland. Mapping protein kinase pathways in mitotic checkpoint control by Kinetworks.
127. 16 June 2003 - University of California San Francisco Cancer Centre, San Francisco, CA, USA. Proteomics analysis of cancer.
128. 15 September 2003 - Parkinson's Disease Conference. Painter's Lodge, BC. Proteomics analysis of neurodegenerstive diseases.
129. 8 October 2003 - Human Proteome Organization Meeting. Montreal, QC. Tracking protein kinase signalling on macroarrays with antibodies and peptide antibody mimetics (PAM's).
130. 20 October 2003 - Strategic Health Institute - Protein Kinase Meeting – Philadelphia, PA, USA. Mapping protein kinase signalling oathways by Kinetworks analysis.
131. 23 October 2003 - IIR Life Science Conference - 2nd Annual Protein Kinase Meeting - Amsterdam, Holland. Monitoring protein kinase networks with arrays of antibodies and peptide antibody mimetics (PAM's).
132. 10-17 Jan 2004 - Cambridge Health Institute - PEPTalk Meeting, San Diego, CA, USA. Tracking protein kinases and protein phosphorylation on macroarrays with antibodies and paptide antibody mimetics (PAM's).
133. 2+3 March 2004 - GenomeCanada presentation in Toronto, ON.
134. 8 March 2004 - Univ. of British Columbia, Robson Square, Public Address for Research Awareness Week. Dr. Professor/Mr. President - The curse of the entrepreneur scientist.
135. 9 June 2004 - Cambridge Health Institute - Protein Kinase targets - Strategies for Drug Development. Boston, MA, USA. Tracking the kinome by multiblotting with antibodies and peptide antibody mimetics (PAM's).
136. 19-23 September 2004 - International Business Communications - CHIPS to Hits, Boston MA,

USA. Kineome analysis: Mapping protein kinase networks.

137. 22-23 Jan. 2005 - Ramandhai Foundation 2nd International Symposium “Current Trends in Pharmaceutical Sciences: Role of Genomics and Proteomics. Ahmedabad, India. (Had to cancel 2 days before departure due to illness)

138. 28 Feb. 2005 - Strategic Research Institute – 3rd Annual Protein Phosphorylation Drug Discovery World Summit, San Diego, CA, USA. Tracking the kineome and phosphoproteome in arrays with antibodies and peptide antibody mimetics (PAM’s).

139. 14 May 2005 - B.C. Pharmacy Association Annual Meeting, Vancouver. The promise of pharmacoproteomics for disease diagnosis and drug discovery.

140. 20 March 2005 - World Congress on Microarray Technology, Vancouver. Tracking the kineome and phosphoproteome in arrays with antibodies and peptide antibody mimetics (PAM’s).

141. 13 September 2005 - International Consortium on Anti-Virals Symposium and Workshop, Trent University, Peterborough, ON. Mapping cell signaling pathways.

142. 28 September 2005 - National Research Council of Canada Genomics and Health Initiative Annual General Meeting. Ottawa, ON. Commercialization of technology.

143. 9 January 2006 - Cambridge Healthtech Institute PepTalk Conference. Coronado, CA. Mapping the phosphoproteome by Kinex™ antibody arrays.

144. 24 March 2006 - World Congress on Microarray Technology, Vancouver. Tracking cell signalling protein expression and phosphorylation by antibody microarrays.

145. 8 May 2006 - GTCbio Protein Kinases in Drug Discovery Conference. Boston, MA, USA. Tracking the regulation of protein kinases and phosphorylation by quantitative antibody microarrays and multi-immunoblotting.

146. 3 July 2006 - IIR's 5th Annual Protein Kinases Congress. Zurich, Switzerland. Kinase pathway analysis for target identification. Chair.

147. 26 September 2006 - NRC-Biotechnology Research Institute, Montreal, QC. Meta-analyses of the human kineome and phosphoproteome.

148. 2 December 2006 - GTCBio Drug Discovery Meeting. Philadelphia, PA. Antibody multi-immunoblotting and microarray analysis for CNS biomarker discovery in Alzheimer, Parkinson and ALS disease.

149. 22 February 2007 - UBC Department of Medicine, Division of Neurology Grand Rounds. Vancouver. Phosphoproteomics and neurodegenerative diseases of the CNS.

150. 8 March 2007 - SSP,.PSC.CSCO.WPS Joint meeting. Banff, AB. Mapping cell signalling networks with multi-immunoblotting and antibody microarrays.

151. 22+24 May 2007 - Workshop Course - Informa 6th Annual Protein Kinases Congress – Biomarker profiling for kinase target evaluation– Principal Instructor and Coordinator. Lisbon, Portugal

152. 18 June 2007 – Frontiers in Bioinformatics Workshop – University of British Columbia, Vancouver. Mapping the human phosphoproteome.

153. 30 June 2007 - Workshop Course - World Congress on Microarray Technology, Vancouver. Tracking cell signalling protein expression and phosphorylation by antibody microarrays.

154. 29 August 2007 – Seminar Presentation - University of Bath, Bath, UK. Tracking the human phosphoproteome.

155. 30 August 2007 – Seminar Presentation - University of Liverpoole, Liverpoole, UK. Tracking the human phosphoproteome.

156. 3 September 2007 - Workshop Course - Discovery – Select European Biomarkers Summit and Proteomics Europe Conference. Principal Instructor and Coordinator. Amsterdam, Holland. Mining the kineome and phosphoproteome with protein microarrays for biomarker and drug target.

157. 28 October 2007 - Seminar Presentation - Joint meeting of 3rd Czech Proteomic conference and 1st Central and Eastern European Proteomic Conference. Olomouc, Czech Republic. Protein microarrays and phosphoproteomics.

158. 6 December 2007 – Seminar Presentation – Lousiana State University Health Sciences Center – Shreveport, LO, USA – Proteomics methodologies.

159. 6 December 2007 – Seminar Presentation – Lousiana State University Health Sciences Center – Shreveport, LO, USA – The human kineome and phosphoproteome.

160. 9 February 2008 – Visiongain Protein Kinase Conference – London, UK (This meeting was cancelled 4 weeks before, but I was invited as a speaker and chairperson)

161. March 11, 2008 – Max Planck Institute– Berlin, Germany. The human kineome and phosphoproteome.

162. March 12, 2008 - Informa 7th Protein Kinase Congress – Berlin, Germany. Antibody-based phosphoproteomics for biomarker and drug target identification. (Speaker and panelist)

163. March 27, 2008 - Canadian-Dutch Dementia Colloquium, University of British Columbia, Vancouver. Proteomic approaches for the diagnosis of Alzheimer's disease: What is the rationale and what are the prospects?

164. April 17, 2008 – Department of Biochemistry, Vanderbilt University, Nashville, TN, USA. The human kineome and phosphoproteome.

165. July 4-17, 2008 – In collaboration with the Japanese company Cosmo-Bio, I gave 90 to 120 minute scientific presentations to the following 13 companies. The number of scientists at these presentations ranged from about 6 to 40. The talk was entitled: Tracking the human kineome and phosphoproteome.

    Daiichi-Sankyo Pharma (Tokyo)

    Ono Pharma (Tsukuba)

    Ono Pharma (Osaka)

    Astella Pharma (Tsukuba)

    Banyu Pharma (Merck) (Tsukuba)

    Takeda Pharma (Tsukuba)

    Takeda Pharma (Osaka)

    Tanabe-Mitsubishi (Saitama)

    Japan Tobacco (Osaka)

    Dainippon-Sumitomo Pharma (Osaka)

    Santen Pharma (Nara)

    Shionogi Pharma (Osaka)

    Nippon Shinyaku (Kyoto)

167. September 8-10 - Informa Drug Discovery Summer School in Cambridge, UK with Dr. Pelech as an invited speaker and chairperson. (This workshop was cancelled 6 weeks before it was to have transpired).

168. September 24, 2008 - IBC ACT 2008: Protein Kinase Target Conference, San Diego, CA. Mapping the human phosphoproteome. (Speaker, panelist and chair)
169. October 23, 2008 – Omeros Pharmaceuticals, Inc., Seattle, WA, USA. Kinase Inhibitors in the Clinic. Tracking the human kinome and phosphoproteome.
170. February 3, 2009 – University of Washington, Seattle, WA, USA. Breakfast Club Seminar. Tracking the kineome and phosphoproteome.
171. March 3, 2009 – Informa 8th Annual Protein Kinase Congress. Barcelona, Spain. Validation of protein kinase drug targets and drug leads with microarray approaches. (Speaker, panelist and chair)
172. May 8, 2009 – Prostate Centre Grand Round at VGH. Vancouver, BC. Mapping the human kineome and phosphoproteome by protein microarray and bioinformatics analyses.
173. August 6, 2009 – Select Biosciences Microarray World Congress. South San Francisco, CA, USA. Antibody microarrays for biomarker discovery and kinase microarrays for drug screening.
174. December 10, 2009 – Bristol Meyer Squibb. Princeton, NJ, USA. Kinase Inhibitors in the Clinic. Phosphoprotein biomarker and kinase drug target discovery with protein microarrays.
175. February 1, 2010 – University of British Columbia, Coop Program Networking Workshop. Vancouver, B.C.
176. June 21-23, 2010 - Cambridge Healthtech "Next–gen kinase inhibitors: Oncology and Beyond" Meeting. Cambridge, MA, USA. Mapping protein kinase networks and drug interactions with protein microarrays and predictive bioinformatics. (Speaker, panelist and chair)
177. March 24, 2010 – University of British Columbia, Department of Biochemistry Career Workshop. Vancouver, B.C.
178. September 10, 2010 – Global Biomarker Conference & Workshop. Vancouver, B.C. Mapping the human kineome and phosphoproteome with predictive bioinformatics and protein microarrays.
179. September 26 to 30, 2010 - International Society of Hypertension 23rd Scientific Meeting (ISH 2010). Vancouver, B.C. Mapping protein kinase networks for diagnostics and therapeutics development.
180. October 29, 2010 – Select Biosciences – Microarray World Congress, La Jolla, CA, USA. Protein and peptide microarrays for tracking human protein kineome regulation.
181. February 27, 2011 – Student Biotechnology Network. University of Victoria, Victoria, BC. Mapping and tracking the human kineome and proteome.
182. June 9, 2011 – Experimental Medicine Research Day Keynote Talk. University of British Columbia. Vancouver, BC. Confronting the uncertain future of biomedical research and the biotechnology industry in this decade.
183. September 30, 2011 – Select Biosciences – Microarray World Congress. South San Francisco, CA, USA. Protein kinase and phosphosite biomarker discovery and validation with protein microarrays with antibodies, lysates, protein kinases and substrate peptides.
184. February 10, 2012 – Bristol-Meyer-Squibb, Wallingford, CT, USA. Signalling network analyses and biomarker discovery and validation with protein and peptide microarrays.
185. March 7, 2012 – Department of Biochemistry Career Workshop. University of British Columbia. Vancouver, B.C.
186. July 10, 2012 - Merck Molecular Biomarkers: Translational Research Deep Dive Conference. Long Branch, NJ, USA. Tracking the human Kineome, Phosphatome and Phosphoproteome for

biomarkers with antibody-based array technologies.

187. July 11, 2012 – Johnson & Johnson Pharmaceuticals. Springfield, PA, USA. Tracking the human Kineome, Phosphatome and Phosphoproteome for biomarkers with antibody-based array technologies.

188. July 12, 2012 - Bristol Myer-Squibb. Princeton, NJ, USA. Tracking the human Kineome, Phosphatome and Phosphoproteome for biomarkers with antibody-based array technologies.

189. July 13, 2012 – Novartis Institute for Biomedical Research Inc., Cambridge, MA, USA. Tracking the human Kineome, Phosphatome and Phosphoproteome for biomarkers with antibody-based array technologies.

190. October 2, 2012 – Purdue University, Department of Biochemistry. West Lafayette, IN, USA. Mapping the human Kineome, Phosphatome and Proteome with cell lysate, antibody and peptide microarrays.

191. March 8, 2013 – University of Missouri, Biochemistry Department. Columbia, MO, USA. Hierarchical molecular, cellular and social intelligence systems in the evolution of life.

192. July 17, 2013 – OMICS Group 3rd International Conference on Proteomics and Bioinformatics. Philadelphia, PA, USA. SigNET KnowledgeBank Workshop.

193. May 29, 2014 – BioConference Live Clinical Diagnostics & Research. On-line, CA, USA. Navigating the complexities of the human oncoproteome with the SigNET KnowledgeBank.

194. August 5, 2014 – OMICS Group 4th International Conference on Proteomics and Bioinformatics. Northbrook (Chicago), IL, USA. Phosphoproteomics and the origin and operations of the kineome. (also session chair)

195. August 6, 2014 – OMICS Group 4th International Conference on Proteomics and Bioinformatics. Northbrook (Chicago), IL, USA. Oncoproteomics for uncovering cancer biomarkers and therapeutics targets. (1 hour workshop)

196. September 10, 2014 – Biochemistry, Biology and Pathology of MAP Kinase II Conference. Vilnius, Lithuania. Navigating human phosphorylation networks with SigNET suite of on-line knowledge bases.

197. September 11, 2014 – Biochemistry, Biology and Pathology of MAP Kinase II Conference. Vilnius, Lithuania. Regulatory roles of conserved phosphorylation sites in the activation T-loop of the MAP kinase ERK1.

198. May 6, 2015 – Division of Neurology, University of British Columbia. Vancouver, BC. The protein kineome: Tracking and manipulating the predominant molecular intelligence system of cells with proteomics and bioinformatics.

199. September 29, 2015 – Human Proteome Organization (HUPO) Conference. Vancouver, BC. Profiling protein expression, modifications and interactions with antibody microarrays.

200. March 14, 2016 – Cure Huntington's Disease Initiative (CHDI) Foundation. Los Angeles, CA, USA. Overview of the Kinexus integrated proteomics and bioinformatics services platform.

201. March 29, 2016 – OMICS Group World Proteomics 6th Meeting. Atlanta, GE, USA. Two oral presentations: The SigNET KnowledgeBank - A series of on-line, open-access proteomics websites for biomarker identification and drug development; Tracking protein expression, modifications and interactions with antibody microarrays. (I also chaired two oral sessions)

202. July 18, 2016 – International Union of Molecular Biology and Biochemistry Meeting. Vancouver, BC. Positive and negative control of protein-serine/threonine kinases by phosphorylation in the catalytic domain T-loop. (I also chaired two oral sessions)

203. February 6, 2017 – Samsung Medical Center. Seoul, Korea. Tracking protein biomarkers in human lung tumour biopsies.

204. February 9, 2017 – 13th Korea Genome Organization (KOGO) Winter Symposium. Vivaldi Park, Korea. Tracking protein expression, modifications and interactions with antibody microarrays.

205. July 24th, 2017 – COSMO Bio. Toyko, Japan. Tracking protein expression, post-translational modifications and interactions with antibody microarrays.

206. July 26th, 2017 – Ono Pharmaceutical. Kyoto, Japan. Tracking protein expression, post-translationa modifications and interactions with antibody microarrays.

207. July 27th and 28th, 2017 – JPrOS 15th JHUPO Conference. Osaka, Japan. Two oral presentations: Tracking protein expression, post-translational modifications and interactions with antibody microarrays; Structure-function analyses of the catalytic domains of eukaryotic protein kinases.

208. August 30, 2017 – Bridging Discovery Research with Therapeutics Conference. Banff, Alberta. Investigations of the multi-site phosphorylation of CTP:phosphocholine cytidylyltransferase in huma cancer cell lines.

209. May 1, 2018 – Vancouver, BC. Tracking cell signalling protein expression, post-translation modifications, interactions and activation with antibody microarrays.

210. July, 2018 – EuroScicon Proteomics Meeting. London, England. Monitoring protein expression, phosphorylation and interactions with high content antibody microarrays. Structure-function studies of the catalytic domains of eukaryotic protein kinases. Meta-analyses of small molecule inhibitors of protein kinases. (Invited chair) (Meeting was cancelled by conference organizers 6 weeks in advance of the meeting)

211. November 19th and 20th, 2018 – 2nd Global Summit & Expo on Proteomics – 2018. Dallas, Texas. Structure-function studies of the catalytic domains of eukaryotic protein kinases. Monitoring protein expression, post-translational modifications and interactions with high content antibody microarrays Workshop – The open-access suite of bioinformatics websites in the SigNET KnowledgeBank. (Invited chair).

212. February 12, 2019 - 15th Korea Genome Organization (KOGO) Winter Symposium. Vivaldi Park, Korea. Tracking protein expression, post-translational modifications and interactions with high content antibody microarrays.

213. February 13, 2019 - Daegu Gyeongbuk Institute of Science and Technology. Daegu, Korea. Trackir protein expression, post-translational modifications and interactions with high content antibody microarrays.

214. January 15, 2021 – Overview of Kinexus Bioinformatics Corporation and the NDR ALS Biomarker Project. Neurodegenerative Disease Research (NDR), Inc. Group via ZOOM in USA

215. October 28, 2021 - Dr Steven Pelech - Science or fear vaccine mandates UBC. UBC Students for Freedom of Expression. Vancouver, B.C.

216. February 2, 2022 – Pandemic of the unvaccinated. Canadian Covid Care Alliance. Live Zoom presentation.

217. April 9, 2022 – Third Annual Med Ed Conference. Lions Gate Hospital Foundation Youth Advisory Committee. My past and your future in medical research and practice. Vancouver, B.C.

218. May 7, 2022 – Unity Conference. COVID-19, natural immunity and vaccines. Kelowna, B.C.

219. May 28 and 29, 2022 - Restore Canada Conference. We Unify Canada. Victoria, B.C.

220. June 22, 2022 – Citizen's Hearing on COVID-19. Canadian COVID Care Alliance, Toronto, Ontario

221. June 23, 2022 – COVID-19 and natural immunity: Do I need to get vaccinated. Langley, B.C.

222. June 30, 2022 – Progress report for the Kinexus Bioinformatics Corporation and the NDR ALS Biomarker Project. Neurodegenerative Disease Research (NDR), Inc. Group via ZOOM in USA

223. September 10, 2022 – Natural versus COVID-19 vaccine-induced immunity. Victory Canada Candlelight Vigil. Vancouver Art Gallery Plaza. Vancouver, B.C.

224. September 26, 2022 – Conference on Idaho Victims of Pandemic Policy and Law. Prevalence of natural and COVID-19 vaccine induced immunity: What does SARS-CoV-2 antibody testing show Via Zoom in USA.

225. October 1, 2022 – White Rock SDA Church. Natural immunity … Science or science fiction? Part 1 and Part 2. White Rock, B.C.

226. December 10, 2022 – Vancouver Art Gallery Plaza. Natural Immunity versus COVID-19 vaccine-induced immunity. The risks are so great. Vancouver, B.C.
https://www.canadiancovidcarealliance.org/all/20628/

227. January 18, 2023 – David Eby Constituent Office. Why Bill 36 is dangerous to our healthcare system. Vancouver, B.C.

228. January 21, 2023 – UBC Cancer Association. The discovery of the molecular basis of cancer. UBC SUB Nest, Vancouver, B.C.

229. January 23, 2023 – Fraserview Community Hall. Natural versus COVID-19 vaccine-induced immunity … The Dwindling case for vaccination. Maple Ridge, B.C.

230. January 29, 2023 – Heritage Hall. Natural versus COVID-19 vaccine-induced immunity … The Dwindling case for vaccination. Canadian Film Workers for Human Rights & Ethics Association Town Hall. Vancouver, B.C.

231. February 4, 2023 - White Rock SDA Church. The crumbling case for COVID-19 vaccination. White Rock, B.C.

232. February 18, 2023 - World Wide Rally for Freedom at 999 Robson Street. Vancouver, B.C.

233. March 13, 2023 – Neurodegenerative diseases – From their molecular basis to societal impacts. KINE 495-Neuro-motor movement control and rehabilitation. Capilano University. North Vancouver, B.C.

234. May 3, 2023 – The COVID-19 Pandemic…What Really Happened. Testimony at the National Citizen's Inquiry in Canada's COVID-19 Response. Langley, B.C. https://www.canadiancovidcarealliance.org/all/dr-pelechs-nci-presentation/

235. May 20, 2023 – World Freedom Rally at 999 Robson Street. Vancouver, B.C.

236. May 26-28, 2023 – Natural and COVID-19 vaccine-based immunity. WeUnify Reclaiming Canada Conference. Victoria, B.C. https://www.youtube.com/watch?v=iCB-h9Cd550 Starting at 1:09:00

237. September 16, 2023 – White Rock SDA Church. Natural Immunity – Update #3. Q&A with Dr. Steven Pelech. White Rock, B.C. https://livestream.com/accounts/23819274/events/9259494/videos/237604548

238. November 26, 2023 – Christine Anderson Canadian Tour – Freedom Rising. Maple Ridge, B.C. https://rumble.com/v3z5r6j-dr.-steven-pelech-documenting-the-science-around-covid-19.html Starting at 3:14

(e) Other Presentations

(f) Other - Poster (only Poster Presentations from 2016 are listed)

1. April 16, 2016 – American Association for Cancer Research Annual Meeting. New Orleans, LA, USA. Steven Pelech, Lambert Yue, Jeff White, Ryan Hounjet, and Dirk Winkler. Profiling signalling protein expression,
modifications and interactions with multi-dimensional antibody microarrays.
2. April, 2016 – Federation of American Societies for Experimental Biology Annual Meeting. San Diego, CA, USA. Two posters: Steven Pelech, Lambert Yue, Jeff White, and Dirk Winkler. Modifications and interactions with multi-dimensional antibody microarrays; Steven Pelech, Lambert Yue, Shenshen Lai, Dirk Winkler, Jane Shi and Hong Zhang. Production and Characterization of polyclonal generic phosphotyrosine-specific antibodies.
3. July 18, 2016 – International Union of Molecular Biology and Biochemistry Meeting. Vancouver, BC. Two posters: Lambert Yue and Steven Pelech - Multi-dimensional analyses of protein expression, modifications and interactions with high content antibody microarrays (PP01.108); Steven Pelech, Shenshen Lai, Javad Safaei and Lambert Yue - Positive and negative regulation of protein-serine/threonine kinases by their phosphorylation upstream of subdomain VIII in the T-loop (CS02.04).
4. April 2017 – American Association for Cancer Research Annual Meeting. Washington, DC. Poster: Lambert Yue and Steven Pelech - Tracking expression, post-translational modifications and interactions of EGF signalling proteins in A431 cells with antibody microarrays.
5. April 2018 – Canadian National Proteomics Network Annual Meeting. Vancouver, BC. Two posters: Kevin Gonzales, Lambert Yue and Steven Pelech - Phosphorylation of CTP:phosphocholine cytidylyltransferase (PCYT1A); Dirk Winkler, Lambert Yue, Javad Safaei, Zhoung Hua and Steven Pelech - Identification of optimal substrate peptides for protein kinases.
6. October 2019 - Canadian Association of Neuropathologists. Kingston, ON. Poster: Koeppen, A., Travis, A.M., Sutter, C., Pelech, S., and Mazurkiewicz, J.E. - Friedreich cardiomyopathy is a secondary desminopathy.
7. November 13-16, 2019 - International Ataxia Research Conference. Washington, DC. Poster:

Koeppen, A.H., Travis, A.M., Qian, J., Mazurkiewicz, J.E., Gelman, B.B., Pelech, S., Sutter, C. The tissue proteome of dorsal root ganglia in Friedreich ataxia.

8. December 11-14, 2021 - American Society for Hematology. Atlanta, GA. Oral presentation: Yen, R, Yue, L. Pelech, S., Jiang, X. Identification of a highly deregulated eIF4F translation initiation complex in drug-resistant BCR-ABL^{+} cells by a phospho-proteomic antibody microarray.

9. June 3, 2022 – American Peptide Society 2022 Symposium. Whistler, B.C. Poster: Winkler, D.F.H., Atrey, A., Kraft, J.C., Wang, J., Zhao, J.Z., Pelech, S. Investigation into the antibody responses of COVID-19 positive individuals.

10. June 24-29, 2023 - American Peptide Society 2022 Symposium. Scottsdale, Arizona. Poster P248: Winkler, DF.H., Pelech, S. SPOT synthesis – Advantages, Challenges, Limitations.

11. 2024 – Monterey, California. Poster: Koeppen, A.H., Mazurkiewicz, J.E., Feustel, P.J., Pelech, S., Sutter, C., Ahmad, S., Khan, H. Cellular proliferation in dorsal root ganglia of Friedreich ataxia.

12. March 5-9, 2024 – Alzheimer's and Parkinson's Diseases Conference. Lisbon, Portugal. Poster: Tânia Soares Martins, T.S., Pelech, S., Ferreira, M., Breitling, B., Hansen, N., Esselmann, H., Wiltfang, J., da Cruz e Silva, O.A.B. Ana Gabriela Henriques, A.G. Blood-derived extracellular vesicles proteome and phosphoproteome profiling in Alzheimer's disease through microarray analysis.

(g) Conference Participation (Organizer, Keynote Speaker, etc.)

1 1991 - Vancouver organizing committee for 1991 Society for the Study of Reproduction International Conference

2 25 October 1992 - Keystone, Colorado A.S.B.M.B. Symposium, Chairperson

3 1996 - 1997 Vancouver organizing committee for 1997 International Society for Heart Research International Conference

10.1 SERVICE TO THE UNIVERSITY

(a) Memberships on committees, including offices held and dates

Departmental

1 1988 - 2023 - Univ. of B.C. Dept. Medicine - Experimental Medicine Graduate Program Committee

In 2022, I attended two formal meetings of the Committee, reviewed over 80 scholarship applications, as well as faculty and student admissions to the graduate program

2 1993 - 1997 - Univ. of B.C. Department of Medicine Grant Review Committee - Active Member

3 1998 - 2002 - Univ. of B.C. Dept. Medicine - Academic Appointments, Reappointments, Promotions and Tenure Committee, Co-chair

4 July 24, 2000 - VHHSC Grant Panel

5 Brain Research Centre – Space Planning Committee – Meetings: April 8, 2009; May 1, 2009;

Divisional

6 1998 - 2004 - Brain Research Centre - Space Planning Committee - Active Member

7 1987 - 1996 - Univ. of B.C. Biomedical Research Centre - Safety Committee - Active Member

Faculty

8 1998 - 2001 - Faculty of Medicine MD/PhD Graduate Program Committee

9 2000 - 2003 - Faculty of Medicine Research Advisory Committee - Member

10 2003 - 2007 - Faculty of Medicine Senior Academic Appointments, Reappointments, Promotions and Tenure Committee - Member

11 2006-2008 – Faculty of Medicine Internal Reviewer (HeRRO) of grants prior to submission to C.I.H.R. (1 grant per year). In 2008, I reviewed a grant application prepared by Dr. Brian Kwon. He was successful in funding.

12 2004-2008 – TAG Workshop Instructor for Preparation of Teaching Dossiers (2-3 workshops per year). In 2008, one was given on March 5 at VGH and another was given on September 22 at Richmond General Hospital.

13 November, 2014 – Reviewer for VCHRI Top Graduate Doctoral Student Award – Preparation of reports for 7 applicants.

14 April 18, 2017 and May 10, 2017 – Facilitator for UBC Responsible Conduct Course

15 January 23, 2018 and February 6, 2018 – Facilitator for UBC Responsible Conduct Course

University

16 1998 - 2007 - Brain Research Centre - Space Planning Committee - Active Member

17 March 14, 1992 Judge - Second Annual Research Workshop, Reproductive & Developmental Sciences Program, Dept. Obstetrics & Gynaecology, U.B.C.

18 June 22, 2000 - Chairman of the Degree Validation Panel convened to review the Proposal for a joint British Columbia Institute of Technology/University of British Columbia Program for a Bachelor of Science degree in Biotechnology

19 2001 - 2004 - Faculty of Medicine Research Planning Committee - Member

20 2001 - 2003 - University of British Columbia Research Awareness Committee Member

21 May 2, 2001 - Canada Research Chairs Selection Committee Member

22 March 12, 2002 - Vancouver Hospital Health Sciences Centre Salary Awards Panel

23 January 24, 2008 – Judge – UBC Faculty of Dentistry Graduate Research Poster Competition

24 February 27, 2008 – Panelist - UBC Department of Biochemistry and Molecular Biology Careers Evening

25 March 13, 2014 – Panel member for 2014 Science Career Information Fair (SCIFair) at the Life Sciences Centre, UBC.

26 March 19, 2014 – Panel member for 2014 Biochemistry Careers Night for the Department of Biochemistry and Molecular Biology at the Abdul Ladha Science Student Centre, UBC.

27 January 11, 2017 – Poster judge for the Faculty of Dentistry Graduate Student Program

28 November 7, 2018 – Poster judge for the UBC Faculty of Medicine and VGH Research Expo

29 January 17, 2019 – Panelist – UBC Computer Science/Life Sciences Panel – Careers Evening

30 March 9, 2019 – Panelist and speaker at 2 workshops - Operation Med School Vancouver (OMS) – Career event for high school students at the Robert H. Lee Alumni Centre

31 October 1, 2020 – present – UBC Senate. Faculty of Graduate and Postdoctoral Studies Representation. Also served on the Senate Admissions Committee, and the Senate Admissions Appeals Committee (2020-2023); the Senate Policy Committee, and the Senate Nominating Committee (2023-present)

(b) Other service, including dates

1 October 25, 1991 Medical Research Council representative for Scholarships Day at UBC

2 September 24, 1992 Medical Research Council Representative for Scholarships Day at UBC

3 October 29, 2008 - Representative for Brain Research Centre for strategic discussion meeting in Waterfront Hotel in downtown Vancouver with Deputy Minister David Molony from Industry Canada to review government support for translational research

4 December 11, 2008 – Representative for UBC for strategic discussion meeting with N.S.E.R.C. at Pinnacle Marriott Hotel in downtown Vancouver to review government support for translational research

5 September 29, 2014 – Panel member for biotechnology curriculum development at the Langara College – Teaching and Curriculum Development Centre

6 October 15, 2020 to December 31, 2022– Panel member for Langara College B.Sc. in Bioinformatics Advisory Committee

Dissertation Committee and Examinations

Ph.D. & M.Sc. Supervisory Committee Membership

1 Dr. Paul Sunga - Dept. of Medicine (1989-1992 until Ph.D.)

2 Dr. Yong Hei - Pharmaceutical Sciences (1990-1993 until Ph.D.)

3 Ms. Elham Ettehadieh - Dept. of Biochemistry (1990-1993)

4 Mr. Brett Gabelman - Dept. of Anatomy (1990-1992 until M.Sc.)

5 Mr. Liren Tang - Dept. of Zoology (1991-1995 until Ph.D. & Ph.D. Examiner)

6 Ms. Rachel Zhande - Dept. of Biochemistry (1991-1998 until Ph.D.)

7 Mr. Aswin Patel - Pharmaceutical Sciences (1992-1996 until Ph.D.)

8 Ms. Patricia Herrera-Velt - Dept. of Microbio. Immunol. (1992-1997 until Ph.D.)

9 Mr. Sep Farahbakhian - Pharmaceutical Sciences (1992-1994 until M.Sc.)

10 Ms. Marie-Terese Little - Dept. Obsteterics & Geynecology (until 1993)

11 Mr. Patrick Tang - Dept. Microbio. Immunol. (1993-1997 until Ph.D.)

12 Mr. Mohammed Hasham - Dept. of Medicine (1994-1995 until M.S.)

13 Ms. Krista McCutcheon - Dept. of Anatomy (1994-1996 until M.Sc.)

14 Mr. Allen Young - Dept. of Oral Biology (1995-1997)

Mr. Brent Hehn - Dept. of Oral Biology (1995-1997 until Ph.D.)
Mr. Steven Drew - Dept. of Medicine (1995-1998 until M.Sc.)
Mr. Alaa El-Husseini - Dept. of Psychiatry (1995-1997 until Ph.D.)
Ms. Julia Mills - Dept. of Psychiatry (1995-1998 until Ph.D.)
Ms. Claire Sutherland - Dept. Microbiology Immunology (1995-1999 until Ph.D.)
Ms. Rochelle Starhe - Dept. of Medicine (1996-2001 until Ph.D.)
Mr. Mark Ware - Dept. of Medicine (1996-2000)
Mr. Vijay Viswanathan - Dept. Psychiatry (1998-2004 until Ph.D.)
Mr. Olaf Heisel - Dept. of Medicine (1999-2001 until Ph.D.)
Mr. Godfrey Miles - Dept. of Plant Sciences (1999-present)
Mr. Jan Ehses - Dept. of Physiology (1999-2003 Ph.D.)
Ms. Shu Hong Li - Pharmaceutical Sciences (2000 until 2001 Ph.D.)
Ms. Doris Chiu - Dept. of Medicine (2000-until 2001 M.Sc.)
Ms. Lucy Marzban - Pharmaceutical Sciences (2000 until 2001 Ph.D.)
Ms. Somrudee Sritubtim - Dept. Plant Sciences (2000 until 2005 Ph.D.)
Mr. Steven Drews - Dept. of Medicine (2000-2003 until Ph.D.)
Mr. Farrell MacKenzie - Dept. of Pathology (2001-2003 until M.Sc)
Ms. Jiehong Ju - Dept. of Kinesiology, Simon Fraser University (2001-2004 until Ph.D.)
Ms. Mannie Fan - Neuroscience Program (2002-2008 until Ph.D.)
Ms. Gina Rossi - Dept of Medicine (2002-2010)
Ms. Michelle Woo - Dept. Medicine (2003-2007 until Ph.D.)
Ms. Catherine Tucker - Dept. Medicine (2004-2007 until Ph.D.)
Mr. Tyson Brust – Neuroscience Program (2005-2008 until Ph.D.)
Mr. Philip Ly – Dept. Medicine (2005-2007 until M.Sc.)
Mr. Ebrima Gibbs – Dept. Medicine (2005-2008 until Ph.D.)
Ms. Shirley Chen – Dept. Medicine (2005-2009)
Mr. Scott Widenmaier – Dept. Cellular Physiological Sciences (2006-2010 until PhD)
Mr. Gobind Sun – Dept. Medicine (2006-2007 until transfer to new supervisor)
Ms. Amy Lai - Dept. Medicine (2007-2008 until transfer to new supervisor)
Ms. Arezoo Ostenehe – Dept. Medicine (2009-2013)
Ms. Shenshen Lai - Dept. Medicine (2009-2015 until Ph.D.)
Mr. Dominik Sommerfeld - Dept. Medicine (2010-2012 until transfer to new supervisor)
Mr. Javad Safaei – Dept. Mathematics & Computer Science (2008-2015 until Ph.D.)
Ms. Trisha Kostesky – Dept. Medicine (2010-2011 until M.Sc.)
Mr. Mazyar Ghaffari – Dept. Medicine (2011-2015)
Ms. Valerie Poirier - Dept. Medicine (2011-2015 until Ph.D.)
Mr. Dennis Wong - Dept. Medicine (2011-2013)

52 Ms. Melissa Richard-Greenblat - Dept. Medicine (2012-2016 until Ph.D.)

53 Ms. Anna Cecilia Sjoestroem – Dept. Medicine (2013-2014 until M.Sc.)

54 Mr. Franco Cavaleri - Dept. Medicine (2014-2017)

55 Mr. Bisher Hassan Abuyassin – Dept. Pharmacology (2015-2018)

56 Mr. Lambert Yue - Dept. Medicine (2016-2020)

57 Mr. Ryan Yen – Dept. Medicine (2017-2022)

58 Ms. Anam Nan Nan Liu – Dept. Pathology and Laboratory Medicine (2017-2019)

Directed Research Studies Supervision

1 Mr. Gordon Cheung – 4th year Zoology (2003-2004) 8 months

2 Ms. Nastaran Mohammadi – 5th year unclassified (2006) 7 months

3 Ms. Sharon Zhao – Department of Mathematics & Computer Sciences, Simon Fraser University. Ph.D. graduate student. Joint MITACS project supervision. (2005-2006) 8 months

4 Mr. Mazyar Ghaffari – 1st year graduate student (2008) 6 months starting March 1

5 Mr. Javad Safaei – Department of Mathematics & Computer Sciences, Simon Fraser University. Ph.D. graduate student. Joint MITACS project supervision. (2008-2015)

6 Ms. Parisa Shoosht – Department of Mathematics & Computer Sciences, Simon Fraser University. Ph.D. graduate student. Joint MITACS project supervision. (2008)

7 Mr. M. Shabab Hossain – Department of Computer Science, University of B.C., M.Sc. graduate student. Joint MITACS project supervision. (2011)

8 Mr. Alireza Davoodi - Department of Computer Science, University of B.C., M.Sc. graduate student. Joint MITACS project supervision. (2013-2014)

9 Ms. Nishima Arora – Biotech Biotechnology, Vellore Institute of Technology, India., undergraduate student. Six months full-time directed research studies (January 1 – June 30, 2015).

10 Mr. Lambert Yue – Department of Biology, University of B.C. 5th undergraduate student. Four months full-time directed research studies (January 1 – April 30, 2016).

11 Mr. Kevin Gonzales – Department of Biology, University of B.C. 5th year undergraduate. Eight months, part-time directed research studies (September 1, 2017-April 30, 2018).

12 Mr. Abiel Kwok – Integrated Sciences Program, University of B.C. 4th year undergraduate. Eight months, part-time directed research studies (September 1, 2019-April 30, 2020).

13 Mr. Kevin Wong – Department of Biology, University of B.C. 3th year undergraduate. Eight months, part-time directed research studies (September 1, 2019-April 30, 2020).

14 Mr. Samuel Bakteria – Pharmaceutical Sciences, University of B.C., 4th year undergraduate. Two months, full-time directed research studies (May 1-June 30, 2023)

B.Sc. Honours Thesis Examiner

1 Ms. Maryam Baghannazary - Dept. of Biology (1992)

2 Mr. Danny Leung - Dept. of Biochemistry, Simon Fraser University (1994)

3 Ms. Monika Aluweilla - Dept. of Biochemistry, Simon Fraser University (1995)

M.Sc. Thesis Examiner

1 Mr. Jonathan Kao - Dept. of Medicine (1990)
2 Ms. Rachel Zhande - Dept. of Biochemistry (1991)
3 Mr. Peter Dreyden - Dept. of Medicine (1992)
4 Mr. John Stingl - Dept. of Anatomy (1992)
5 Mr. Brett Gabelman - Dept. of Anatomy (1992)
6 Mr. Sep Farahbakhian - Pharmaceutical Sciences, U.B.C (1994)
7 Mr. Mohammed Hasham - Dept. of Medicine, UBC (1996)
8 Ms. Krista McCutcheon - Dept. of Anatomy, UBC (1996)
9 Mr. Steven Drew - Dept. of Medicine (May 19, 1998)
10 Ms. Shu Hong Li - Pharmaceutical Sciences, UBC (May 23, 2000)
11 Mr. Tom Yokogawa - Dept. of Medicine (October 10, 2000)
12 Ms. Doris Chiu - Dept. of Medicine (October 4, 2001)
13 Mr. Farrell Mackenzie - Dept. Pathology (April 23, 2003)
14 Mr. Geoff Karjala – Dept. of Biochemistry & Molecular Biology (November 30, 2004)
15 Mr. Philip Ly – Dept. of Medicine (October 9, 2007)
16 Ms. Trisha Kostesky – Dept. Medicine (June 21, 2011)
17 Ms. Anna Cecilia Sjoestroem – Dept. of Medicine (October 7, 2013)
18 Ms. Anam Lui - Dept. of Medicine (September 30, 2019)

Ph.D. Oral Comprehensive Examiner

1 Ms. Marie Terese Little - Dept. Obstetrics & Gynaecology (June 10, 1991)
2 Dr. Amanda Jones - Dept. Medicine (December 11, 1991)
3 Ms. Patricia Herrarez - Dept. Microbiol. Immunol. (December 14, 1992)
4 Ms. Julia Mills - Dept. Psychiatry (June 21, 1995)
5 Mr. Alaa El-Husseini - Dept. Psychiatry (January 24, 1996)
6 Ms. Rochelle Starhe - Dept. of Medicine (May 27, 1997)
7 Mr. Olaf Heisel - Dept. of Medicine (2000)
8 Mr. Vijay Viswanathan - Dept. Psychiatry (June 15, 2000)
9 Mr. Godfrey Miles - Dept. Plant Sciences (September 15, 2000)
10 Mr. Jan Ehses - Dept. of Physiology (November 21, 2000)
11 Mr. Mohamed Sayed - Dept. of Medicine (December 19, 2000)
12 Mr. Steven Drews - Dept. of Medicine (February 7, 2001)
13 Mr. Kelvin Chang - Dept. of Obstetrics and Gynaecology (April 17, 2002)
14 Ms. Gina Rossi - Dept. Medicine (Sept 17 and Nov 10, 2004)
15 Mr. Gobind Sun – Dept. Medicine (May 28, 2007)

16 Mr. Scott Weidermaier – Dept. of Physiology (September 30, 2008)
17 Ms. Arezoo Astenehe – Dept. of Medicine (April 17, 2009)
18 Mr. Dennis Wong – Dept. of Medicine (September 30, 2009)
19 Mr. Darryl Bannon - Dept. of Medicine (November 10, 2011)
20 Ms. Valerie Poirer - Dept. of Medicine (November 25, 2011)
21 Ms. Shenshen Lai - Dept. of Medicine (December 14, 2011)
22 Mr. Darryl Bannon - Dept. of Medicine (May 17, 2012)
23 Ms. Joanna Triscott - Dept. of Medicine (June 4, 2012)
24 Ms. Melissa Richard – Dept. of Medicine (February 7, 2013)
25 Mr. Franco Cavaleri – Dept. of Medicine (April 17, 2015)
26 Mr. Bisher Hassan Abuyassin – Dept. of Medicine (December 12, 2016)
27 Mr. Ryan Yen – Dept. of Medicine (January 17, 2019)

Ph.D. Thesis Examiner
1 Mr. Grant Hatch - Dept. of Biochemistry, University of Manitoba (1989)
2 Dr. Poul Sorenson - Dept. of Pathology, UBC (1990)
3 Ms. Alice Mui - Dept. of Pathology, UBC (1992)
4 Mr. Paul Sunga - Dept. of Medicine, UBC (1992)
5 Dr. Jong Hei - Pharmaceutical Sciences, UBC (1993)
6 Mr. Guy Mordret - Dept. of Biochemistry, University of Brest, France (1993)
7 Ms. Corinne Reimer - Dept. of Anatomy, UBC (1994)
8 Mr. John Hill - Dept. of Pathology, UBC (1994)
9 Ms. Ruth Lanius - Dept. of Opthomology, UBC (1994)
10 Mr. Ashwin Patel - Pharmaceutical Sciences, UBC (1996)
11 Mr. Patrick Rebstein - Dept. of Microbiol. Immunol., UBC (1996)
12 Ms. Patricia Herrera-Velt - Dept. Microbio. Immunol, UBC (1997)
13 Mr. Xi-Long Zheng - Dept. of Medical Biochemistry, University of Calgary (June 23, 1997)
14 Mr. Vuk Stambolic - Dept. of Biochemistry, University of Toronto (August 7, 1997)
15 Mr. Alaa El-Husseini - Dept. of Psychiatry, UBC (October 17, 1997)
16 Ms. Rachel Zhande - Dept. of Biochemistry, UBC (December 1, 1997)
17 Mr. David Ng - Dept. of Microbio. Immunol., UBC (April 24, 1998)
18 Mr. Jeffrey Posaconi - Dept. of Chemistry, UBC (June 19, 1998)
19 Ms. Adrienne Boone - Dept. Biochemistry, UBC (April 5, 2000)
20 Ms. Zahara Jaffer - Dept. Microbiol. & Immunology, UBC (August 14, 2000)
21 Mr. Abdulaziz Al-Fahim - Dept. of Medicine, UBC (August 11, 2000)
22 Ms. Ravenska Wagey - Dept. of Medicine (December 14, 2000)

23 Ms. Amy Dambrowitz - Dept. of Biochemistry (June 6, 2001)
24 Ms. Rochelle Heisel - Dept. of Medicine (July 30, 2001)
25 Ms. Lucy Marzban - Faculty of Pharmaceutical Sciences (September 6, 2001)
26 Mr. Mohamed Sayed - Dept. of Medicine (October 26, 2001)
27 Ms. Xiaoli Cheng - Dept. of Biochemistry (December 10, 2002)
28 Mr. Steven Drews - Dept. Medicine (June 24, 2003)
29 Mr. Jan Ehsus - Dept. Physiology (July 18, 2003)
30 Mr. Kelvin Cheng - Dept. Gynaecology and Obstretics (Feb 4, 2004)
31 Ms. Sherri Christian - Dept. Microbiology and Immunology (May 5, 2004)
32 Ms. Elizabeth Slow - Dept. Medicine (November 26, 2004)
33 Ms. Rita Maghsoodi – (January 17, 2005) - Chair
34 Ms. Tanya Griffith – Department of Biochemistry and Molecular Biology (January 27, 2006) - Chair
35 Ms. Zhou Hongyan – University of Hong Kong (November 12, 2006) – External Examiner
36 Ms. Justine Karst – Department of Botany (July 9, 2007) - Chair
37 Mr. Robert Ferdman – Department of Astronomy (December 13, 2007) - Chair
38 Ms. Catherine Tucker – Department of Medicine (December 21, 2007)
39 Ms. Jin Suk Lee – Department of Botany (January 18, 2008) – University Examiner
40 Mr. Ebrima Gibbs – Dept. of Medicine (August 22, 2008)
41 Mr. Mark Romanish – Faculty of Science (July 22, 2009) – Chair
42 Mr. Douglas Sweeney – Faculty of Engineering (Nov. 12, 2009) - Chair
43 Mr. Scott Widenmaier – Dept. Cellular Physiological Sciences (June 30, 2010)
44 Mr. David Morin – Dept. of Medicine (December 22, 2011) - Chair
45 Ms. Grace Lee Kam – Dept. of Medicine (December 23, 2011)
46 Ms. Valerie Poirier – Dept. of Medicine (January 23, 2015)
47 Mr. Too Jin Park – Dept. of Medicine (February 10, 2015)
48 Ms. Shenshen Lai – Dept. of Medicine (March 25, 2015)
49 Mr. Javad Safaei – Dept. of Computer Science and Mathematics (April 9, 2015)
50 Ms. Melissa Richard – Dept. of Medicine (June 28, 2016)
51 Ms. Sylvia Cheung – Dept. of Surgery (September 15, 2016)
52 Mr. Saleem Iqbal – Crystallography and Biophysics, University of Madras, Chennai, India (November 9, 2018) – External Examiner
53 Mr. Bisher Hassan Abuyassin – Dept. of Medicine (December 21, 2018)
54 Mr. Ryan Yen – Dept. of Medicine (August 25, 2022)
55 Mr. Andrew Santos – Dept. Microbiology and Immunology (December 15, 2022)

10.2 SERVICE TO THE HOSPITAL

(a) Memberships on committees, including offices held and dates

(b) Other service, including dates

11. SERVICE TO THE COMMUNITY

(a) Memberships on scholarly societies, including offices held and dates

1 1990-present Canadian Society for Biochemistry and Molecular Biology - Active Member

2 1990-1992 Society for the Study of Reproduction (on local organizing committee for 1991 S.S.R. International Conference)

3 1996-1997 International Society for Heart Research (on local organizing committee for 1997 I.S.H.R. Conference)

4 1996-1999 American Society for Microbiology - Active Member

5 2016-2018 American Society for Biochemistry and Molecular Biology – Active Member

(b) Memberships on other societies, including offices held and dates

1 1980-1987, Canadian for Health Research - Active Member

2 1996-2002, 2008 Vancouver Public Aquarium - Active Member

2021-present, Vice-President, Chair of the Scientific and Medical Advisory Panel, Canadian Citizens Care Alliance (formerly Canadian Covid Care Alliance)

(c) Memberships on scholarly committees, including offices held and dates

1 1992-present Lunar Society - Active Member

(d) Memberships on other committees, including offices held and dates

1 1980-1983 - Executive Committee of B.C. Chapter of Canadian for Health Research

2 1991-1993 - M.R.C. of Canada Studentship Committee

3 1991-1994 – Canadian Heart & Stroke Foundation Operating Grant Panel

4 1994-1995 - Committee for West Vancouver High Schools Cooperative Education Program

5 1994- M.R.C. of Canada Program Grant Committee

6 1994- American Heart Association Grant Panel

7 1995-1996 -M.R.C. of Canada Operating Grant Committee - Biochem. Mol. Biol. Panel B

8 May 29-31, 2000 - Invited Member Strategic Planning Committee for the National Research Council of Canada Industrial Research Assistance Program

9 November 6-9, 2000 - Canadian Institute for Health Research - Operating Grant Committee - Cardiovascular Panel

10 July 31, 2001 - Michael Smith Foundation for Medical Research Senior Scholars and Scientist Award

Committee

11 2001 - 2006 - Member Advisory Committee for the National Research Council of Canada Industrial Research Assistance Program

12 2001-2006 - Genome Prairie Scientific Advisory Board

13 2002 - 2007 - Simon Fraser University Biotechnology Advisory Council - Member

14 2003-2005 - Canadian Bioinformatics Resource Initiative - Chairman

15 2004-2010 - National Research Council of Canada Genome Health Initiative Expert Panel. In 2009, I attended the Annual Meeting of the GHI in Montreal in June 1st and 2nd, and provided mid-term reviews of 5 GHI projects for the NRC at an Expert Panel Meeting in Ottawa on December 6. In 2010, I judged new GHI projects on September 27 & 28 in Ottawa.

16 2005-2007 - Simon Fraser University Master of Technology Advisory Board

17 2005 - U.S. National Institutes of Health Director's Roadmap Initiatives, Technology Centers for Networks and Pathways (TCNP) Grant Panel (I was invited to join this panel again in 2008, but declined due to a timing conflict.)

18 2006 – Alberta Cancer Board Grant Review Panel for Programs of Distinction

19 2009 – Canadian Institutes for Health Research - Catalyst Grant: Invention and High-Risk, High-Benefit Research Panel. June 3-5 in Ottawa.

20 2010 – Canadian Institutes for Health Research - Catalyst Grant: Invention and High-Risk, High-Benefit Research Panel. June 3-5 in Ottawa.

21 2021 – 2022 Langara University Bioinformatics Advisory Committee

(e) Reviewer (journal, agency, etc. including dates) - Peer-reviewer of grant-in-aid applications

1 Medical Research Foundation of Canada: 1988 - 4; 1989 - 9; 1990 - 4; 1991 - 2; 1993 - 5; 1994 - 20; 1995 - 21; 1996 - 19; 1997 - 11; 1998 -6; 1999 -10; 2000 -5

2 Alberta Heritage Foundation: 1988 - 1; 1990 - 1; 1991 - 3; 1992- 2; 1993 - 4; 1994 -1; 1995 -2; 2000 - 4; 2001-1; 2005-1

3 Canadian Diabetes Association: 1988 - 1; 1990 - 1; 1993 -1; 1994 -2; 1995 - 2; 1996 -1; 2002-2; 2003-3

4 Canadian Arthritis Society: 1988 - 1; 1989 - 1

5 National Cancer Institute of Canada: 1988 - 1; 1995 -1; 2001 -8

6 Heart & Stroke Foundation of Canada: 1988 - 1; 1990 - 1; 1991 - 16; 1992 - 16; 1993 - 16, 1994 - 12; 1998 -1; 1999 -3; 2000-4; 2002-1

7 Kidney Foundation of Canada: 1989 - 1; 1990 - 1

8 Natural Sciences & Research Council of Canada: 1990 - 1; 1995 -1; 1996 -1; 2002-1; 2004-2; 2006-1; 2015-1; 2016-1

9 Manitoba Health Research Council: 1992 - 1; 1993 -1; 1994 -1; 1997-2

10 National Science Foundation (USA): 1992 - 1; 1993 - 4; 1994 -2; 1996 -1; 1997 -2; 1998 -2; 2004-1

11 American Diabetes Association: 1994-1

12 Israel Science Foundation: 1994-1; 1996 - 4
13 American Heart Association (USA): 1994 - 5
14 Alberta Cancer Board: 1996 - 2; 2000 –1; 2007-2
15 U.S.-Israel Binational Science Foundation: 1996 -1
16 British Columbia Health Research Foundation: 1999 -7
17 Canadian Institute for Health Research: 2000 -11; 2001-5; 2002-2; 2003-2; 2004-1; 2005-1; 2009-12; 2010-13
18 Hong Kong Research Granting Council: 2000 -1; 2003-2
19 Vancouver Hospital Health Sciences Centre: 2000 -2; 2002-5; 2005-1; 2006-1
20 Michael Smith Foundation Health Research: 2001-4; 2003-1
21 GenomePrairie: 2001-21; 2003-3; 2004-5; 2006-2
22 B.C. Lung Assoc.: 2002-1
23 Canadian Blood Services: 2002-1
24 Carcinogenesis: 2002-2
25 Biotechniques: 2002-1
26 Scottish Rite Charitable Foundation: 2003-1
27 International Cancer Research Agency: 2004-1
28 Biotechnology and Biological Sciences Research Council (United Kingdom): 2004-1
29 National Research Council of Canada: 2004-5; 2006-5; 2007-16; 2009-5; 2010-3
30 U.S. National Institutes of Health: 2005-13
31 Singapore Biomedical Research Council: 2010-1
32 Genome Alberta: 2012-4
33 Cancer Research UK: 2012-1

(f) Reviewer (journal, agency, etc. including dates) - Peer-reviewer of scientific manuscripts

1 Analytical Chemistry: 2005 - 2
2 Biochem. Cell Biology: 1989 - 1; 1990 - 1; 1992 - 1; 1993 -2
3 Biochim. Biophys. Acta: 1989 - 9; 1990 - 5; 1991 - 4; 1992 - 3; 1993 -1; 1994 - 3; 1995 - 3; 1998 -1; 2000 –1; 2005 - 2
4 Brain Research: 2005 - 1
5 Molecular Cellular Biology: 1989 - 2; 1992 - 1; 1993 - 5; 1994 - 3; 1995 -2; 1996-1; 2003-1
6 Science: 1989 - 1; 1991 - 1, 1992 - 1; 1993 -1; 1994 - 2
7 Digestive Diseases & Sciences: 1990 -1; 1991 -1
8 Endocrinology: 1990 -1
9 Experimental Eye Research: 1990 - 1
10 FEBS Reviews: 2005 - 1

11 Journal Biol. Chem.: 1989 - 1, 1997 -1
12 Journal of Interferon Research: 1990 - 1
13 Journal Clinical Invest.: 1992 - 1
14 Journal of Immunology: 1992 - 2, 1995 -1
15 Nature: 1992 - 2, 1993 - 4
16 Proc. Natl. Acad. Sci. USA: 1992 -1, 1994 - 3; 1995 -1
17 American Journal of Physiology: 1993 - 1
18 Developmental Biology: 1993 -2
19 Diabetes: 1993 -1
20 European J. Biochemistry: 1994-2, 1995-1
21 Blood: 1993 -1; 1995 -1; 1998 -1;1999 -1
22 Analytical Biochemistry: 1996 - 2
23 Trends in Cardiovascular Medicine: 1996 -1
24 Cancer Res.: 1997 -1
25 Journal of Neurochemistry: 1997- 2; 2001-1
26 Neurobiology of Aging: 1998 -1
27 Biochemistry: 2000 -1
28 Journal of Endotoxin Research: 2000 -2
29 Life Sciences: 2000 -1
30 Carcinogenesis: 2007-1
31 Public Library of Science (PloS): 2008-1
32 Journal of Neurological Sciences: 2010-1
33 Science – Cell Signaling: 2010-1
34 Systems Biology of Free Radicals and Anti-oxidants – 2012-1
35 Proteomics – 2016-1
36 Molecular and Cellular Proteomics – 2016-1
37 Journal of Proteome Research – 2017 -1
38 Cell Signalling – 2019-1
39 J. Alzheimer's Disease – 2021 - 1
40 Vaccines – 2022 – 2; 2023 -1
41 Journal of Radiology and Oncology – 2023 -1
42 Exploration of Drug Science – 2023-1
43 International Journal of Molecular Science – 2023-1
44 Medicina – 2024-1

(g) External examiner (indicate universities and dates)

1 1989 Ph.D. Defence of Grant Hatch - Dept. of Biochemistry, Univ. of Manitoba

2 1993 Ph.D. Defence of Guy Mordret - Dept. of Biochemistry, Univ. of Brest, France

3 1997 Ph.D. Defence of Xi-Long Zheng - Dept. of Medical Biochemistry, Univ. of Calgary

4 1997 Ph.D. Defence of Vuk Stambolic - Dept. of Biochemistry, Univ. of Toronto

5 2006 Ph.D. Defence of Zhou Hongyan - Department of Biochemistry, Univ. of Hong Kong

6 2018 Ph.D. Defence of Saleem Iqbal – Crystallography and Biophysics, Univ. of Madras, Chennai, India

(h) Consultant (indicate organization and dates)

1 1991-1999 Upstate Biotechnology Inc., Lake Placid, N.Y.

2 1995-present Kinections Consulting Ltd, Richmond, B.C.

3 1995-1999 Biozyme, Vancouver, B.C. (member of scientific advisory board)

4 1996-2000 Viratest, Burnaby, B.C. (member of scientific advisory board)

5 1997-2000 StressGen, Victoria, B.C.

6 1999 - present Kinexus Bioinformatics Corporation, Vancouver, B.C. (member Board of Directors)

7 2001 - 2006 GenomePraire Scientific Advisory Board

8 2001 - ARC Pharmaceuticals, Vancouver BC (member of Scientific Advisory Board)

9 2018 - present – GLG, Austin, Texas and London, UK (member of advisory council for industry)

10 2020 – present – Neurodegenerative Disease Research, Inc. (member of research consortium)

(i) Other service to the community

1 1990-present - Cooperative Education Program - Simon Fraser University

2 1991-2007 - Scientist in The School Program - coordinated by Science World

3 1992 – 2010 - Cooperative Education Program - University of Victoria

4 March 9, 1993 - Volunteer for Careers Presentation - Science World, Vancouver.

5 February 14, 1993 - Scientists and Innovators in the Schools, Kitsilano Secondary School, Vancouver

6 1994-present - Cooperative Education Program - West Vancouver Secondary Schools

7 1994-present - Mentor for B.C. Institute of Technology Biotechnology Program

8 1996-present Cooperative Education Program - University of B.C.

9 March 1, 1996 - Volunteer for Careers Presentation - Science World, Vancouver.

10 January 24, 1997 - Scientists & Innovators in the Schools, Gladstone Secondary School, Vancouver.

11 April 2, 1998 - Judge for 1998 Greater Vancouver Regional Science Fair at the University of BC

12 February 4, 1999 - Judge for 1999 BC Biotechnology Alliance Awards

13 April 8, 1999 - Judge for 1999 Greater Vancouver Regional Science Fair at the University of BC

14 April 19, 1999 - Judge for 1999 Caunaught Biotechnology Science Fair, Vancouver

15 February 8, 2000 - Judge for 2000 BC Biotechnology Alliance Awards

16 April 6, 2000 - Judge for 2000 Greater Vancouver Regional Science Fair at the University of BC

17 2001 - Judge for 2001 Aventis Biotechnology Science Fair

18 February 1, 2001 - Judge for 2001 BC Biotechnology Alliance Awards

19 April 26, 2001 - Judge for 2001 Aventis Biotechnology Science Fair

20 March 2002 - Scientists & Innovators in the Schools, University Hill Secondary School, Vancouver.

21 2002 - Judge for 2002 Aventis Biotechnology Science Fair

22 January 17, 2019 - Invited Panelist – UBC Computer Science/Life Sciences Panel –
23 Careers Evening

March 9, 2019 - Invited Speaker at Operation Med School Vancouver (OMS) Workshop for high school students. Career mentoring workshop (2 x 30 minute sessions) held at the
24 Robert H. Lee Alumni Centre at UBC

September 1, 2020 – 2022 – Langara College Bioinformatics Advisory Board member

12. AWARDS AND DISTINCTIONS

(a) Awards for Teaching (indicate name of award, awarding organizations, date)

1 2001 Faculty of Medicine Distinguished lecturer - Basic Sciences

(b) Awards for Scholarship (indicate name of award, awarding organizations, date)

2 1975 Killarney Secondary School Scholarship, Killarney Sec. School, Vancouver

3 1975 B.C. Government Scholarship, Killarney Sec. School, Vancouver

4 1977 Canadian Found. for Diseases of the Liver Summer Studentship, Univ. of B.C.

5 1978 Natural Sciences and Engineering Research Council of Canada Postgraduate Scholarship, Univ. of B.C.

6 1979-1982 Medical Research Council of Canada Studentship, Univ. of B.C.

7 1982 Univ. of B.C. Graduate Student Speaker Competition (1st Place)

8 1982 Izaak Walton Killam Postdoctoral Fellowship

9 1982-1984 M.R.C. of Canada Postdoctoral Fellowship

10 1985 M.R.C. of Canada 1967 Centennial Fellowship

11 1988-1993 M.R.C. of Canada Scholarship Award

12 1993-1996 M.R.C. of Canada Scientist Award

13 1996-1998 M.R.C. of Canada Industrial Scientist Award

(d) Other Awards

14 1993 Canadian Soc. for Biochem. & Molec. Biol. Merck-Frosst Award - for outstanding research in the area of biochemistry and molecular biology in Canada

15 1993 Martin M. Hoffman Award - Univ. of B.C. Hospital Site for Research in Dept. of Medicine

16 1996 Business in Vancouver Top Forty Under Forty Award for Business Achievement

17 1998 International Who's Who

18 2001 Faculty of Medicine 2001 Distinguished Lecturer, University of BC

Fellowship Awards (won by Post-Doctoral Fellows under supervision)

19 Lefebrve, D. - MRC Fellowship 1995-1996

20 Sahl, B. -MRC Fellowship 1995-1997

21 Bhanot, S. - BC Heart & Stroke Fellowship 1995-1997

22 Bhanot, S. - MRC Fellowship (declined) 1995-1997

23 Koide, B. - MRC Fellowship 1995

24 Xu, Yan-Jun - MRC Fellowship 1998-1999

25 Zhang, Hong - NSERC Industrial Fellowship 2003-2004

Studentship Awards (won by Graduate Students under supervision)

26 Palaty, C. - NSERC Studentship 1991-1994

27 Samiei, M. - MRC Studentship 1992-1994

28 Charest, D. L. - Walter Babicki Studentship 1992

29 Charlton, L. - NSERC Studentship 1992-1995

30 Charest, D. L. - MRC Studentship 1993-1997

31 Morrison, D. L. - MRC Studentship 1993-1997

32 Tudan, C. - MRC Studentship 1993-1996

33 Kim, S. - MRC Studentship 1993-1997

34 Palaty, C. - Walter Babicki Studentship 1995

35 Charlton, L. - Killam Studentship 1996-1997

36 Wagey, V. - University Graduate Fellowship 1997-1998

37 Marotta, A. - Evelyn Martin Fellowship 1998-1999

38 Sayed, M. - MRC Studentship 2000-2002

39 Shenshen Lai – University of B.C. Graduate Fellowship 2010-2014

40 Lambert Yue – UBC Experimental Medicine Graduate Program Entrance Award (2016); NSERC Graduate Fellowship 2017-2018; UBC 4YF Scholarship 2018-2020

41 Hamidreza Galavi - UBC Experimental Medicine Graduate Program Entrance Award (2020); UBC 4YF Scholarship 2020-2023; Vanier Award 2022-2024

13. OTHER RELEVANT INFORMATION (Maximum One Page)

1992-1998 - President, CEO and major stock owner of Kinetek Pharmaceuticals, Inc.

Kinetek was a private, early stage biotechnology company that employed 15 Ph.D./M.D. level scientists and 25 other technical and other supporting personnel at the time that I left the company. It was engaged in the discovery and development of drugs for the treatment of cancer, diabetes and other chronic diseases of aging. The Kinetek activities occupied over 18,000 square feet at two locations in south Vancouver. It was acquired by QLT, Inc. in 2004.

1995 - present - President and major stock owner of Kinections Consulting Ltd.

Kinections is a private company that provides consulting advise related to cellular signal transduction and the biotechnology industry. Its services also include the preparation of scientific reports and illustrations.

1999 - present - Founder, President, Chief Scientific Officer and major stock owner of Kinexus Bioinformatics Corporation

Kinexus Bioinformatics is a private company that provides analytical services related to the tracking of protein kinases and bioinformatics related to protein kinases. It has provided proteomics services to over 2000 laboratories in 40 countries. Over 200 of the company's clients are in companies. Twenty-nine of the top 30 pharmaceutical companies in the world are clients of Kinexus.

2021 – present – Founder, Vice-President, Co-Chair of the Scientific and Medical Advisory Committee (SMAC) of the Canadian Citizens Care Alliance (CCCA) (originally called the Canadian Covid Care Alliance). The CCCA was founded to provide balanced, evidence-based and scientifically sound analyses of recommendations related to COVID-19 with respect to it diagnosis, prevention and treatment. It has over 1700 members across Canada, which includes over 600 research scientists, professors, medical doctors and other health practitioners, and lawyers amongst other professionals. I participated in weekly meetings throughout 2021, 2022 and 2023, Tuesdays 4:00 pm - 5:00 pm – SMAC meetings, Tuesdays 5:00 pm - 8:00 pm – Steering Committee meetings, Wednesdays 5:00 pm - 8:00 pm – General Membership meetings. These meetings are now biweekly.

14. SCIENTIFIC PUBLICATIONS

Total Peer Reviewed in Published in Journals: 200 + 2 submitted
Total Reviews, Book Chapters, Pre-prints Published: 73 + 1 submitted book with 14 authored chapters
Patents Applied and Issued: 3
Websites: 9

i. REFEREED PUBLICATIONS IN PEER-REVIEWED JOURNALS

1. PELECH, S.L., Pritchard, P.H., and Vance, D.E. cAMP analogues inhibit phosphatidylcholine biosynthesis in cultured rat hepatocytes. J. Biol. Chem. 256: 8283-8286 (1981).

2. Pritchard, P.H., PELECH, S.L., and Vance, D.E. Analogues of cAMP inhibit phosphatidylethanolamine N-methylation by cultured rat hepatocytes. Biochim. Biophys. Acta 666: 301-306 (1981).

3. PELECH, S.L. and Vance, D.E. Regulation of rat liver cytosolic CTP:phosphocholine cytidylyltransferase by phosphorylation and dephosphorylation. J. Biol. Chem. 257: 14198-14202 (1982).

4. PELECH, S.L., Pritchard, P.H., and Vance, D.E. Prolonged effects of cyclic AMP analogues on phosphatidylcholine biosynthesis in cultured rat hepatocytes. Biochim. Biophys. Acta 713:260-269 (1982).

5. PELECH, S.L., Pritchard, P.H., Brindley, D.N. & Vance, D.E. Fatty acids promote translocation of CTP:phosphocholine cytidylyltransferase to the endoplasmic reticulum and stimulate rat hepatic phosphatidylcholine synthesis. J. Biol. Chem. 258: 6782-6788 (1983).

6. PELECH, S.L., Jetha, F. & Vance, D.E. Trifluoperazine and other anaesthetics inhibit rat liver CTP: phosphocholine cytidylyltransferase. FEBS Lett. 158: 89-92 (1983).

7. PELECH, S.L., Pritchard, P.H., Brindley, D.N. & Vance, D.E. Fatty acids reverse the cyclic AMP inhibition of triacylglycerol and phosphatidylcholine synthesis in rat hepatocytes. Biochem. J. 216: 129-136 (1983).

8. PELECH, S.L., Power, E. and Vance, D.E. Activities of the phosphatidylcholine biosynthetic enzymes in rat liver during development. Can. J. Biochem. Cell Biol. 61: 1147-1152 (1983).

9. Audubert, F., PELECH, S.L. & Vance, D.E. Fatty acids inhibit N-methylation of phosphatidylethanolamine in rat hepatocytes and liver microsomes. Biochim. Biophys. Acta 792: 348-357 (1984).

10. PELECH, S.L., Pritchard, P.H., Sommerman, E.F., Percival-Smith, A. & Vance, D.E. Glucagon inhibits phosphatidylcholine biosynthesis via the CDP-choline and transmethylation pathways in cultured rat hepatocytes. Can. J. Biochem. Cell Biol. 62: 196-202 (1984).

11. PELECH, S.L., Cook, H.W., Paddon, H.B. & Vance, D.E. Membrane-bound CTP: phosphocholine cytidylyltransferase regulates the rate of phosphatidylcholine synthesis in HeLa cells treated with unsaturated fatty acids. Biochim. Biophys. Acta 795: 433-440 (1984).

12. PELECH, S.L. & Vance, D.E. Trifluoperazine and chlorpromazine inhibit phosphatidylcholine biosynthesis and CTP:phosphocholine cytidylyltransferase in HeLa cells. Biochim. Biophys. Acta 795: 441-446 (1984).

13. PELECH, S.L., Paddon, H.B. & Vance, D.E. Phorbol esters stimulate phosphatidylcholine biosynthesis by translocation of CTP: phosphocholine cytidylyltransferase from cytosol to microsomes. Biochim. Biophys. Acta 795: 447-451 (1984).

14. PELECH, S.L., Cohen, P., Fisher, M.J., Pogson, C.I., El-Maghrabi, M.R. & Pilkis, S.J. The protein phosphates involved in cellular regulation: Glycolysis, gluconeogenesis and aromatic amino acid breakdown in rat liver. Eur. J. Biochem. 145: 39-49 (1984).

15. PELECH, S.L. & Cohen, P. The protein phosphatase involved in cellular regulation: Modulation of protein phosphatases-1 and 2A by histone H1, protamine, polylysine and heparin. Eur. J. Biochem. 148: 245-251 (1985).

16. Tung, H.Y.L., PELECH, S., Fisher, M.J., Pogson, C.I. & Cohen, P. The protein phosphatases involved in cellular regulation: Influence of polyamines on the activities of protein phosphatase-1 and protein phosphatase-2A. Eur. J. Biochem. 149: 305-313 (1985).

17. Alemany, S., PELECH, S., Brierley, C.H. & Cohen, P. The protein phosphatases involved in cellular regulation: Evidence that dephosphorylation of glycogen phosphorylase and glycogen synthase in glycogen and microsomal fractions of rat liver are catalysed by the same enzyme: protein phosphatase-1. Eur. J. Biochem. 156: 101-110 (1986).

18. PELECH, S.L., Ozen, N., Audubert, F. & Vance, D.E. Regulation of rat liver phosphatidylethanolamine N-methyltransferase by cytosolic factors- Examination of a role for reversible protein phosphorylation. Biochem. Cell Biol. 64: 565-574 (1986).

19. PELECH, S.L., Olwin, B.B. & Krebs, E.G. Fibroblast growth factor treatment of Swiss 3T3 cells activates an S6 kinase which phosphorylates a synthetic peptide substrate. Proc. Natl. Acad. Sci. U.S.A. 83:5968-5972 (1986).

20. PELECH, S., Meier, K. & Krebs, E.G. A rapid microassay for protein kinase C translocation in mitogen-treated Swiss 3T3 cells. Biochemistry 25: 8348-8353 (1986).

21. PELECH, S.L. & Krebs, E.G. Mitogen-activated S6 kinase is stimulated via protein kinase C-dependent and independent pathways in Swiss 3T3 cells. J. Biol. Chem. 262:11598-11606 (1987).

22. PELECH, S.L., Meijer, L. & Krebs, E.G. Characterization of maturation-activated histone H1 and ribosomal S6 kinases in sea star oocytes. Biochemistry 26:7960-7968 (1987).

23. Meijer, L., PELECH, S.L. & Krebs, E.G. Differential regulation of histone H1 and ribosomal S6 kinases during sea star oocyte maturation. Biochemistry 26:7968-7974 (1987).

24. Cicirelli, M.F., PELECH, S.L. & Krebs, E.G. Kinase activation during the burst in protein phosphorylation that precedes meiotic cell division in Xenopus oocytes. J. Biol. Chem. 263:2009-2019 (1988).

25. PELECH, S.L., Tombes, R.M., Meijer, L. & Krebs, E.G. Activation of myelin basic protein kinases during echinoderm oocyte maturation and egg fertilization. Devel. Biol. 130:28-36 (1988).

26. Cicirelli, M.F., PELECH, S.L. & Krebs, E.G. Insulin and progesterone activate a common ribosomal protein S6 peptide kinase in Xenopus oocytes. FEBS Lett. 241:195-201 (1988).

27. PELECH, S.L., Paddon, H.B., Kwong, L.C. & Weeks, G. Characterization of developmentally regulated cAMP/Ca2+-independent protein kinases from *Dictyostelium discoideum*. Dev. Growth. Differ. 31:351-361 (1989).

28. Duronio, V., & PELECH, S.L. Interleukin 3 stimulates the turnover of phosphatidylcholine in the mast cell/megakaryocyte line R6-XE.4. Biochem. Biophys. Res. Commun. 164:804-808 (1989).

29. Sanghera, J.S., Paddon, H.B., Bader, S.A., & PELECH, S.L. Purification and characterization of a maturation-activated myelin basic protein kinase from sea star oocytes. J. Biol. Chem. 265, 52-57 (1990).

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33. Salari, H., Duronio, V., Howard, S., Demos, M, & PELECH, S. L. Translocation-independent activation of protein kinase C by platelet activating factor, thrombin and prostacyclin. Biochem. J. 267:689-696 (1990).

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38. PELECH, S. L., Samiei, M., Charest, D. L., Howard, S. L., & Salari, H. Production of calcium-independent forms of protein kinase C-in phorbol ester-treated rabbit platelets. J. Biol. Chem. 266:8696-8705 (1991).

39. Daya-Makin, M., PELECH, S. L., Levitzki, A., & Hudson, A. T. Erbstatin and tyrophostins block protein-serine kinase activation and meiotic maturation of sea star oocytes. Biochim. Biophys. Acta 1093:87-94 (1991).

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41. Chung, J., PELECH, S. L., & Blenis, J. Mitogen-activated Swiss mouse 3T3 rsk kinases I and II are related to pp44mpk from sea star oocytes and particpate in the regulation of p90rsk activity. Proc. Natl. Acad. Sci. U.S.A. 88:4981-4985 (1991).

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44. Sanghera, J. S., McNabb, C., Tonks, N., & PELECH, S. L. Tyrosyl phosphorylation and activation of the myelin basic protein kinase p44mpk during sea star oocyte maturation. Biochim. Biophys. Acta 1095:153-160 (1991).

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46. Mukhopadhyay, N. K., Price, D. J., Kyriakis, J. M., PELECH, S., Sanghera, J. S., & Avruch, J. An array of insulin-activated, proline-directed serine/threonine protein kinases phosphorylate the p70 S6 kinase. J. Biol. Chem. 267:3325-3335 (1992).

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50. Daya-Makin, M., Szankasi, P., Tang, MacRae, D., & PELECH, S. L. Regulation of p105wee1 and p34cdc2 during meiosis in Schizosaccharomyces pombe. Biochem. Cell. Biol. 70:1088-1096 (1992).

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vi. WEBSITES

In the last few years, I have begun to develop on-line, open-access databases and knowledgebases with comprehensive information on proteins, their mRNA and protein expression as well as their phosphorylation. While many people have been involved in the coding of the interfaces for these websites, I have personally devoted much of my time into their conception, design, data annotation, data inspection and coordinating their production. The following is a listing of these websites.

1. KiNET-IB – Kinetworks™ Immunoblotting DataBase (www.kinet.ca)
   First in 2006, KiNET-IB features over 200,000 measurements of the expression and phosphorylation states of hundreds of signal transduction proteins from over 6000 Kinetworks™ multi-immunoblots performed with control and treated tissue/cell samples. Immunoblotting remains the gold standard for protein quantification and the Kinetworks™ methodology was originally developed in my UBC lab. KiNET-IB is a useful tool for evaluating proteins that may

participate in the control of diverse cellular processes and their connection with other proteins in signaling pathways. Over 95% of this data has been previously unpublished.

2. KiNET-AM – Kinex™ Antibody Microarray DataBase (www.kinet-am.ca)

   First launched in 2011, KiNET-AM features the quantitative results from nearly 2000 Kinex™ Antibody Microarray analyses with over 1.5 million measurements of 650 to 800 hundred different signalling proteins and phosphosites tracked per microarray. The data can be queried based on biological samples, treatments, specific proteins and phosphosites. Over 98% of this data has not been previously unpublished and was produced from analyses performed at Kinexus.

3. PhosphoNET – Human Phosphorylation Site KnowledgeBase (www.phosphonet.ca)
   First launched in 2010, PhosphoNET is the world's largest repository of known and predicted information on human phosphorylation sites, their evolutionary conservation and the identities of protein kinases that may target these sites. PhosphoNET presently holds data on over 970,000 known and putative phosphorylation sites (P-sites) in over 20,000 human proteins that have been collected from the scientific literature and other reputable websites. Over 177,000 of these phosphosites have been experimentally validated. The rest have been predicted with a novel Phosphosite Predictor algorithm developed at Kinexus. With the PhosphoNET Evolution module, this website also provides information about cognate proteins in over 20 other species that may share these human phospho-sites. This helps to define the most functionally important phosphosites as these are expected to be highly conserved in nature. With the Kinase Predictor module, listings are provided for the top 50 human protein kinases that are likely to phosphorylate each of these phospho-sites using another proprietary kinase substrate prediction algorithm that I helped to develop at Kinexus. With the Phosphosite Match module added in 2017, it is possible to identify phosphosites that are highly related in amino acid sequence. This helps to identity phosphosites that may be detected in cross-reactive off target proteins with phosphosite-specific antibodies. Over 8 million kinase-substrate phospho-site pairs are quantified in PhosphoNET, and over 200 signalling pathway maps are available.

4. TranscriptoNET – Human mRNA Expression KnowledgeBase (http://207.150.202.175)
   First launched in 2011, TranscriptoNET features comprehensive information on the mRNA expression levels of about 21,000 genes in about 600 types of human organs, tissues and cells as measured with gene microarrays. The original data used in TranscriptoNET was retrieved from the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO), which serves as a repository of experimental gene microarray results submitted by diverse academic and industrial laboratories around the world. We normalized the data from over 900 different studies with over 6000 biological specimens to permit investigations of gene expression and potential interactions that can only be undertaken with such a large dataset of over 125 million gene expression measurements. This normalization process was based on the identification of 60 genes that were commonly and highly expressed in all of the biological samples. This site was first posted in 2013.

5. DrugKiNET – Human Kinase Drug Interaction KnowledgeBase (www.drugkinet.ca)
   First launched in 2013, DrugKiNET is an open-access, online resource to foster the identification and characterization of inhibitors of protein kinases for academic and industrial research. It features comprehensive information on over 850 compounds that have been experimentally determined to inhibit human protein kinases. This includes the retrieval of the lowest reported compound IC50, Ki and Kd values from several sources, including the National Center for Biotechnology Information (NCBI) PubChem Compound database, the Kinase SARfari database

from the European Molecular Biology Laboratory (EMBL) European Bioinformatics Institute, The International Centre for Kinase Profiling at the University of Dundee, Ambit Biosciences and hundreds of original research publications. In some cases, estimates for IC50 values were derived from limited measurements of kinase inhibition at only one to three different concentrations of the compounds. Using over 105,000 experimentally tested, non-redundant kinase-compound pairs for training, we have developed two kinase inhibitor prediction algorithms to further predict another 200,000 kinase-compound interactions. In 2017, we added a new module to DrugKiNET that provides information on the bond distances between the atoms of over 1500 drugs and the atoms in protein kinases as determined from their x-ray crystallographic structures.

6. OncoNET – Human Cancer Protein KnowledgeBase (www.onconet.ca)
This website features comprehensive information on the mutations and mRNA expression levels for about 3,000 genes in diverse types of human cancers. The mRNA expression data used in OncoNET was originally retrieved from the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO), which serves as a repository of experimental gene microarray results submitted by diverse academic and industrial laboratories around the world. We normalized the data from hundreds of different gene microarray studies using a normalization protocol based on the identification of 60 genes that were commonly and highly expressed in all of the biological samples. To explore the mutation of human cancer-related genes, we relied primarily on the collection of data from the Wellcome Trust Sanger Institute's Catalogue of Somatic Mutations in Cancer (COSMIC) database. Further information on these genes and their encoded proteins was annotated from several other sources, including UniProt and the Atlas of Genetics and Cytogenetics in Oncology and Haematology websites. I have used this database to identify new potential oncogenes, tumour suppressor genes and tumour requiring protein genes. This site was first posted in 2013.

7. KinaseNET – Human Protein Kinase KnowledgeBase (www.kinasenet.ca)
KinaseNET features comprehensive information on 536 human protein kinases, including their primary and tertiary structure, regulation, distribution, evolutionary conservation, protein substrate targets, pathway maps, sensitivities to compounds and linkages to human diseases. Each protein kinase is represented with a separate webpage. KinaseNET also serves as a portal to many other useful websites with additional data about protein kinases. This site was first posted in 2015 and updated in 2017.

8. Kinetica Online – E-journal for Intelligence Systems Research (www.kinexus.ca/kinetica)
This website has not yet been officially launched, but a beta-version is available for viewing since 2013. This unique resource features commentaries, original research publications, databases and knowledgebases, and it also serve as portal to hundreds of other websites that should be useful to researchers engaged in the investigation of cell signalling. All of the articles in Kinetica Online have been published elsewhere.

9. KinATLAS – Human Protein Interaction Altas
(http://kinatlas.ca:8080/KinAtlas/KinaseDrugQuery.html)
This website is in development and a beta version with the first (Kinase-drug interactions) and second modules (Protein-protein interactions) are available for viewing since 2016. The underlying database is complete, and the web interface is still in the process of being coded for the third module (Kinase-substrate interactions). It will show tissue/cell-specific maps of protein-protein and kinase-drug interactions. The kinase-substrate interactions are prioritized using our updated

kinase prediction algorithms, and the viewer will contain filters to permit generation of more customized maps.

10. DrugProNET – Human Protein – Drug Interaction KnowledgeBase (www.drugpronet.ca)
This website provides for the identification of the most critical atomic interactions between drugs and their protein targets based on 3D x-ray crystallographic analyses. Defining the key amino acid residues for drug binding in proteins permits the prediction of specific mutations in human genomes that will affect the sensitivities of individuals to these compounds. The bond distances in Angstroms between the closest protein and drug atoms in each crystal complex are provided in downloadable tables, along with definition of the closest amino acid residue side-chains. The single nucleotide variants (SNV's) that would affect these critical amino acid residues involved in drug interactions are also identified in DrugProNET. This website features comprehensive information on over 2000 compounds that have been co-crystallized with over 480 different human proteins in over 4400 protein-compound structures retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Databank (PDB).

11. KiNector – Human Protein Kinase-Protein Substrate+Phosphosite Interaction KnowledgeBase (www.kinector.ca)
Over 21,450 human kinase-substrate relationships (KSRs) were retrieved from several sources, including the PhosphoNET, PhosphoSitePlus and PhosphoNetworks websites and the scientific literature. The data are presented in a graphic format as maps, and full functional information was provided for at least 6000 of these KSRs. KiNector shows both direct and indirect linkages between a starting protein kinase and a phosphoprotein target that acts downstream in signalling pathways. KiNector also serves as a portal to other reputable websites that contain detailed information on these kinases and substrates, and provides direct links to the Kinexus Products website, which features over 3500 images of full Western blots performed with lysates from diverse rodent tissue panels and human cancer cell lines.

vii. ARTISTIC WORKS

1. Smith, J., Xu, Y., and PELECH, S.L. Human protein kineome. (2006) [This is a large wall chart that contains the identification of all of the known domains and phosphorylation sites in 515 human protein kinases. It was printed and distributed by Kinexus Bioinformatics Corporation.]

2. PELECH, S.L. and Bowyer, C. The human operating system. (2008) [This is a large wall chart that features over 180 cell signalling pathways. It was printed and distributed by Kinexus Bioinformatics Corporation.]

4. PELECH, S.L, Smith, J., and Xu, Y. Human protein kineome. (2010) [This is an updated, large wall chart that contains the identification of all of the known domains sites in 515 human protein kinases, along with Uniprot, size and substrate specificity information. It was printed and distributed by Kinexus Bioinformatics Corporation.]

5. PELECH, S. L. Human Cancer Protein Interaction Network. (2017). This is a wall chart that shows how over 100 of the most frequently mutated oncoproteins and tumour suppressor proteins interact with each other. It was presented and distributed at the 2017 American Association for

Cancer Research Meeting and is downloadable from the Kinexus website (http://www.kinexus.ca/pdf/OncoNET_Poster.pdf).

viii. BLOG COMMENTARIES

Over the last decade, I have written commentaries on over 300 blogs as part of an outreach effort to inform the broader scientific community on a wide range of issues ranging from career development to genomics to biotechnology. I have only listed those commentaries that appeared primarily at the GenomeWeb website. Unfortunately, these, like all previous commentaries, are no longer accessible at the GenomeWeb site, but mine can be viewed at www.kineticaonline.ca in the Blog Comments section.

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ix. MEDIA INTERVIEWS

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Charles Hoffe, Francis Christian, Mark Trozzi, Paul Alexander and Stephen Malthouse. https://www.bitchute.com/video/f0do2DOXG4x9/

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31. Dr. Steven Pelech – What you should know about the vaccine. An interview with BC radio personality Kid Carson (2/9/2022). https://www.kidcarson.com/71-dr-steven-pelech-what-you-should-know-about-the-vaccine/

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33. Prevalence of natural and COVID-19 vaccine induced immunity: What does SARS-CoV-2 antibody testing show? Conference on Idaho Victims of Pandemic Policy and Law. (26/9/2022). This was covered Epoch times, Stew Peters, gateway pundit, Dr. Paul Alexander substack. https://www.theepochtimes.com/victims-of-pandemic-policy-law_4753445.html https://rumble.com/v1llpah-live-hearing-vaccine-injured-speak-out-stew-peters-and-vaxx-injured-testify.html

34. Natural immunity … Science or science fiction? Part 1 and Part 2. White Rock, B.C. White Rock SDA Church (1/10/2022). https://livestream.com/whiterocksdachurch/events/9259494/videos/233136255

35. Jessica Rose, Ph.D. and Steven Pelech, Ph.D. – Antibody deception. Jessica's Universe - CHD-TV (28/10/2022). http://www.rumble.com/v1qbrwd-good-morning-chd-episode-165-antibody-deception-with-steven-pelech-ph.d.html?mref=6zof&mrefc=2

36. Jessica Rose, Steven Pelech and Bernadette Pajer – It's all about the spike - CHD-TV (1/11/2022). https://live.childrenshealthdefense.org/chd-tv/shows/an-informed-life-radio-with-bernadette-pajer/its-all-about-that-spike-with-jessica-rose-phd--steven-pelech-phd/

37. Steven Pelech and Nathan Barrett – Accountability…Class action certification hearings. (28/11/2022). https://www.instagram.com/reel/ClnZRN9LZn2/?igshid=OTRmMjhlYjM%3D

38. Live with Steven Pelech and Laura-Lynn Tyler-Thompson (13/1/2023). https://www.lauralynn.tv/2023/01/live-with-dr-steven-pelech.html

39. The crumbling case for COVID-19 vaccination. White Rock, B.C. White Rock SDA Church (4/2/2023). https://livestream.com/whiterocksdachurch/events/9259494/videos/234894719

40. Rebel News interview of Dr. Pelech by Tamara Ugolini. (8/3/2023). https://www.canadiancovidcarealliance.org/all/rebel-news-interview-of-dr-pelech/

41. Dr. Steven Pelech and Controversial Topics. Interview with Maryann Pousette Gebauer as part of the MaryAnn and the Professor series (4/8/2023). https://www.bitchute.com/video/qlPJGDIn1Pfe/.

42. The COVID-19 Pandemic…What Really Happened. Testimony at the National Citizen's Inquiry in Canada's COVID-19 Response (5/3/2023). https://rumble.com/v2m3z3s-ubc-professor-dr-steven-pelech-gives-presentation-on-the-virus-and-vaccine-.html

42. Canadian doctors testify. Good Morning CHD. Episode 121. Live interview with Drs. Christopher Shaw, Charles Hoffe and Stephen Malthouse. (5/12/2023). https://live.childrenshealthdefense.org/chd-tv/shows/good-morning-chd/canadian-doctors-testify/

43. The power of natural immunity, Bill 36 & Dr. Bonnie Henry's April 6 Public Health Order with mandatory COVID-19 vaccination of all BC health care workers. Live with Steven Pelech and Laura-Lynn Tyler-Thompson (12/6/2023). https://rumble.com/v2tsvtw-live-with-dr.-steven-pelech.html

44. The Real Science: Dr. Steven Pelech. Will Dove Interview. Iron Will Report. (15/6/2023) https://ironwillreport.com/interviews/paged-2/7/

45. Natural and COVID-19 vaccine induced immunity. Canadian Covid Care Alliance Roundtable presentation. (9/8/2023)

46. Organ transplant denied, Dr. Pelech on the death of Sheila Lewis. Interview with Anita Krishna (30/8/2023). https://rumble.com/v3e00ye-organ-transplant-denied-dr.-pelech-on-the-death-of-sheila-lewis..html

x. TRAINING VIDEOS

1. Kinex KAM-850 Antibody Microarray Kit Components – Directed, scripted and designed by Steven Pelech. Starring Catherine Sutter. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=JtMn-Gk0q_4&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k&index=1
2. Stage 1: Preparation of Lysates from Cultured Cells for Proteomics Analyses – Directed, scripted and designed by Steven Pelech. Starring Dominik Sommerfeld. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=0_YdxuOdGhU&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k&index=2

3. Stage 2: Measurement of Protein Concentrations with the Bradford Protein Assay. Directed, scripted and designed by Steven Pelech. Starring Shenshen Lai. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=TAMrj0Z9FOk&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k&index=3
4. Stage 3: Dye Labelling Cell and Tissue Lysates for the Kinex™ KAM Antibody Microarray. Directed, scripted and designed by Steven Pelech. Starring Jane Shi. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=3sMaRnAC7-4&index=4&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k
5. Stage 4: Incubation of the Kinex™ KAM Antibody Microarray with Dye-Labelled Lysate Protein. Directed and designed by Steven Pelech, and scripted and designed by Hong Zhang and Steven Pelech. Starring Jane Shi. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=LcuQ-1CYJrw&list=PL15H9uvi7IpGvnpoYaSr62CeBHFgzO28k&index=5
6. Stage 5: Kinex™ KAM Antibody Microarray Scanning and Quantitation. Directed, scripted and designed by Steven Pelech. Starring Jane Shi and Winnie So. Narrated by Catherine Sutter. Filmed and edited by Keefer Pelech. Title and credit animations by Cameron Bowyer. Music by William Campbell. Produced by Kinexus Bioinformatics. Posted on You-tube on Jan 25, 2014. https://www.youtube.com/watch?v=wBf0t4xhV5g

xi. EXPERT REPORTS FOR COURT CASES

Over the three years, I have been asked to prepare, expert reports with respect to natural immunity and COVID-19 vaccines for several court and arbitration cases in Canada, South Africa and Ireland. These are usually sworn and notarized documents, and in several cases I have undergone cross-examination in Canadian courts. This is a listing of many of the court cases that I have served in.

1.	COURT FILE NUMBER	210600780
	COURT	COURT OF QUEEN'S BENCH OF ALBERTA
	JUDICIAL CENTRE	LETHBRIDGE
	APPLICANT	HAYLEY NASSICHUK-DEAN
	RESPONDENT	UNIVERSITY OF LETHBRIDGE Cross-examination Feb. 16, 2022
2.	COURT FILE NUMBER	T-1694-21
	COURT	FEDERAL COURT OF CANADA (Trial Division)
	APPLICANT	DAVID LAVERGNE-POITRAS
	RESPONDENTS	ATTORNEY GENERAL OF CANADA (Minister of Public Services and Procurement) – and – PMG TECHNOLOGIES INC. Cross-examination September 8, 2022

3.	COURT FILE NUMBER	T-168-22-ID-1
	COURT	FEDERAL COURT OF CANADA
	APPLICANT	THE HONOURABLE A. BRIAN PECKFORD, LEESHA NIKKANEN, KEN BAIGENT, DREW BELOBABA, NATALIE GRCIC, AND AEDAN MACDONALD
	RESPONDENTS	THE MINISTER OF TRANSPORT and THE ATTORNEY GENERAL OF CANADA Cross-examination May 13 and 16, 2022
4.	COURT FILE NUMBER	2101-13202
	COURT	COURT OF QUEEN'S BENCH OF ALBERTA
	JUDICIAL CENTRE	CALGARY
	APPLICANTS	DR. ERIC T. PAYNE, DR. JOANNE J. MOSER, DR. DAVID W. L. LOEWEN and DR. GREGORY CHAN
	RESPONDENTS	ALBERTA HEALTH SERVICES, DR. VERNA YIU IN HER CAPACITY AS CHIEF EXECUTIVE OFFICER OF ALBERTA HEALTH SERVICES, DR. JOHN T. CHMELICEK IN HIS CAPACITY AS POST GRADUATE PROGRAM DIRECTOR, DEPARTMENT OF FAMILY MEDICINE, UNIVERSITY OF ALBERTA -and- THE UNIVERSITY OF ALBERTA
5.	COURT FILE NUMBER	CV-21-00670360-0000
	COURT	SUPERIOR COURT OF JUSTICE ONTARIO
	APPLICANTS	SARAH HARJEE, EVAN KRAAYENBRINK, HIBAH AOUN, SARAH LAMB, SAM SABOURIN, JACKIE RAMNAUTH, MARK MCDONOUGH -and- LINDA MCDONOUGH
	RESPONDENT	HER MAJESTY THE QUEEN IN RIGHT OF THE PROVINCE OF ONTARIO Cross-examination April 28 & May 5, 2022
6.	COURT FILE NUMBER	FDF-443-19
	COURT	COURT OF QUEEN'S BENCH OF NEW BRUNSWICK
	JUDICIAL CENTRE	FAMILY DIVISION JUDICIAL DISTRICT OF FREDERICTON
	APPLICANT	VICTORIA LYNN MITHAM
	RESPONDENT	BRADLEY SCOTT FOLLETT

7.	COURT FILE NUMBER	72/2022
	COURT	HIGH COURT OF SOUTH AFRICA
	JUDICIAL CENTRE	FREE STATE DIVISION, HELD AT BLOEMFONTEIN
	APPLICANT	SOLIDARITY obo MEMBERS, SOLIDARITY YOUTH Obo MEMBERS, JOANNA STANDER, SHANIQUE PIENAAR, ALICE FLORENCE MARINA STANDER - and - ANNELI BOTHA
	RESPONDENTS	CHAIRMAN OF THE COUNCIL OF THE UNIVERSITY OF THE FREE STATE– and – THE UNIVERSITY OF THE FREE STATE
8.	COURT FILE NUMBER	C.A.C.V.3903of202 C.A.C.V.3904of2021 C.A.C.V.3908of2021
	COURT	COURT OF APPEAL FOR SASKATCHEWAN ON APPEAL FROM THE QUEEN'S BENCH (FAMILY LAW DIVISION)
	JUDICIAL CENTRE	JUDICIAL CENTRE OF SASKATOON DIV. No. 625 of 2012
	APPLICANT	OLENA MYKOLAYIVNA SCHEMENAUER
	RESPONDENT	EVAN JOSEPH SCHEMENAUER
9.	COURT FILE NUMBER	FD 19-01-22922
	COURT	COURT OF QUEEN'S BENCH (Family Division)
	JUDICIAL CENTRE	WINNIPEG CENTRE
	APPLICANT	JORDAN SARAH CURÉ
	RESPONDENT	KENNETH PETER TYSON CURÉ
10.	COURT FILE NUMBER	E59176
	COURT	SUPREME COURT OF BRITISH COLUMBIA
	JUDICIAL CENTRE	NEW WESTMINISTER
	APPLICANT	VICTORIA LARA DRAPER AKA VICTORIA LARA DRAPER-SMITH
	RESPONDENT	MATTHEW LAWRENCE NEALE SMITH
11.	COURT FILE NUMBER	E17315
	COURT	SUPREME COURT OF BRITISH COLUMBIA
	JUDICIAL CENTRE	CHILLIWACK REGISTRY
	APPLICANT	DALE JAMES HOOGENDOORN
	RESPONDENT	KATIE NADINE HOOGENDOORN Testimony Feb. 17, 2022.
12.	COURT FILE NUMBER	FC-13-917-02
	COURT	SUPERIOR COURT OF JUSTICE FAMILY COURT BRANCH
	JUDICIAL CENTRE	OSHAWA REGISTRY
	APPLICANT	KAREN DIAZ (BOL)
	RESPONDENT	BRENT BOL

13.	COURT FILE NUMBER	2022/1456 P
	COURT	HIGH COURT OF IRELAND
	APPLICANTS	DAVID EGAN AND SHARON BROWNE AND EMMANUEL LAVERY
	RESPONDENTS	MINISTER FOR HEALTH, AN TAOISEACH, AND HSE
14.	ARBITRATION	
	EMPLOYER	HUMBER RIVER HOSPITAL
	UNION	NATIONAL ORGANIZED WORKERS UNION Grievances: NOWU Policy Service #170,2021 (All Bargaining Units) Covid Directive 6, NOWU Policy Service #01,2022 (All Bargaining Units) Covid Policy, 2022-NOWU-Clerical-55-HRH; Grievance of Gail Ackie Cross-examination Feb. 20, 22 & 29, 2023
15.	COURT FILE NUMBER	No. S2110229
	COURT	SUPREME COURT OF BRITISH COLUMBIA
	JUDICIAL CENTRE	NEW WESTMINISTER
	APPLICANTS	CANADIAN SOCIETY FOR THE ADVANCEMENT OF SCIENCE IN PUBLIC POLICY and KIPLING WARNER
	RESPONDENT	DR. BONNIE HENRY IN HER CAPACITY AS PROVINCIAL HEALTH OFFICER FOR THE PROVINCE OF BRITISH COLUMBIA
16.	COURT	ONTARIO
	APPLICANT	VALERIE ALAGNA
	RESPONDENT	HAMILTON HEALTH SCIENCES CORPORATION
17.	DISCIPLINARY HEARING	
	CASE	2021-AF-01136
	COLLEGE	COLLEGE OF NURSES OF ONTARIO
	DEFENDENT	SARAH A. CHOUJOUNIAN-ABULU Cross-examination April 13 & 14, May 19, June 9 & 30, July 8, 2023
18.	DISCIPLINARY HEARING	
	COLLEGE	BC COLLEGE OF NURSES AND MIDWIVES
	DEFENDENT	SEAN TAYLOR Cross-examination July 19 & 20, 2023
19.	DISCIPLINARY HEARING	
	CASE	CPSID 17223; IC2021-0481; IC2021-0535
	COLLEGE	COLLEGE OF PHYSICIANS AND SURGEONS OF BC
	DEFENDENT	DR. CHARLES HOFFE
20.	COURT FILE NUMBER	CV-22-0069-1880-0000
	COURT	ONTARIO SUPERIOR COURT OF JUSTICE
	APPLICANT	DR. BYRAM BRIDLE

	RESPONDENTS	UNIVERSITY OF GUELPH, JEFFREY WICHTEL, LAURIE ARNOTT, CHARLOTTE YATES, SCOTT WEESE, GLEN PYLE, ANDREW PEREGRINE, DOROTHEE BIENZLE, AMY GREER, DAVID FISMAN, NICK DULEY, JANE OR JOHN DOE JUNIOR SCIENTIST
21.	COURT	COURT OF KING'S BENCH ALBERTA
	JUDICIAL CENTRE	GRANDE PRAIRIE
	APPLICANT	ANNETTE LEWIS
	RESPONDENTS	ALBERTA HEALTH SERVICES AND REDACTED PARTIES
22.	DISCIPLINARY HEARING	
	CASE	24-20220001146; 30-21-3125
	PLANTIFF	GILLES MARION, syndic ad hoc COLLÈGE DES MÉDECINS DU QUÉBEC
	DEFENDENT	DR. MARC LACROIX
23.	COURT FILE NUMBER	SCBC Action E222370
	COURT	SUPREME COURT OF BRITISH COLUMBIA
	JUDICIAL CENTRE	VANCOUVER REGISTRY
	APPLICANT	TRICIA MARIE BARR ALLARD
	RESPONDENT	PATRICK JAMES ALLARD
24.	DISCIPLINARY INVESTIGATION	
	CASE	IC 2022-0489
	COLLEGE	COLLEGE OF PHYSICIANS AND SURGEONS OF BC
	DEFENDENT	DR. SOFIA T. BAYFIELD

This is Exhibit “B” referred to in the
Expert Report of Steven Pelech

Letter from Mr. Lee Turner

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Our File: 138084-1
December 17, 2023

By E-mail spelech@shaw.ca

Dr. Steven Pelech

Attention: Dr. Pelech

Dear Dr. Pelech:

Re: Our Client: Dr. Charles Hoffe
Citation Issued by the College of Physicians and Surgeons of British Columbia, Canada
Virtual Disciplinary Hearing March 4-18, 2024

As discussed, we are legal counsel for Dr. Charles Hoffe with respect to a citation that has been issued against him by the College of Physicians and Surgeons of British Columbia, Canada (the "College"). We confirm that we want to engage you to obtain your independent professional opinion concerning:

1. the effectiveness of natural immunity versus vaccine immunity for Covid 19 ;

2. if there were any differences between the methods used to manufacture Covid 19 vaccines used in the clinical trials, and those that were distributed to the public, and the significance of same;

3. the presence of, and significance of, DNA plasmid contamination, including SV40, and endotoxins;

4. what the statistics, data and literature say about the prevalence of adverse reactions to the covid-19 vaccines;

5. the efficacy of the Covid 19 vaccines;

6. whether or not the Covid 19 vaccines are or were asked experimental at the time they were distributed to the public, and the basis for your conclusions; and

7. safety of the vaccines in adults and children.

We also would like you to comment on the opinion expressed by the "expert", Dr. Trevor Corneil, relied upon by the College concerning these issues in his report dated September 26, 2022, specifically in sections 5.3-5.7, 6.1, 6.8, and 6.9 which are referenced in the index on page 2 of his report.

We enclose a copy of the following information for your review:

1. Dr. Corneil's report dated September 26, 2022;

2. Further Amended Citation to Appear dated July 19, 2023 (the "Citation");

3. Correspondence dated July 28, 2022 from Ng Ariss Fong, Lawyers on behalf of the College, providing further particulars pertaining to the Citation (the "Particulars");

Please refer to the paragraph a, b, f, j, and h. of the Particulars to see what the College and our government officials have had to say about these issues.

Please carefully read the instructions below regarding the preparation of your report.

When you write your report, please remember that you are essentially taking on the role of a teacher in the area of your expertise. While the details of your analysis and opinion are important, what is equally, if not more important, is what those details mean. The reader of your report will include members of the panel of the disciplinary committee, College counsel, and other experts who may be informed by your opinion and analysis. They need to understand your opinion and the basis for it. If you must use technical terms from your area of speciality, please also define them as simply as possible in words that everyone will understand. If you can use diagrams, photographs, video, models or other demonstrative aids to help the reader understand your report, we encourage you to do so.

We ask that you set out in your report the following information:

1. your name, address and area of expertise (you may attach a CV as an appendix to your report);

2. your qualifications and employment and educational experience in your area of expertise;

3. the instructions we have provided to you in relation to the proceeding (for which you can reference and attach a copy of this letter to your report if you wish);

4. the nature of the opinion being sought and the issues in the proceeding to which the opinion relates;

5. your opinion respecting those issues;

6. your reasons for your opinion, including

   (a) a description of the factual assumptions on which your opinion is based,

   (b) a description of any research conducted by you that led you to form your opinion, and

   (c) a list of every document, if any, relied on by you in forming your opinion.

In your report, please also certify that you:

- are aware of your duty to assist the panel;

- are not an advocate for any party;
- have prepared your report in conformity with your duty and
- will, if called upon to give oral or written testimony, give that testimony in conformity with your duty.

Including the foregoing information in your report allows us to file your report in evidence at the hearing.

Please retain all notes and file contents pertaining to the provision of your opinion, whether digital or written, as these may be required to be made available for production to counsel at or before the hearing.

It is very important that the body of your report contains a list of **all** of the facts and assumptions which you have relied upon in arriving at your opinion, **and only** those facts and assumptions. It is important that the facts known or assumed are immediately apparent when reading your report. You are encouraged experts to use headings, and numbered paragraphs to simplify and streamline your report.

With respect to any records that you review, you can set out a list of the records you reviewed in an appendix, but you need not summarize those records in the appendix. If however, you have relied upon facts set out in the records that you have reviewed, those facts should be clearly set out in the body of your report, rather than in an appendix. If you present your report in terms of specifying the facts that you rely on, including the specific entry in the record where that fact is contained, it will be easier for the panel to understand the foundation for your opinion and for us to ensure that the necessary facts are proven that are essential to support your opinion.

If you think it would be helpful to include a glossary of scientific or technical terms in an appendix, this can be of assistance to the panel.

As for other medical legal reports you review, like Dr. Corneil's report, it is important that you state any opinions you may agree or disagree with, together with your reasons for doing so.

Your opinion, and the reasons for your opinion, should be expressed in the simplest of terms, bearing in mind that the challenge an expert witness faces is to make their evidence easily understood.

You should refrain from offering opinion on any area outside of your qualifications and area of expertise.

It is helpful for you to use headings, page numbers and paragraph numbers in the format of your report for ease of reference to specific portions of your report. While it is preferred that your report be concise, the Courts have indicated that if a lengthy report is required, including an index for your report would be appreciated.

If you have any questions or concerns about the form or structure of your report as outlined above, please do not hesitate to call the writer.

If you have any questions about what is required, please do not hesitate to contact the writer.

We would appreciate receiving your report on or before January 5, 2024 if at all possible so we can ensure that it can be served on opposing counsel in accordance with the disclosure timelines.

Thank you for your assistance, and we look forward to hearing from you.

Yours truly,

DOAK SHIRREFF LAWYERS LLP

Per: 

Lee C. Turner
(Professional Law Corporation)

LCT/lct
Enclosures

cc: Client

This is Exhibit “C” referred to in the
Expert Report of Steven Pelech

Introduction to Basic Concepts in Molecular Biology, Virology, Immunology, Vaccine and Drug Development

Prepared by Dr. Steven Pelech, Ph.D.

Table of Contents

Chapter 1:

Agents and Transmission of Infectious Diseases

1.1. Deaths from Infectious and Other Diseases in Canada

While infectious diseases have taken a significant toll in Canada, they are not the major causes of morbidity and mortality in Canada. From 2001 to 2016, infectious diseases accounted for 1.4 to 1.6 deaths per 100,000 Canadians annually, which increased to about 2.4 deaths per 100,000 in 2019. In 2020, the first official year of the COVID-19 pandemic and in the absence of any suitable vaccines for SARS-CoV-2, this number remained unchanged from 2019.[1]

With a population of around 38 million at the time, the total number of deaths from all causes in Canada was 285,270 in 2019, and 307,205 in 2020.[2] Infectious diseases accounted for only 8.6% of these deaths in 2019 and 12.6% of deaths in 2020, whereas cancer and cardiovascular diseases (including strokes) accounted for 27.0% and 23.2% of all deaths in Canada, respectively. In 2020, the total number of deaths with COVID-19 was 16,151 (of which about half was due to a co-morbidity or contributing medical conditions), which accounted for 5.25% of all deaths.[2] Most of these COVID-19 deaths were ultimately from (secondary and) terminal bacterial pneumonia and could likely have been better averted by treatment with antibiotics.

In some of the Canadian provinces such as British Columbia, Alberta and Ontario, daily deaths by illicit drug overdose approached or surpassed those from COVID-19 during the pandemic. Presently, drug overdose is the leading cause of death in these provinces for those under 60 years of age. Since the onset of COVID-19, the rate of accidental apparent opioid toxicity deaths has doubled from pre-COVID-19 rates, worsening the opioid crisis that first started significantly rising in 2016.[3] The vast majority of these deaths were from fentanyl overdoses, and usually in those in the 20- to 59-year-old age bracket. Since most COVID-19 deaths in Canada and elsewhere in the last 4 years have been in the very elderly, drug overdose has resulted in more years of life lost than COVID-19.

1.2. Infectious Diseases Caused by Bacteria and Viruses

Infectious diseases are caused by pathogens that replicate in living organisms or cells. Such pathogens include helminths (parasitic worms), protozoa, fungi, bacteria, viruses, and even proteins like the prion proteins that cause mad cow disease, scrapie in sheep and Creutzfeldt-Jakob disease in humans. These pathogens are unable to reproduce and spread without the assistance of a host. Large parasites and bacteria flourish in the gut, blood stream, skin, or in certain organs of a host. In fact, most successful parasites are benign to their hosts and do not induce disease. One of the most successful drugs for treating parasitic infections is ivermectin, which has also been demonstrated to be very promising in the treatment of COVID-19.

In humans, over a thousand, different species of bacteria can co-exist with each other and with the body, especially in the intestines, and constitute what is known as the resident flora or microbiota. In total, some 40 trillion bacteria co-exist with the approximately 50 trillion human cells in an adult human body.[4] A thriving gut flora helps maintain body weight,[5] and reduces the risk of inflammatory bowel disease such as ulcerative colitis.[6] These bacteria aid in digestion, produce vitamin K, and help fight off pathogenic bacteria that can cause disease. There are only around a hundred different bacterial species that are known to be pathogenic to humans, despite the existence of over ten thousand documented bacterial species and more likely tens of millions of bacterial species on the planet.[7]

There are some 200 species of viruses that are known to cause disease in humans,[8] even though about 300,000 species of viruses have been suggested to infect mammals.[9] There are viruses, called bacteriophages, which infect bacteria. There are even viruses, called virophages, which are genetic parasites of giant viruses.[10] The total number of viruses that reside in a healthy human body has been estimated to be close to 380 trillion, the vast majority of which simply co-exist without causing disease.[11] Some of these are integrated into the human genome as proviruses or endogenous viral elements.[12] Every person appears to have a unique virome and microbiome.

The reason why so few viruses or bacteria can infect and cause disease in humans and other species is because they must co-evolve with those or highly related species. To enter a host cell, viruses and bacteria need to have evolved proteins on their surfaces that can tightly bind to specific proteins

or sugars that are on the surface of the host's cells. Then they must traverse through the cell's outer membrane known as the plasma membrane, which is a lipid (fat) and protein barrier to keep the contents of the host cell in and the undesirable substances and microbes out. Once inside a cell, a virus must hijack the cell's biosynthetic enzymes to produce proteins, nucleic acids, sugars and lipids that are the building blocks for forming new, infectious viral particles. This requires precision production of viral proteins that can efficiently interact with and hijack the cell's own enzymes. It might take thousands of years before a virus can evolve to infect a new host species, but the process can be much faster if the virus has already been adapted to a highly related host species. When this happens, it is known as cross-species transmission. If the virus is transferred from a non-human species to humans and results in disease, this is called zoonosis. Just a few complementary mutations in the structure of the genome of the virus might be sufficient to allow the leap between species in a matter of months.

Ideally, for a virus or bacteria to flourish in a population, it must be very durable, highly infectious, and should not harm its host. A host that is unaware of its active infection with a virus or bacteria is more likely to live as normal and interact with other potential hosts, which more readily spreads the infecting pathogen. During transit from host to host, the virus or bacteria must also be able to survive the changing environment. Some viruses have tough protein shells that assume geodesic polyhedron shapes to withstand the elements. However, other viruses have lipid membranes that can easily dry out and become destroyed. To be infectious, the virus must have proteins on its own surface that can recognize with high affinity a protein, glycoprotein or glycolipid on the surface of a host cell to which it can attach for entry. But the real challenge is to subvert the cell's own enzymes to replicate the genome and proteins of the virus.

To appreciate how difficult this really is, it is necessary to have some appreciation of basic biochemistry and molecular biology.

1.3. DNA makes RNA makes Proteins

The chromosomes of animals, plants and microbes are comprised of long polymers of deoxynucleic acids called DNA and structural proteins called histones. Known as the genome, the DNA component contains the stored genetic information for the construction of all of the deoxyribonucleic acids (RNA) and proteins in cells, and ultimately their functionalities. DNA features nucleotide bases

that are interlinked like beads in incredibly long chains. Each bead is built from one of four possible types: Adenine (A); Thymine (T); Cytosine (C); and Guanine (G). These building blocks called bases are joined in combinations that store information on how to construct ribonucleic acids (RNA), and functional proteins. Just as computer code written in binary (Base Two) with 0's and 1's allows for storing information, the genetic code operates in quaternary (Base Four) in living organisms for the same purpose.

DNA is found in chromosomes, and humans have two sets of 23 separate chromosomes in most cells of the body. In each cell, the length of the genome (genetic material) in each set of chromosomes is about 3.2 billion base pairs long,[13] which when unraveled and put end to end is about 2 meters in length.

The human genome features about 20,000 genes that encode proteins as well as over a thousand other genes that specify RNA molecules that play functional and structural roles (*e.g.,* transfer-RNAs and ribosomal-RNAs) and regulatory roles (*e.g.,* micro-RNAs).[14] Remarkably, less than 4% of the human genome DNA harbors genes for proteins or RNA. Another 4% encodes the remnants of past viral integrations into the human genome of our ancestors. The bulk of the human genome appears to be non-essential baggage described as "junk" or "dark" DNA, although it also encodes various obscure regulatory, non-coding elements.

To make proteins, the DNA sequence of nucleotide bases in a gene needs to be re-written, *i.e.*, transcribed by enzymes called RNA polymerases into RNA copies. RNA uses similar building blocks to DNA, including A, C and G bases, but T is replaced with Uracil (U). The sequence of nucleotides in the complimentary RNA copy is dictated by the DNA template by base-pairing, in which an A selectively binds to a U, and a G specifically binds to a C. Consequently, a short strand of DNA with the sequence AAATTTCCCGGG will be transcribed by an RNA polymerase into the RNA sequence UUUAAAGGGCCC. Actually, genes can be thousands of nucleotide bases long, as will be their RNA copies. These resultant RNA copies are known as messenger-RNA (mRNA) molecules. These mRNAs are positive, single-stranded RNA polymers of nucleotides that are readable by protein synthesis factories known as ribosomes. Whereas DNA is very stable and found deep inside the nucleus of cells, mRNA is very transient and rapidly degraded. However, this mRNA can last long enough to leave the nucleus of cells and encounter ribosomes that are found in the cytoplasm of cells.

Proteins are long beaded chains of interconnected amino acids. Thermodynamic forces and weak chemical bonds help fold the protein chain into distinct functional three-dimensional structures. There are twenty types of common amino acids found in proteins. In humans, ten of these amino acids must be acquired in the food we eat, whereas we can produce the other ten by biosynthetic enzymes that operate within the metabolic pathways in cells. These enzymes are themselves proteins. Like molecular robots, proteins can build and degrade other proteins, nucleic acids, sugars, lipids, and other small molecules, acting as biological catalysts of the biochemical reactions that allow cells to live, reproduce and even die when required. Each of the ~20,000 proteins encoded by the human genome have a specialized function that is dictated by the amino acid sequence of each protein. The primary amino acid sequence of proteins ultimately determines their three-dimensional structures, which permits them to carry out their diverse activities, including their interactions with other proteins and other molecules. In addition to acting as biological catalysts of biochemical reactions, proteins can also play structural roles to maintain the shape and facilitate the mobility of cells.

The ribosomes are large complexes of proteins and ribosomal RNA that together function as protein synthesis factories. They read the sequence of nucleotide bases as triplets in the mRNA to find and assemble the corresponding amino acids into a growing protein that is specified by the RNA nucleotide sequence. Essentially, the ribosomes are translators of specific RNA sequences to generate the corresponding protein sequences. In these molecular assembly plants, each new amino acid is affixed to the previously selected amino acid by the binding of transfer-RNA molecules that are also specifically attached to one of the twenty possible amino acids and ferry them to the ribosomes.

Sequential triplets of the nucleotides specify each amino acid in what is known as the Genetic Code. Sixty-one possible nucleotide triplets select one to six of the 20 possible amino acids. This redundancy in the genetic code means that certain amino acids can be specified by up to six triplet combinations of the four possible nucleotides. For example, the amino acid arginine is selected when the RNA sequence of a triplet is CGU, CGC, CGA, CGG, AGA or AGG. Other amino acids like methionine and tryptophan are uniquely specified by AUG and UGG, respectively. For example, the portion of the RNA sequence UUUAAAGGGCCC described earlier would be translated by ribosomes to yield a portion of a protein with the sequence phenylalanine-lysine-glycine-proline.

All life forms on the Earth, including viruses, use the same genetic code for the triplets of nucleotides in transfer-RNAs that select each amino acid. Thus, all living organisms use the same nucleotides and amino acids and have very similar biochemistry in what has been referred to as central metabolism. This shared biochemistry is why parasitic viruses and organisms are able to take advantage of their hosts if they can gain entry.

The bottom line is that many steps are required for a virus to be able to successfully replicate itself in a host. Because viruses have very small genomes relative to those found in host cells, they must take advantage of, and be compatible with, the proteins and other molecules of host cells. Without the ability to divert the normal functions of the host proteins toward their own ends, these parasitic entities are unable to replicate for their propagation in new hosts. Viruses appear to have evolved from cells during evolution of life, in part from the loss of most genes that are found in cells and in part from the development of novel genes that are specialized to penetrate into and hijack host cells to optimize viral replication[16]

The simpler the structure of the virus, the more durable it may be, the faster it can be produced, and the quicker it can evolve from random mutations. Such mutation can arise from the low rate of fidelity in the reproduction of genomes by enzymes or by chemical mutagens or radiation in the environment. Most mutations are inconsequential or even deleterious to infectious pathogens, but occasionally these mutations might improve their ability to infect and replicate in a host. Bacteria can replicate quickly in a matter of minutes, although not as fast as viruses. By contrast, animal and plant cells typically take a few days to reproduce. After birth, most multicellular organisms require months or years to reach a mature, reproductive stage. Consequently, there are magnitudes of order greater opportunities for viruses to mutate than their hosts. However, hosts have developed counter-defenses to resist new infectious disease-causing pathogens. Before consideration of the immune systems of hosts, it is useful to discuss how infectious diseases spread.

1.4. Transmission of Infectious Diseases

Many deadly infectious diseases like the bubonic plague (Black Death caused by the bacterium *Yersinia pestis*) and disfiguring diseases like leprosy (caused by *Mycobacterium leprae*) have been known for thousands of years. The pathogenic bacteria that are responsible for these and many other

infectious diseases only became visible and identifiable through magnification with the advent of light microscopes. Other infectious diseases like smallpox, chickenpox, measles, and polio, all caused by viruses, have also been known for thousands of years. Over a hundred years ago, many other diseases were recognized as being caused by very tiny pathogens that easily penetrated very fine filters that normally trapped bacterial cells and larger microbes. They only became recognizable with the development of more powerful electron microscopes in the 1930's. Over the centuries, knowledge has continued to accumulate about these small pathogens that affect humans, such as how they propagate, and most recently their further identification by genomic sequencing. Following the completion of the Human Genome project, the tremendous advancements in the efficiencies of DNA sequencing technologies with dramatic reductions in costs have resulted in the identifications of thousands of new microbial and viral species in the 21st century.

For transmission of an infectious disease to occur, there is a chain of events that depends on independent links that must be strung together in the proper order. Six of these links can be described as follows:

1.4.1. Link 1- Sufficient Dose of an Infectious Pathogen

In the controlled environment of a laboratory, it is possible to calculate the infective or lethal dose of a pathogen. It is, however, impossible to determine a precise infective dose for human pathogens out in the real world. Although different species of pathogens vary widely in their ability to cause disease (*e.g.,* a single *Rickettsia tsutsugamushi* microbe can cause an infection as opposed to a million of more of the organism *Salmonella typhi*),[17] the level of the infective dose varies with the competency of a new host's defense mechanisms.

Two factors are essential if a potential pathogen is to cause disease. Firstly, it must establish itself in or on the host tissue. This necessitates that at a location within the host there is an environment with appropriate pH and oxygen tension levels, temperature, and nutrients that are suitable for the survival and growth of the pathogen. This is referred to as "the fertile soil" of the pathogen.[17] Due to this necessity, pathogens tend to favor specific anatomic locations. For example, the unique environment of the skin is conducive to the growth and infectivity of the bacteria, *Staphylococcus*

aureus and *Streptococcus pyogenes*, whereas the completely different acidic nature of the gastrointestinal tract is better suited to infection by *Escherichia coli and Salmonella enterica.*

Secondly, apart from locating in fertile soil, a pathogen must overcome the defense system of the potential host to attain a critical mass, which for that pathogen in that host, produces overt evidence of an infection.

1.4.2. Link 2 - Existence of a Viable Infectious Pathogen

To induce infection, not only must there be a critical mass of a pathogen, that mass must remain viable. A potentially infectious mass of a pathogen relocated from its fertile soil to a hostile environment loses its viability and its infectivity. Viruses are intracellular parasites and must be so located if their viability is to be retained. A door handle often does not provide that environment. Viruses from the handle might have their viability resuscitated through sophisticated laboratory techniques, but that does not imply that the door handle is a fomite, *i.e.,* a source of viable infectious pathogens. Notably, the fear of COVID-19 viruses on fomites was an early, and mistaken, concern propagated by many health authorities.

1.4.3. Link 3 - A Portal of Escape

A pathogen prior to its invasion of a new host must escape from its primary source. The portal of escape is usually related to where the pathogen is located on the body. Human pathogens leave the body from the respiratory tract, in fecal material, and in body fluids such as blood, semen, vaginal secretions, urine, saliva, sweat and breast milk. In some cases, they may be released from erupted blisters in pus or drainage as occurs, for example, with chickenpox and varicella zoster virus infection, and with hand-foot-mouse disease with coxsackie virus infection.

1.4.4. Link 4 - A Mode of Transmission

Once a sufficient dose of a viable pathogen leaves its primary source, it must be transmitted to its new host before the potential for infection exists. Sneezing and coughing produce a spray of respiratory pathogens that might be inhaled by potential new hosts. COVID-19, tuberculosis and streptococcal pharyngitis are spread by this route. Direct person to person contacts spreads infectious mononucleosis by kissing, and venereal disease by intimate sexual behavior. A less direct route of

transmission occurs when a food handler shedding *shigella* or *salmonella* pathogens or the hepatitis A virus contaminates food because of inappropriate hand washing.[17] The sharing of syringes containing contaminated blood is a common method of transmitting the hepatitis B virus among intravenous drug abusers. Microorganisms pathogenic to humans can also be transmitted by vectors such as mosquitoes, fleas, and ticks.

In summary, the common routes of transmission are respiratory via inhalation, fecal - oral from ingestion of contaminated fecal material, sexual from direct contact with mucous membranes, body fluids from infected blood, puss, semen, sweat and urine, and via vectors such as insects and animals that bite.

1.4.5. Link 5 - A Portal of Entry

The potential for infection does not exist unless the transmitted critical mass of a viable pathogen accesses the fertile soil of host tissues. The usual portals of entry are the same as the portals of escape. They include the respiratory, gastrointestinal, and genitourinary tracts plus skin and mucous membrane surfaces that are broken or otherwise compromised.

1.4.6. Link 6 - A Susceptible Host

The ability of a sufficient dose of an invading viable pathogen to elicit disease is dependent on the susceptibility of the potential new host to that pathogen. Factors that contribute to susceptibility include general malaise, poor socio-economic and living conditions, malnutrition, chronic disease, obesity, increasing age, stress, and the frequency of previous infectious diseases.[17] More significantly, the resistance to susceptibility is enhanced by a healthy lifestyle, a balanced diet, a functioning immune system, and low stress.[17] Thus, a young, physically fit individual would be much more tolerant of high numbers of a particular pathogen than would an older, infirm person with diabetes mellitus.

An important factor governing susceptibility is the capacity to develop an immune response in time to prevent the multiplying pathogen from reaching a critical mass. For example, a robust immune system might not resist a low dose of a highly virulent rapidly multiplying pathogen. Similarly, a large mass of a low virulent pathogen could overcome a delayed and weakened immune response.

1.4.7. Analyzing the Links

Critical to the development of an infection, the six links constituting the Chain of Infection must be joined in the order of: Sufficient Dose of an Infectious Pathogen → Existence of a Viable Infectious Pathogen → A Portal of Escape → A Mode of Transmission → A Portal of Entry → A Susceptible Host. Breaking this chain by removing or incapacitating one of the links prevents the transmission of an infectious disease. Although each link is critical, the most significant one regarding the transmission of an infectious disease is host susceptibility.

The clinical importance of this conclusion is more readily appreciated by focusing on host resistance rather than host susceptibility. This allows the probability of an infectious disease occurring to be represented by the following equation.[18]

$$\text{Infection} = \frac{\text{Virulence of the Pathogen x Dose of the Pathogen}}{\text{Host Resistance}}$$

This equation illustrates two factors relevant to the transmission of all infectious diseases. First, infection is not an inevitable outcome of exposure to a pathogen but depends on an interrelated series of events constituting the Chain of Infection. Second, host resistance is more pertinent to the development of an infectious disease than are the specific characteristics of a potential pathogen.[17] The significance of this factor is appreciated when the heterogeneous nature of a population is considered.

The factors that decrease host resistance (increase susceptibility) not only accumulate with advancing age but have an increasing variability within each successive decade of life. For example, two young cousins ages 5 and 8 years are likely to share similar health and socio-economic circumstances resulting in both having a similar resistance to infection no matter the potency of the pathogen. However, their respective grandparents ranging in age from 65-75 years could have a wide spectrum of life and health experiences resulting in each of them having vastly different co-morbidities and consequently various levels of resistance and susceptibility to a potential pathogen. Public health programs to prevent the spread of an infectious disease will be of questionable utility if they ignore the diversity of susceptibility to infection that exists within all populations. However, this is precisely what happens with broad vaccine mandates.

The noted medical historian, Dr. Mary Dobson of Cambridge University emphasized this fundamental concept in her 2007 book, *Disease: The extraordinary stories behind history's deadliest killers,* when she said, *"…there is always a complex set of inter-related biological, genetic, environmental and social factors meaning that some people succumb, while others survive or remain untouched by the circulating pathogen or potentially fatal disorder*."[19]

Apart from appreciating the significant roles of host resistance and susceptibility in disease transmission, disease prevention programs must address what constitutes the diagnosis of an infectious disease and recognize the concept of asymptomatic transmission as both relate to the identification and understanding of infectious disease transmission.

1.5. Diagnosis of an Infectious Disease

A confirmed case of an infectious disease is dependent on the co-existence of two essential factors. One is the presence of its characteristic symptoms and the other is the identification of the causative pathogen.[20] For example, an individual might have the typical signs and symptoms of a flu from influenza. However, unless laboratory tests reveal the presence of one of the flu viruses, a confirmed diagnosis of flu cannot be made. Similarly, an appreciation for the Chain of Infection indicates that a noncritical mass of *Streptococcus pyogenes* could be present on a throat swab, but without the appropriate symptoms, a diagnosis of strep throat is questionable.

The methods and criteria associated with testing for SARS-CoV-2 will be discussed later in Chapter 4. However, their complexities combined with the non-specific nature of COVID-19 symptoms (cough, fever, chills, fatigue) have likely led to an overestimation of the number of COVID-19 cases, hospitalizations, and deaths during times of high testing (during times of low testing, underestimations were likely produced).

1.6. Asymptomatic Transmission

The concept of asymptomatic transmission is that an individual who has no symptoms of an infectious disease can still transmit it. But in healthcare, a patient who no longer has symptoms is considered well. Therefore, the question is, "Can a well patient transmit an infection?" In addition, can a person at the early stages of an infectious disease be transmitting that disease? The idea of

asymptomatic transmission has been a major driver of policies, procedures and mandates associated with infections and has been a feature in many of the public health policies during the COVID-19 pandemic.

The Chain of Infection dictates that for infection to occur, a sufficient dose of viable respiratory virus like influenza must be transmitted through the air from an infectious carrier to a potentially susceptible new host. It is the force associated with the symptoms of coughs and sneezes that expels infectious doses of a respiratory virus from the respiratory tract of the primary host with sufficient velocity to be transmitted as aerosols through the air and be inhaled by a new host where they must overcome that person's natural defenses (intact mucous membranes) and immunological responses. Without coughs and sneezes the potential for a respiratory virus transmission is very low and generally rare.

The Chain of Infection reveals that an individual might harbor a virus and have non-existent to mild non-specific symptoms, but unless the viable virus is expelled in sufficient amounts by sneezing or coughing and overcomes the resistance of a new host, the potential for transmission does not practically exist. Nevertheless, the promotion by government and media sources that a healthy, well, symptom-free person could transmit a respiratory virus, enhanced the levels of public fear and paranoia, and facilitated the introduction of mandated procedures such as societal lockdowns, travel restrictions, and school closures. If it does occur, the concept of asymptomatic transmission through the air is a rare phenomenon and should not be used to justify public health policies and procedures.

In January 2020, before the onset of the pandemic, Dr. Anthony Fauci, the director of the US National Institute of Allergy and Infectious Diseases at that time supported this concept when he said, *"In all the history of respiratory borne viruses of any type, asymptomatic transmission has never been the driver of outbreaks. The driver of outbreaks is always a symptomatic person."*[21] Further evidence on the low level of asymptomatic transmission for SARS-CoV-2 was provided by Dr. Maria Van Kerkhove, head of WHO's emerging diseases and zoonosis unit, on June 8, 2020, when she said that, *"from the data we have, it still seems to be rare that an asymptomatic person actually transmits onward to a secondary individual.*" She continued to say that "*We have a number of reports from countries who are doing very detailed contact tracing. They're following asymptomatic cases. They're following contacts. And they're not finding secondary transmission onward. It's very rare.*"[22]

The role of asymptomatic transmission in spreading a respiratory virus like SARS-CoV-2 appears to be inconsequential compared to the way in which the Chain of Infection governs the transmission of this and other pathogens. Recent studies have shown that only about 9% of 242 asymptomatic patients at a tertiary care facility had detectable minus-strand SARS-CoV-2 RNA, which is a measure of active virus.[23] (The minus strand of RNA is an intermediate opposite copy of the sense-strand of RNA, and is required to make more copies of the RNA for packaging into new virus particles. It cannot be used by ribosomes to make proteins.) This demonstrated that the vast majority asymptomatic patients that had tested positive by traditional Polymerase Chain Reaction (PCR) methods (see Chapter 4.1 and 4.2 for more about PCR tests) were actually not infectious..

1.7. Application of the Chain of Infection to COVID-19

The principles governing the transmission of infectious diseases are multidisciplinary. The following chapters will discuss the role these specialties have in unravelling the numerous contradictions and dilemmas associated with SARS-CoV-2 and COVID-19. By defining certain terms and assembling the Chain of Infection, this chapter has provided a primer on the basic elements controlling the transmission of an infectious disease.

These factors reveal that a one size fits all approach to combating a respiratory disease pandemic fails to account for the diverse range of susceptibility to the disease. An understanding of the Chain of Infection would have directed targeted preventive measures to the least resistant rather than assume that everyone was equally susceptible. Similarly, public health efforts to increase resistance to infection within all strata of society would have been not only universally beneficial but would have recognized the fundamental concepts inherent in the Chain of Infection.

The diagnosis of an infectious disease requires that its symptoms be present, and its causative pathogen identified. As shall be seen in chapters that follow, the spectrum of symptoms associated with COVID-19 and the laboratory manipulations required to identify viable SARS-CoV-2 should have tempered the enthusiasm for readily confirming cases of COVID-19. The specter of SARS-CoV-2 being transmitted by healthy individuals incited public fear and paranoia. An elementary knowledge of the Chain of Infection would have revealed the implausibility of such an occurrence. The concepts inherent in the Chain of Infection are time tested and easy to understand. Ensuring that it was intact and

operational when dealing with COVID-19 would have reduced much of the misunderstanding associated with this rather standard infectious disease.

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Chapter 2:

SARS-CoV-2 and Coronaviruses and Other Respiratory Disease Viruses

2.1. Viral Respiratory Diseases

Many human infectious diseases are caused by air-borne viruses. Notably, these include respiratory syncytial virus, influenza and coronaviruses. These viruses are highly contagious, mainly transmitted in aerosols received through the mouths and noses of victims. They produce very similar symptoms, which include runny nose, coughing, sneezing, wheezing, fever and decrease in appetite. The symptoms are largely consequences of the body's counter-reactions to a respiratory infection. These viruses infect humans largely by inhalation of virus laden air. As such, their first opportunity to infect the human body occurs in the larger passages of the upper respiratory tract - the nose, pharynx, larynx, trachea and bronchi.

Once these viruses invade cells of the upper airways, they hijack the human intracellular machinery to replicate, and often cause cell damage in the process by lysing the infected cells. If the human body responds well, the immune system will prevent these viruses from spreading beyond the upper airways and will quickly terminate any illnesses induced by these viruses. If the immune response is insufficient, the infection might spread into the lower airways (alveoli) and develop into a much more serious systemic infection (including secondary infections such as bacterial pneumonia). The immune response to respiratory viruses in airway spaces is rather different when compared to an infection of the bloodstream from a skin wound or even an injection of a vaccine.

2.2. *Respiratory Syncytial Virus (RSV)*

RSV generally induces mild, cold-like symptoms, and most people recover within two weeks or less. It produces a seasonal disease that occurs mostly early in the Fall. RSV, however, can also cause serious lung infections in some infants and older adults, especially those with pre-existing serious medical problems. One study noted that 42% of adults infected with RSV are asymptomatic, but they transmit the virus at a very much lower rate than those who were symptomatic.[24] RSV normally infects about 97% of children before the end of their second year of life, with a lethality rate of less than 1 in 2,500 for children under 5 years, who usually also have significant co-morbidities.[25] The actual RSV case

fatality rates (deaths due to RSV/all patients who develop RSV infection) are difficult to estimate. The reported numbers vary dramatically from 0 deaths in smaller studies, to between 1 in 714 to 1 in 7,805 in a few of the larger US studies. With about 23 million children under the age of 5 years in the US, and the number of RSV deaths annually ranging from 100 to 300 deaths per year, rates of close to 1 death per 77,000 RSV infections annually in this age group can be calculated.

In 2019 (pre-COVID-19), there were almost 19,000 RSV cases reported in Canada. From August, 2020 until May, 2021, there were just 239 cases. This remarkable 98.5% decrease was attributed to masking, distancing, handwashing, and closure of day-care and schools. However, it is likely that many RSV cases were incorrectly attributed to be COVID-19 cases. By late October 2022, RSV cases had 'surged' to 486 according to one mainstream article.[26] This increase of over 100% compared to the previous period was actually a mere 2.5% of the 2019 count, which itself was consistent with previous years. A 2019 investigation noted that in Canada during 2003 -2013, a total of 79 RSV-associated infant deaths were recorded with 32 of these being attributable solely to an RSV infection.[27]

Along with the rarity of severe RSV in babies, it is also easily treatable with drugs such as palivizumab and ribavirin, which can be used prophylactically.[28] [29]

In the Fall of 2022, there were increased incidences of RSV, COVID-19, and influenza infections. As a result, Canadian public health authorities expressed concern that pediatric units in hospitals could be overwhelmed by a surge in those infections.[30] It was evident that the median age of RSV cases in hospitalized infants was higher in 2022 than typically observed prior to the onset of COVID-19 in Canada.[31] Thus, the guidelines and efforts to "flatten the curve" for reducing hospital cases of COVID-19 in the early years of the pandemic, ultimately delayed and then concentrated the cases of RSV and influenza in hospitals in 2022.

2.3. Influenza

Influenza has been recognized as a seasonal illness for over a century with annual variations in prevalence and severity. Typically, adults become infectious about a day before they manifest any symptoms, and they can remain infectious for 5 to 7 days after the appearance of flu symptoms. These symptoms can include fever, cough, runny nose, body aches, nausea, vomiting, and diarrhea. The symptoms can be very mild to severe, with full recovery occurring in usually 1 to 2 weeks.

From the Orthomyxoviridae family, the influenza viruses occur in four types, A, B, C and D. The A and B types are mainly responsible for seasonal epidemics of the flu, whereas the C type produces mild illness, and the D type primarily infects cattle.[32] Their genomes consist of 8 segments of negative-sense single-stranded RNA. Co-infection of the same cell with two different influenza viruses allows the mixing of these segments to generate new variants, which can be extremely novel if one of the influenza strains is from another animal species.

The Influenza A viruses are divided into subtypes based on two proteins, *i.e*., hemagglutinin (H) and neuraminidase (N), which are located on the surface of the virus. There are 18 different hemagglutinin subtypes (H1 though H18) and 11 different neuraminidase subtypes (N1 through N11). More than 130 influenza A subtype combinations have been identified in nature, mainly from wild birds, but there are likely additional influenza A subtype combinations given the propensity for virus "reassortment" of the 8 RNA segments. The H1N1 and H3N2 subtypes have been responsible for the more recent influenza pandemics.

The most devastating influenza pandemic on record is the 1918 Spanish flu, which was caused by the H1N1 influenza virus A. It has been estimated to have infected 500 million people, about a third of the world's population at the time, and resulted in around 50 million deaths.[33] There were four waves of the Spanish flu, with the first occurring between February 15 to June 1, 1918, and the last wave persisting from December 1, 1919, to April 30, 1920.[34] Some 50,000 Canadians and 675,000 Americans appear to have succumbed to this H1N1 influenza A virus between 1919 and 1920. It had an estimated mortality rate of 2.5% (2,500 death/100,000 infected), and primarily affected 25- to 40-year-olds. The high lethality rate of the Spanish flu was likely a reflection in part of the high rates of war injuries, including damage to the airways and lungs by gas warfare, poor nutrition and inadequate sanitation, and high stress levels during the end and aftermath of World War I. On the termination of the war, the spread of the flu was exacerbated by the return of soldiers to their home countries.

H1N1 influenza subtypes were prevalent in the 1950's and then largely disappeared until 1977 when they reappeared causing a pandemic that originated in the former USSR.[35] The 1977 H1N1 subtype had a fatality rate of less than 0.005% and was fairly mild, and it affected primarily those that were 26 years of age or younger. The gene sequence of the 1977 H1N1 was almost identical to the N1H1 subtype from 1950,[36] and this is thought to be an example of an "escape" from a laboratory that

was developing a vaccine against influenza.[37] Those who were older than 26 years of age in 1977 probably already had lasting immunity against the H1N1 strain due to prior exposure. However, influenza A viruses tend to mutate faster than influenza B type viruses, and so evasion of pre-existing immunity is more likely with influenza A viruses. The H1N1 subtype that emerged during the 2009-2010 flu season was caused by a combination of influenza A viruses that infected pigs, birds, and humans.

Vaccines against influenza are usually developed for North America based on a mix of the subtypes that appear to be prevalent during the prior flu season in the southern hemisphere. Often, these predictions fail, and new influenza vaccines prove to be less effective than desired for the new flu season. For example, current vaccines include those developed against a H3N2 subtype that predominated in 2023, which produces more severe flu symptoms than the H1N1 subtype, but has only about 29% relative efficacy (*i.e.*, relative risk reduction). In a meta-analysis study of vaccine effectiveness from the 2009-2010 influenza pandemic, it was estimated that in the northern hemisphere it was only 22% effective.[38] When most circulating flu viruses are well-matched to those used to make flu vaccines, a relative risk reduction of flu illness between 40% to 60% can typically be observed.[39]

In the 2019-2020 flu season from November 17, 2019 to March 28, 2020, there were higher than usual levels of influenza detections (55,379 cases), and hospitalizations (2,493 cases) in Canada, although still lower than normally seen annually, and the flu season ended about 8 weeks sooner than the average end of flu season.[40]

One of the mysteries during the COVID-19 pandemic was why the incidence of influenza cases in Canada and world-wide so dramatically declined. In the 2020-2021 flu season, there was essentially no community spread of influenza, with only 69 confirmed detections of the influenza virus in Canada, usually occurring in people under 20 years of age, and none were associated with hospitalization.[41] Despite double the average annual testing rates in Canada, influenza percent positivity did not exceed 0.01% of tested cases. Like RSV, the number of these influenza cases was historically low when compared to the previous 6 years. The same trends were also observed in the US, and in most countries in both the northern and southern hemispheres. Depending on the country, the historical average rates of influenza positivity ranged from 0.8 to 25.1% of those tested.[41]

About 45% of the recorded influenza cases in Canada in the 2020-2021 season were in people who were recently vaccinated against the virus.[41] Since the influenza viruses in vaccines tend to be attenuated, *i.e.,* weaker strains of influenza A viruses, there is always a risk that some individuals who have weak immune systems that are unable to mount a sufficiently protective immune response, might contract the disease. The very low rates of influenza cases in Canada continued in the 2021-2022 flu season, which began on August 29, 2021. There was a resurgence of influenza cases in the 2022-2023 flu season in Canada, but these were still lower in number than typically seen in the flu seasons that preceded COVID-19. From August 28 to December 31, 2022, there were only 59,459 reported influenza cases nationally.[42]

It should be noted that most people who die with influenza actually die from pneumonia. For that reason, Statistics Canada usually reports deaths from both influenza and pneumonia together. In the 2019-2020 flu season, there were 306 ICU admissions and 120 deaths with influenza in Canada., and over 70% were from Influenza A. Over 90% of the deaths were associated with at least one co-morbidity, usually hypertension or another heart disorder. Typically, about 3,500 deaths with influenza occur annually in Canada.[43] It should be appreciated that the risk of death for children under 15 years of age is about 10- to 100-times higher from influenza than from COVID-19.[44]

It seems reasonable that the reductions of flu–like illnesses in Canada during 2020-2021 and 2021-2022 were partly due to misdiagnosis as COVID-19 cases. But why would the incidence of COVID-19 in the first two years of the pandemic result in almost complete suppression of the spread of influenza? It has been estimated that over 430,000 people arrived in the US from China during the early phase of the COVID-19 pandemic, before the Trump administration imposed travel restrictions.[45] Consequently, there was still ample opportunity for the latest influenza variants from China to travel to North America in January through to mid-March of 2022. One possible explanation for the reduction in influenza cases in the 2020-2021 and 2021-2022 flu seasons is the widespread infection with the novel SARS-CoV-2 virus. Apart from stimulating an adaptive immune response to SARS-CoV-2, there might have been a general upregulation of the innate immune response at the same time. While this is less specific, the innate immune response would confer protection against infections in general. For example, it is reported that people who received the bacillus Calmette–Guérin (*BCG*) *vaccine* for tuberculosis were much less prone to getting severe COVID-19.[46, 47] However, this BCG vaccine-effect on COVID-19 incidence has been controversial.[48]

Even without prior immune protection from previous infection or vaccination, influenza can be successfully treated in most cases with antiviral drugs. Influenza A and influenza B viruses are sensitive to the recent antivirals oseltamivir (Tamiflu) from Roche and zanamivir (Relenza from GalaxoSmithKline). These are inhibitors of the neuraminidase enzyme on the surface of the influenza particles, which is needed to permit budding of the virus from infected host cells.

2.4. Common Cold Coronaviruses

The first time a coronavirus was identified as being responsible for a respiratory infection was back in 1937, when this virus produced a devastating effect on the poultry industry. By 1965, it was demonstrated that coronaviruses were responsible for approximately 15% to 30% of common colds in humans.[49] Amongst the most common human coronaviruses are the alphacoronaviruses 229E and NL63, and the beta coronaviruses HKU1 and OC43. All of these coronaviruses produce relatively mild, but inconvenient symptoms that rarely require hospitalization.[50] The symptoms include runny nose, sore throat, headache, fever, cough and a general feeling of malaise. There is a risk of further development into lower-respiratory tract illness, such as bronchitis or pneumonia, particularly in people with heart and lung (cardiopulmonary) disease, those that are immune-compromised, young infants and the elderly. In addition to the above coronaviruses, there are several types of viruses that can potentially cause the common cold, including rhinoviruses, enteroviruses, and human metapneumovirus.

The OC43 coronavirus shows 51% nucleotide identity in its whole genome with SARS-CoV-2, and the encoded Spike proteins share 28% amino acid identity.[51] The more similar the nucleotide sequences of two genes, the more likely it is that they have a common origin. The more similar the amino acid sequences of two proteins, the more likely that they arise from the same or related genes. Nucleotide identity means that exactly the same nucleotide base types (out of 4 possible types) appear in precisely the same aligned position in the two gene sequences that are being compared. “Amino acid identity” means that exactly the same amino acid type (out of 20 possible amino acids) is located in the same aligned position in the two protein sequences that are being compared. “Amino acid similarity” comparisons make allowances for highly related amino acids being substituted with each other in making such comparisons (*e.g.,* a negatively charged amino acid replacing another negatively charged amino acid, or a positively charged amino acid replacing another positively charged amino

acid). Thus, two proteins can have lower amino acid identity and more amino acid similarity. In the example of OC43 having 51% nucleotide identity in its whole genome with SARS-CoV-2, this indicates that both viruses emerged from a common ancestor in the distant past. However, they will not necessarily behave exactly the same way regarding virulence and host infectivity.

As with other coronaviruses, these particular common cold viruses are characterized by their "crown-like" appearance in electron microscopic images. The projections correspond to bundles of three interwoven copies of the large Spike protein that is encoded by the S gene in the genomes of this family of single-stranded RNA viruses, which are embedded in a lipid membrane that envelopes the virus. The interaction of the Spike protein trimer with a receptor that is normally present on surface of a suitable host cell is critical in permitting entry, by first allowing the virus to latch on to it. In the cases of OC43 and HKU1, their Spike proteins interact with 9-O-acetylsialic acid to invade host cells.[52, 53] The 229E Spike protein exploits amino-peptidase N (ANPEP) as its host cell receptor to mediate viral infection,[54] whereas the NL63 Spike protein utilizes angiotensin-converting enzyme 2 (ACE2) as its host receptor.[55] ACE2 is an important enzyme in the regulation of blood pressure. In addition to NL63, the Spike proteins of SARS-CoV-1, and SARS-CoV-2 utilize ACE2 as a receptor for viral attachment to host cells.

In one study of serum antibody samples collected from 251 people between August 2013 to March 2020, 2.2% had cross-reactive antibodies against full-length SARS-CoV-2 Spike protein, 0.6% had antibodies against its receptor-binding domain, and 23.9% had antibodies against its Nucleocapsid protein.[59] In the same study, the authors reported that SARS-CoV-2 infection increased the detection of antibodies against the OC43 Spike protein. However, the presence of these antibodies against OC43 Spike protein did not correlate with a reduced risk of acquiring a SARS-CoV-2 infection as demonstrated with a PCR test (see Chapter 4.1 and 4.2) performed with a nasal swab sample when the 251 people that were positive for SARS-CoV-2 RNA were compared to 251 people that did not test positive for the virus. Another study showed that those individuals with an infection between 2015 and 2020 with the endemic 229E, NL63, HKU1 or OC43 (eCoV-positive) had a similar rate of SARS-CoV2 infections as measured by PCR tests when compared to those without previous recent infection with these cold coronaviruses (eCoV-negative). However, prior exposure to endemic 229E, NL63, HKU1 or OC43 was associated with 90% reductions in intensive care unit (ICU) admissions and a trend toward lower odds of mechanical ventilation compared to those without (eCoV-negative).[57] The percentage of

hospitalized patients who eventually died over follow-up was also lower in the eCoV-positive (4.8%) group as compared with the eCoV-negative (17.7%) group. Thus, antibodies against the common cold coronaviruses may not have prevented SARS-CoV-2 infection, but they may have reduced the severity of COVID-19 illness and death. This likely accounts for the low rates of COVID-19 deaths in the Downtown Eastside of Vancouver, British Columbia, a zone with a disproportionately high levels of drug use, homelessness, poverty, crime, mental illness and sex work, and also in international refugee camps.

2.5. SARS-CoV-1

The first report of a SARS-CoV-1 (originally called SARS-CoV) case with more severe pneumonia-like symptoms was in late 2002 in Guangdong province in southern China.[58] The new disease was named severe acute respiratory syndrome (SARS) and appeared to have a high mortality rate of about 3%.[59] Earlier estimates placed the mortality rate as high as 11%, but this underestimated the number of people who were actually infected and was based largely on total hospitalized cases of SARS.

The SARS-CoV-1 virus spread to over 28 countries, but was predominately in five countries, including Canada, during its short course. It caused over 8,000 hospitalizations and resulted in over 800 deaths worldwide, although 83% of all SARS deaths were in Mainland China and Hong Kong. Canada experienced its main SARS outbreak in Toronto, Ontario hospitals starting in February 2003, and resulted in around 438 probable SARS cases and 44 deaths in the country.[60]

Within a month of its detection, the complete genome structure of the SARS-CoV-1 virus was first elucidated at the Genome Sciences Centre in Vancouver, British Columbia in collaboration with the National Microbiology Laboratory (NML) in Winnipeg, Manitoba,[61] and a week later it was also reported by the US CDC.[62]

The successful containment of SARS-CoV-1 has been attributed to most infections occurring in hospital settings during the late and symptomatic phase of the disease.[63, 64] However, it is remarkable that the SARS-CoV-1 virus disappeared from the human scene within two years of its emergence, without the use of preventive measures such as vaccines or specific anti-viral treatments. The last probable SARS-CoV-1 cases were reported in China in April 2004.[65]

Masked palm civets (*Paguma larvata, a member of the mongoose family*), which are known to be sold in the animal markets of the Chinese city of Guangzhou, were initially hypothesized to be the source of SARS-CoV-1 infection into humans.[66] It should be appreciated that there were two SARS-CoV-1 outbreaks in 2002-2004, each arising from separate palm civet-to-human transmission events. The first emerged in late 2002 and ended in August, 2003, and the second arose in late 2003 from a lingering population of SARS-CoV progenitors in civets.

A decade and a half later, the origin of SARS-CoV-1 was eventually traced back to a remote cave in Yunnan province in China, to a single population of horseshoe bats of the *Rhinophidae* family, which harbors various virus strains that have high genetic similarity to SARS-CoV-1.[67, 68, 69] Amongst the bat coronaviruses isolated from the Yunnan cave, the Rs3367, RsSHC014, WIV1 and WIV16 strains were the closest matches to SARS-CoV-1 with respect to their overall genetic sequences. This included the regions encompassing the S (Spike), ORF3 and ORF8 genes, which are known to be more variable between coronaviruses. ORF's are open-reading frames in genome sequences that are known or suspected to encode proteins. Furthermore, the proteins produced from the genomes of these bat coronavirus (including from the ORF1a, ORF1b, Envelope (E), Membrane (M) and Nucleocapsid (N) genes) share greater than 98% amino acid sequence identities with the human/civet SARS-CoV's.

It remains a puzzle as to how a virus from bats in Yunnan could travel to infect animals and humans about a 1,000 kilometers away in Guangdong, without causing any suspected cases in the Yunnan area itself. This reduces the likelihood that a bat from Yunnan directly transmitted SARS-CoV-1 to a human. It is feasible that the masked palm civets were infected by a bat SARS coronavirus that was the direct progenitor of SARS-CoV-1. This progenitor was generated from a series of recombination events with highly related bat coronaviruses. However, the closest civet SARS coronavirus lacks portions of the S1 Spike protein gene that permits optimal binding of the virus to human ACE2 protein, which is the primary host receptor for the SARS-CoV-1.[70] Of note, the SARS-CoV-1 virus itself shows 79% nucleotide identity in the whole genome with SARS-CoV-2, and their Spike proteins share 76% amino acid identity.[51] SARS-CoV-1 was less infectious than SARS-CoV-2, but it was more virulent in causing severe illness and death.

2.6. MERS-CoV

In 2012, at least eight years after SARS mysteriously disappeared, another pandemic outbreak with a SARS coronavirus erupted in the Middle East, with a small number of imported cases in Europe, North Africa, Asia, and North America. This was designated Middle East Respiratory Syndrome coronavirus (MERS-CoV), and it ultimately infected and hospitalized around 2,500 people primarily in Saudi Arabia.[71]

The mortality rate appeared to be higher than SARS, since approximately 35% of the MERS patients who were reported to the World Health Organization (WHO) died. The disease is manifested by severe respiratory infection, often with kidney (renal) and other multi-organ failure.

About 80% of cases of MERS-CoV infections in humans were the results of direct or indirect contact with camels or infected individuals, with the latter largely being healthcare workers. The dromedaries were the principal host for the virus and the only known zoonotic source. For MERS-CoV transmission, direct close contact with an infected individual was necessary. MERS-CoV binds to host cells by attachment to dipeptidyl peptidase 4 (DPP4), which is expressed in the upper respiratory tract of epithelial cells of camels, but much less so in humans. DDP4 is an example of a protease, which is a class of enzymes that cleave other proteins into smaller segments. This lack of expression of this serine exoprotease in the human upper respiratory tract has been proposed to account for the restricted transmission of MERS-CoV in humans.[72] DPP4 as a MERS-CoV Spike protein receptor is known to be expressed in different human tissues and cell types, including kidney cells, small intestine cells, and immune T-cells.[73]

The MERS-CoV virus displays 53% nucleotide identity in its whole genome with SARS-CoV-2, and the respective Spike proteins share 26% amino acid identity.[51] The lower rate of Spike protein amino acid identity with SARS-CoV-1 and SARS-CoV-2 likely accounts in part for the differences in their Spike protein recognition of host cell proteins. The interaction of MERS-CoV with DPP4 is mediated via its Spike protein.

The Spike proteins of coronaviruses not only are important for host cell receptor recognition, but they facilitate the fusion of the host cell surface membrane with the coronavirus lipid membrane. This provides for the delivery of the genetic material, *i.e.,* the RNA genome of the virus into the host cell.

The cell and virus membrane fusion mediated by the Spike protein is improved following its cleavage at subunits by the protease furin for certain coronaviruses like MERS-CoV.[74] Proteases are enzymes, also known as proteinases, that cut other proteins between specific amino acid sequences. This can lead to their target protein's activation, inactivation, or ultimate degradation. The furin recognition sequence motif in MERS-CoV, which results in the formation of the S1 and S2 subunits of the Spike protein and increases the infectivity of MERS-CoV also occurs in SARS-CoV-2, but not in common cold coronaviruses, SARS-CoV-1 or the closest bat and civet coronaviruses that are related to SARS-CoV. MERS-CoV also features an additional furin cleavage site in the S2 subunit that is not found in SARS-CoV-2. In the human body, furin is widely expressed in different tissues and cell types.[75] MERS-CoV is also able to enter cells using an alternative pathway at the cell surface with activation by the transmembrane protease serine 2 (TMPRSS2) and by TMPRSS4, which can also target SARS-CoV-2 at the S1/S2 furin cleavage site. [76] Once the viral load is high enough to establish a MERS-CoV infection, the increased affinity for DPP4 by the furin cleavage might contribute to the higher rate of multiple system failure and death caused by MERS.[76]

There are many different respiratory viruses that produce very similar symptoms. Some of these are seasonal as RSV, influenza and the cold coronaviruses. However, SARS-CoV-1 and MERS-CoV had very limited runs, and ultimately fizzled out as viruses of concerns with relatively little imposition of public health measures to curtail their spread. For the coronaviruses, the Spike protein is central to their ability to infect host cells, and while ACE2 was a common target for many of them, other host cell proteins were exploited by some of the coronaviruses.

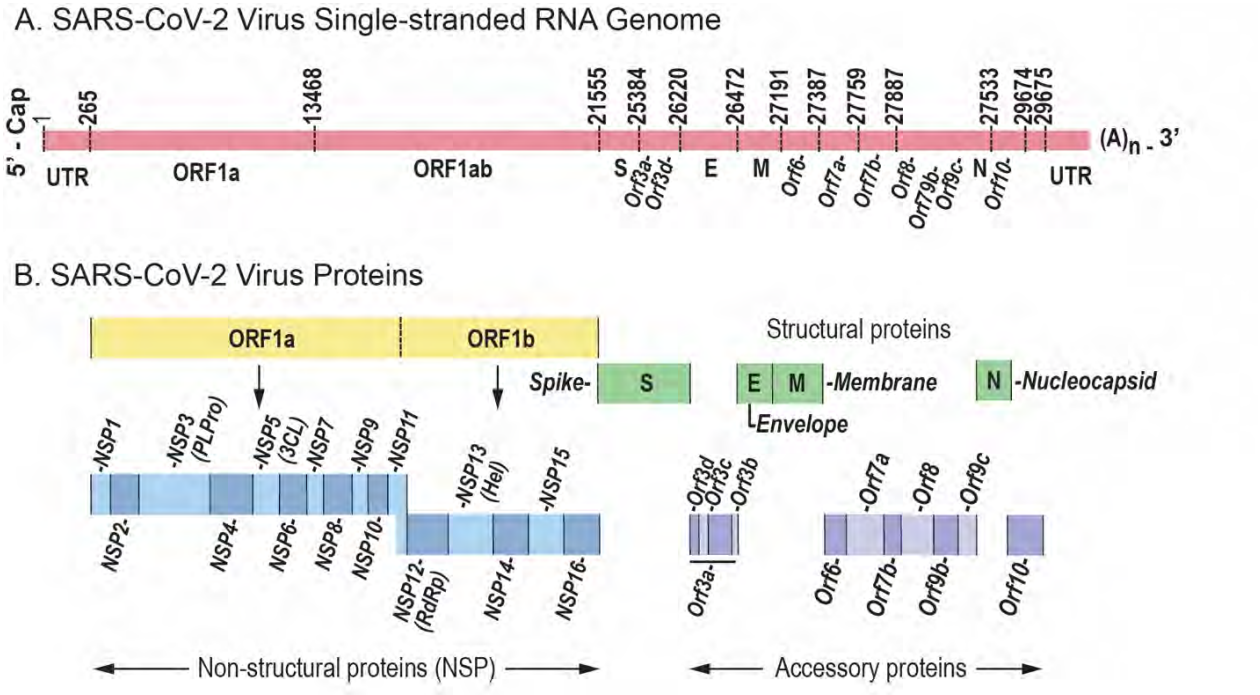
2.7. SARS-CoV-2

SARS-CoV-2 is the seventh major coronavirus, after HKU1, NL63, OC43 and 229E, SARS-CoV, and MERS-CoV, known to infect humans in recent times.[77] It is taxonomically placed in the order *Nidovirales*, subfamily *Orthocoronavirinae*, which has four genera, namely *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronovirus* and *Deltacoronoavirus*. Like SARS-CoV-1 and MERS-CoV, SARS-CoV-2 is a betacoronavirus.[78]

2.7.1. The Structure of SARS-CoV-2 Genome and Proteins

Characteristic of coronaviruses, SARS-CoV-2 is a ribonucleic acid (RNA) containing virus that has a positive-sense, single-stranded genome around 29,903 nucleotides long. Its genome encodes the information for construction of at least 28 different viral proteins that permit the reproduction of the infectious viral particle. The locations of the genes that encode the SARS-CoV-2 structural and non-structural (NSP) proteins are illustrated in Figure 1. Non-structural proteins are generally considered those proteins that are not found in the completed infectious viral particle.

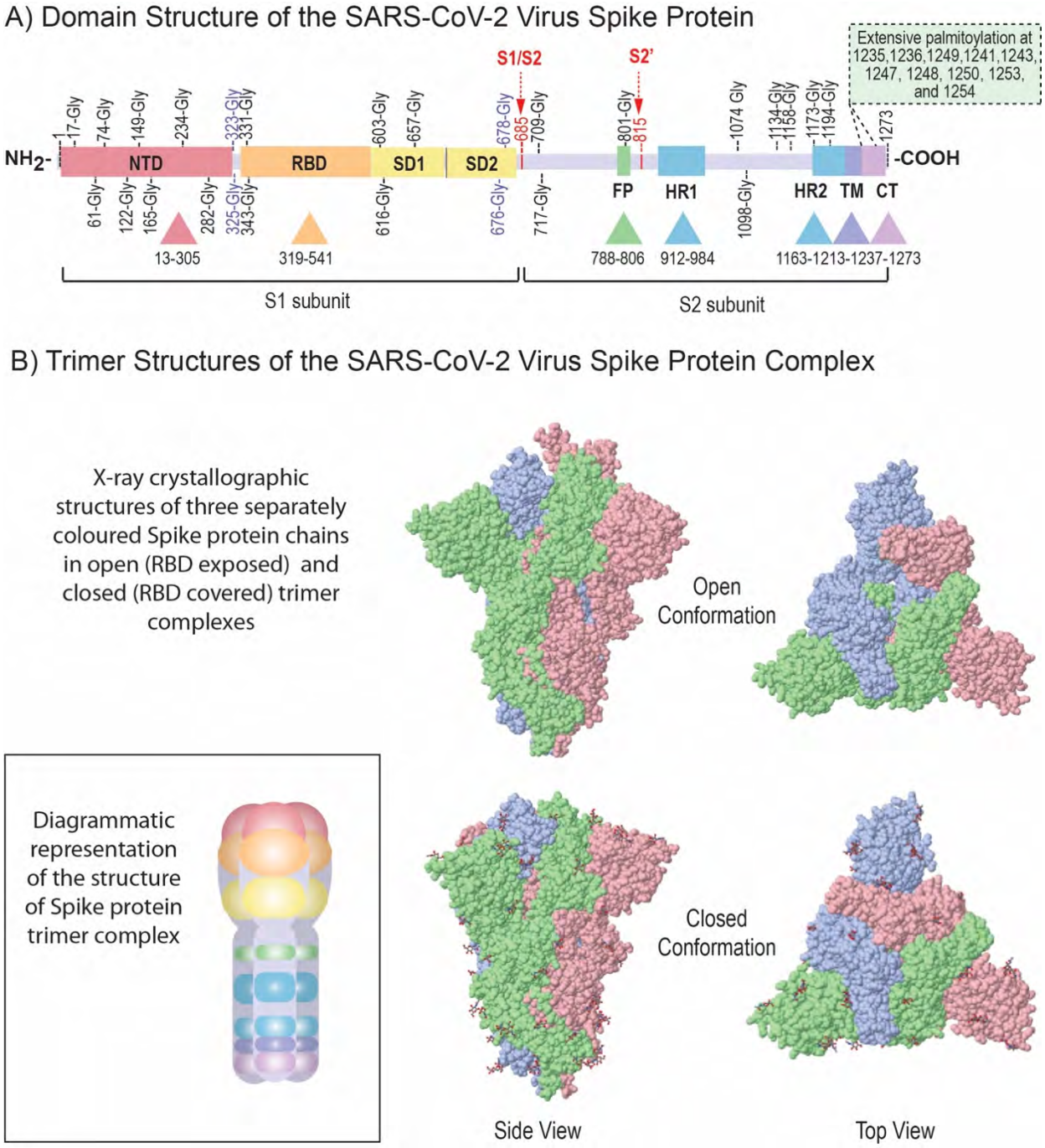
Figure 1. Location of protein-encoding genes in SARS-CoV-2 genome (**A**) and the proteins that they encode (**B**). Of particular relevance are the Spike (S), Membrane (M), Envelope (E) and Nucleocapsid (N) proteins, which are found in the final virus particle along with a single strand of viral RNA. Adapted from Figure 2 of Tali *et al.* (2021)[79] and Figure 1 of Yadav *et al.* (2021).[80] UTR corresponds the untranslated regions of the viral genome, which do not encode viral proteins. At the 3' end of the RNA is a poly-adenine tail (A_n), which may be 30 to 60 nucleotides long. When produced, the ORF1a and ORF1b proteins are further processed by partial proteolysis to generate 16 non-structural proteins (NSP), which play a role in the replication of the virus inside of host cells.



Each protein has an amino acid composition and sequence that is dictated by the sequences of the nucleotides in the SARS-CoV-2 virus genes. Like other viruses in the coronavirus family, it is characterized by a crown-like appearance under an electron microscope, which arises from the location of multiple large Spike protein complexes on the viral particle surface. The Spike protein, which is made

initially as a 1273 to 1278 amino acid long precursor protein, is clipped into S1 and S2 subunits that remain tightly interlinked (Figure 2). When expressed on the surface of a virus or cell, the Spike protein is located in trimeric complexes of three S1 subunits and three S2 subunits that are intertwined. The S1 subunit features a region called the receptor binding domain (RBD) through which the virus can attach to receptors on host cells, including particularly the angiotensin converting enzyme – 2 (ACE2) protein, thus gaining access to cells where it has the potential replicate.

Figure 2. Domain structure of the SARS-CoV-2 Spike protein (**A**) and its trimer complex structures (**B**). Adapted from Huang *et al.* (2020)[81] and Zhao *et al.* (2021).[82] Like other coronaviruses, SARS-CoV-2 binds to host cells via its Spike protein, which has an affinity for ACE2. The RBD (receptor binding domain) region is critical for binding to ACE2. A protease cleavage site (S1/S2), not found in other beta-coronaviruses (like SARS-CoV and MERS-CoV), and targeted by common human proteases including furin and TMPRSS2, increases the infectivity of SARS-CoV-2. The N-terminus domain (NTD) is the first part of the protein that is made during protein synthesis by the ribosomes, and the C-terminus domain (CT) is the last part that is made. Just before the CT is the transmembrane domain (TM), which is a hydrophobic patch of about 17 amino acid residues in length, which anchors the Spike protein into the lipid membrane that envelopes the virus. The C-terminus also features covalently-bound fatty acid side chains *(i.e.,* it is heavily palmitoylated), which further strongly affixes the Spike protein complex to lipid membranes.[81] The locations of glycan groups that are also attached to the Spike protein are also shown.[82] The Spike protein is extensively glycosylated (Gly) at about 26 sites: 22 glycans are N-linked to asparagine amino acid residues (black) and 4 glycans are O-linked to threonine amino acid residues (purple). The Fusion Peptide (FP) mediates the fusion of the virus particle with the plasma membrane of the host cell. HR1 and HR2 correspond to heptad repeat domains, which also participate in membrane fusion. The front end of proteins is called the N-terminus, because it usually features a free amino (NH_2) group, and the back end of proteins is known as the C-terminus, because it usually has a carboxyl (COOH) group. The N-terminus features 13 amino acids that serve as a signal peptide for membrane insertion. Amino acid numbering is based on the UniProt P0DTC2 entry for SARS-CoV-2. The X-ray crystallographic structures from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Base (PDB) of the SARS-CoV-2 Spike trimer in open (RBD up) and closed (RBD down) conformations are from PDB files 7DDN and 7DF3, respectively.



Apart from copies of the Membrane and Envelope proteins that are also exposed on the outside of the virus, any of the other viral proteins that are present in the fully formed viral particle are buried in its interior. The other SARS-CoV-2 genome-encoded proteins are not likely to be commonly present in the viral particle, except for the Nucleocapsid protein, which interacts with the RNA genome to facilitate its packing. Internal viral proteins are less useful for immune cell recognition of the intact virus particle for its removal. However, antibodies that are produced against the Nucleocapsid can be

useful to indicate a past infection with SARS-CoV-2 long after recovery from COVID-19 or an asymptomatic infection.

In view of the virus surface accessibility and large size of the Spike protein complex, it has been specifically targeted for the production of vaccines that can evoke the adaptive immune system in people to produce two main classes of lymphocytes, *i.e.*, B-cells and T-cells. Activated B-cells produce antibodies which will recognize the Spike protein on the virus particle, and stimulated T-cells will attack virus-infected cells.

The bivalent COVID-19 vaccines produced mixed versions of the Spike protein gene from both the original Wuhan strain and Omicron BA.4/5 strains that predominated in mid-2022, all of which were essentially extinct and supplanted by the Omicron XBB strains by early 2023. The bivalent COVID-19 vaccines allow for the formation of four possible combinations of triplets, two of which are not found naturally in any virus strains. X-ray crystallographic structures of the spike protein complexes isolated from cells that have been treated with bivalent vaccines have not been described in the scientific literature. The effects of the mixed, heterogeneous versions of the Spike protein complexes that result from the new bivalent vaccines are unclear.

2.7.2. Receptors for the SARS-CoV-2 Spike Protein

As mentioned above, the Spike protein via its RBD is able to attach to the ACE2 protein, which is expressed on the surface of diverse human cell types. Attachment to ACE2 is possible when the RBD is accessible following flipping to the open position in the S1 subunit. When the Spike protein is finally presented on the surface of the SARS-CoV-2 virus or on the surface of host cells following the uptake of COVID-19 genetic vaccines, it can exist in both open and closed conformations.

It should be appreciated that ACE2 is not the only host cell protein that SARS-CoV-2 can bind via its Spike protein. Neuropilin (NRP1) is another target receptor for the Spike protein.[83] NRP1 binds to vascular endothelial growth factor-A (VEGF-A), which mediates pain reception and growth of blood vessels.[84] Like ACE2, NRP1 is highly present in the endothelial and epithelial cells of the nose and lungs. Moreover, a wide range of immune cell receptors, including CCR9, CD2, CD4, CD7, CD26, CD50, CD56, CD106, CD150 and XCR1, have been predicted to have high affinity for the RBD of the Spike protein

based on molecular modeling studies.[85] Furthermore, the nicotinic acetylcholine receptor has been implicated as another target for the Spike protein by molecular modeling studies.[86]

ACE2 is one of the main enzymes of the renin-angiotensin system (RAS), which is central to the regulation of blood pressure, fluid and salt balance.[87, 88] As a protease, ACE2 clips the 8-amino acid long hormone angiotensin 2 to a slightly shorter 7 amino acid long peptide called Ang (1-7), which then mediates vasodilation, and increases blood flow.[89]

By contrast, angiotenin 2 promotes vasoconstriction of blood vessels, inflammation, and subsequent thickening and scarring of tissues. By binding to its receptor ACE1, angiotensin 2 turns on signaling pathways inside of cells to ultimately increase blood pressure, directly by causing constriction of small arteries and indirectly by causing the release of the hormones aldosterone from the adrenal glands above the kidneys and vasopressin from the pituitary gland at the base of the brain. The binding of SARS-CoV-2 to cells appears to inhibit the enzymatic activity of ACE2, and permit accumulation of angiotensin 2.

ACE2 is widely and differentially expressed in diverse human tissues. Among the 31 tested human tissues in one study, ACE2 gene expression was highest in cells of the testes, small intestine, kidneys, heart, thyroid, and adipose tissue, and lowest in blood, spleen, brain, and skeletal muscle.[90] Similarly, the Human Protein Atlas (HPA)[91] database shows that ACE2 has relatively high ACE2 protein expression levels in the duodenum, small intestine, gallbladder, kidneys, testes, seminal vesicles, colon, rectum, and adrenal glands.

As often observed with diverse viruses, SARS-CoV-2 spike protein can interact with multiple cell receptors leading to pathophysiological consequences linked to the perturbation of the normal activity of the cells expressing those receptors. Amongst the myriad of symptoms associated with COVID-19**,** immune-related complications, such as lymphocytopenia and “cytokine storms”, are common in severe disease. One possible path for such pathologies is the recent finding that SARS-CoV-2 Spike protein can also bind to CD4 receptor and mediate its entry in T-helper cells, thereby affecting its normal function and leading to viral persistence and disease severity.[92] T-helper cells play a critical role in mediating the activation of the adaptive immune systems, and are also targeted by the human immunodeficiency virus-(HIV) in acquired immunodeficiency syndrome (AIDS). More about how the immune system fights viral infection will be provided in Chapter 3.

2.7.4. Demographics of SARS-CoV-2 Hosts

The structure of the ACE2 receptor in different species largely dictates whether SARS-CoV-2 can infect them. Initially in the COVID-19 pandemic, the Wuhan strain of SARS-CoV-2 poorly infected rats and mice. The inability to evoke responses in these rodents compromised early pre-clinical safety studies of vaccines, and necessitated the production of transgenic mice that expressed the human version of ACE2 in their tissues to study drugs that might potentially block infection of the virus and its replication. However, as the SARS-CoV-2 mutated within the human population, it was able to expand its range of potential host species. For example, wild rats in the sewers of New York City ultimately became susceptible to infection with the Alpha, Delta, and Omicron variants of SARS-CoV-2.[93]

SARS-CoV-2 has also been shown to infect a wide range of other wild, domestic and captive animals since its early identification in pangolins and civets. An ever-expanding list of infected animals includes ferrets, minks, Syrian golden hamsters, bushy-tailed woodrats, striped skunks, domestic cats, lions and tigers, wild deer, and gorillas.[94, 95, 96, 97, 98, 99, 100] So far, cotton tail rabbits, fox squirrels, Wyoming ground squirrels, black-tailed prairie dogs, house mice and raccoons have been resistant to SARS-CoV-2 infection.[97] This ability of SARS-CoV-2 to infect and propagate in so many diverse species means that even if the human population could temporarily eliminate the virus, it will be able to re-infect humans in the future from animal reservoirs.

2.7.4. Roles of SARS-CoV-2 Viral Proteins

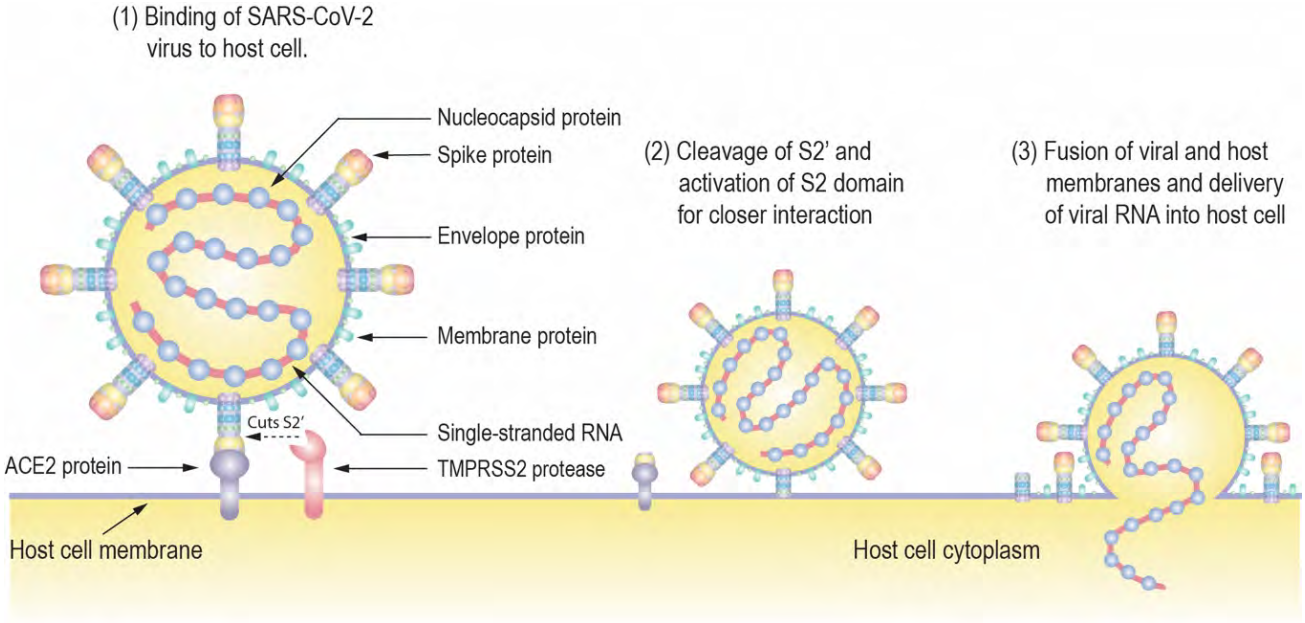
In additions to the actions of furin and/or transmembrane protease serine 2 (TMPRSS2), which generates the S1 and S2 subunits of the Spike protein during formation of the Spike trimer complex, it may also be cleaved by proteases in the cathepsin family.[101, 102, 103] Other proteases that might also cleave the S1 and S2 subunits include cathepsin L, TMPRSS11D and TMPRSS13.[104, 105]

Binding of SARS-CoV-2 to the ACE2 protein on a suitable host cell triggers a cascade of events that lead to internalization of the virus into the cell as shown in Figure 3. After the attachment of SARS-CoV-2 to ACE2 via its RBD, the transmembrane protease serine 2 (TMPRSS2), which is present on the surface of the host cells, further clips the Spike S2 subunit into two fragments. The resultant conformational change in the cleaved S2 subunits facilitates fusion of the outer membrane of the virus

particle with the plasma membrane on the surface of the host cells. This results in the release of the viral ribonucleoprotein complex into the cytoplasm of the host cell. The ribonucleoprotein component is the positive-sense, single strand of RNA decorated with Nucleocapsid proteins.

While this is the main means of entry into most host cells, there are other routes, including the capture of the viral particle by a process known as endocytosis.

Figure 3. Binding and internalization of the SARS-CoV-2 to host cells. The TMPRSS2 protease further cleaves the Spike protein S2 subunit in two to facilitates the fusion of membranes of the virus and host cell to permit the entry of the viral genome into the host cell. Based in part on Figure 1 from Lamers and Haagmans (2022).[106]



Once inside the host-cell, the viral RNA genome is released and later replicated through viral proteins that are encoded by the SARS-CoV-2 genome. The RNA sequence is the template that allows for the production of the viral proteins. It is unclear how many intact virus particles are produced that can be assembled and then spread to nearby cells. A large portion of the packaged viral particles contain RNA that is missing the back end and is defective for producing new virus.[107] Such defective viral genomes are commonly produced with other single-stranded RNA viruses, including RSV, measles, influenza, Ebola, and dengue viruses.

Through a series of subsequent steps for which the details remain sketchy, different genes are translated by ribosomes into viral proteins with the aid of existing host proteins that further facilitate

the production of negative-sense RNA copies of the positive-sense RNA genome. These negative-sense RNA copies, in turn serve as templates to make several more positive-sense RNA genomes, which are eventually packaged into new infectious virus particles. The non-structural protein and accessory proteins encoded by the viral genome ultimately provide for the synthesis of viral Spike (S), Envelope (E), Membrane (M) and Nucleocapsid (N) proteins, which are required components in the completed virus particle.

The Spike protein is a type I transmembrane protein that is 1273 to 1279 amino acids long with several polysaccharide attachments (*i.e.,* it is N-linked and O-linked glycosylated with polymers of various sugars). Some of these N-glycans are thought to be important in modulating the conformation of the RBDs. Glycosylation of foreign proteins can also reduce their recognition by host antibodies. About three-quarters of the surface of the Spike protein trimer complex is shielded by the glycan chains.

The viral Membrane protein is 223 amino acid long, occurs in a dimeric form, and is also glycosylated (*i.e.,* it is O-linked glycosylated). Although it is found in the lipid membrane of the virus particle, it binds the Nucleocapsid protein, which in turn is also associated with the viral RNA genome. This plays an important role in the final assembly of the virus particle so that it contains the genetic payload.

The viral Envelope protein is 75 amino acids long, and it plays a role in the assembly and release of the viral particle. Like the Spike and Membrane proteins, the Envelope protein features a trafficking signal sequence that enables its integration into the endoplasmic reticulum (ER) membranes of the cell.

The viral Nucleocapsid protein is 420 amino acids long, and it has three highly evolutionary conserved domains: an N-terminus domain, an RNA-binding domain, and a C-terminus domain. The RNA-binding domain undergoes heavy modification by a process known as protein phosphorylation, which appears to be essential for the ability of the Nucleocapsid protein to bind RNA and in the replication of the virus. In combination with adenosine-triphosphate (ATP), this appears to be performed by an enzyme known as glycogen synthase kinase-3, and inhibitors of this protein kinase block SARS-CoV-2 replication in cells in culture.[108] Multiple Nucleocapsid proteins work together to

facilitate the packaging of RNA in the viral particle. The protein also enhances virus transcriptional efficiency.

Upon entry into the host cell, the ORF-1a and ORF-1ab genes found in the first half of the SARS-CoV-2 genome are translated by the ribosomes to produce two large polyproteins, pp1a and pp1ab, which undergo proteolytic cleavage to form several smaller proteins (NSPs 1 to 16) (Figure 1). Some of these reassemble into a functional viral RNA polymerase that is sometimes referred to as a replicase. The pp1a non-structural protein is processed by proteolysis into NSP1 to NSP11 and the pp1ab non-structural protein is similarly processed to produce NSP12 to NSP16. The second half of the viral genome encodes the remainder of the viral proteins, including the Spike, Envelope, Membrane, Nucleocapsid and NSPs specified by the RF3a, ORF3d, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF14, and ORF10 genes. These latter proteins are generated by a carefully orchestrated sequence of replication-transcription events that lead to the synthesis of subgenomic RNAs from the negative-sense RNA strand that was produced by the replicase complex. These shorter positive-sense RNAs are translated to produce several of the other structural and accessory proteins that participate in the assembly and encapsulation of the genomic RNA into the final virus particle.

The roles of many of the other 25 proteins encoded by the SARS-CoV-2 have been elucidated, in part due to their similarity with other coronavirus proteins.[80] For example, the NSP9 proteins of SARS-CoV-1 and SARS-CoV-2 share about 97% amino acid sequence similarity.[109] Many of these viral proteins are RNA polymerases, which are enzymes that act to replicate the RNA genome and produce mRNAs that encode for the viral proteins that are required at the later stages of the assembly and export of the final virus particles. Several of the other viral proteins are proteases that cleave the viral proteins into intermediate and mature functional proteins. Some of these viral RNA polymerases and proteases have been targeted for development of antiviral drugs against SARS-CoV-2. Many of the other viral proteins target the production of immune cell mediators known as cytokines, which are released from infected host cells to recruit immune cells to the site of the infection. Interferon regulatory transcription factor-3 (IRF3) is often affected in the infected host cells, which results in reduced or enhanced production of interferons (IFNs). Many of the actions of the NSP and the accessory ORF proteins appear to be in conflict with inhibiting or activating the immune system, although there is a trend towards early suppressions of host cell efforts to recruit the immune system.

The process of viral replication with RNA viruses necessitates the creation of a double- stranded RNA molecule intermediate. This can trigger a cascade of events leading to antiviral effects by the host cell. Double-stranded RNA is not normally found in host cells, and there are sensory proteins, such as double-stranded RNA-dependent protein kinase, which can activate counter measures, such as the production of IFNs. SARS-CoV-2 is able through several of the NSPs and some of the ORF viral proteins to suppress IFN production as well as general cellular mRNA translation to support viral mRNA translation. For example, NSP5 and the Nucleocapsid protein have been found to suppress the formation of stress granules in host cells, which are important the cellular protective responses to viral infection, including type I and type III IFN responses.[110]

The specific NSP and ORF protein encoded by the SARS-CoV-2 genome are listed in Table 1.

Table 1 – Roles of non-structural (NSP) and other open reading frame (ORF) proteins encoded by the SARS-CoV-2 genome.

SARS-CoV-2 Protein	No. of Amino Acids	Roles
NSP1	180	Part of the viral replicase complex, also acts to degrade host cell mRNAs.
NSP2	638	Part of the viral replicase complex, that binds to a translation repressor complex (GIGYF2/4EHP), which results in inhibition of the production of Type I interferon-beta (IFNβ).[101]
NSP3	1945	Large, multi-functional, transmembrane protein, which acts as a papain-like protease (PLpro) to catalyze the release of NSP1, NSP2 and NSP3 from the N-terminal region of pp1a and pp1ab, and also targets other cellular host proteins.
NSP4	500	Transmembrane protein and part of the viral replicase complex, which along with NSP3 and NSP6 help modify the host endoplasmic reticulum (ER) membranes to induce the formation of double-membrane vesicles (DMVs).
NSP5	306	Protease (3C-like) that cleaves precursor viral proteins into intermediate nonstructural proteins and mature proteins, as well as host cell proteins (*e.g.*, NLRP12 and TAB1).[102]
NSP6	290	Transmembrane protein with NSP3 and NSP4 that induces the formation of ER-derived double-membrane vesicles (DMV's), excludes host cell proteins to DMVs, and recruits lipid drops to populate their lipid membranes.[103]

NSP7	83	RNA-dependent RNA polymerase that complexes with NSP8 and NSP12 to produce viral RNA.
NSP8	198	RNA polymerase that complexes with NSP7 and NSP12 to produce viral RNA.
NSP9	198	Single-stranded RNA binding protein that in a dimeric form may assist helicases to unwind double stranded RNA and participate with the NSP7/NSP8/NSP12 RNA-dependent RNA polymerase complex.
NSP10	139	Related to the NSP10 protein of SARS-CoV-1, which interacts with NSP14 and NSP16 to stimulate their exoribonuclease and methyltransferase activities, respectively.[104]
NSP11	13	Identical to the first part of NSP12, with unclear function.
NSP12	932	RNA-dependent RNA polymerase that complexes with NSP7 and NSP8 to produce viral RNA, and inhibits the production of interferon from virus infected cells.[105]
NSP13	932	Helicase enzyme that binds to double-stranded RNA to facilitate its unwinding.[106]
NSP14	527	Proofreading exoribonuclease that degrades RNA, and has been linked with increased production of the cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8).[107]
NSP15	346	Uridine-specific endoribonuclease that cleaves RNA, but its role in viral replication is unclear, although it has been implicated in other coronaviruses in the evasion of host immune responses.[108]
NSP16	298	2'-O-methyltransferase that methylates the front of mRNAs, and through interaction with NSP10 is important in immune system evasion.[109]
ORF3a	274	Transmembrane multifunctional protein that is O-linked glycosylated and might form, after dimerization, an ion channel for positively charged ions that interferes with ion channels in host plasma and internal membranes, and can induce cellular innate and proinflammatory immune responses such as production of interferons, interleukins and chemokines.[110]
ORF3d	154	Protein with unknown function, but elicits a strong antibody immune response.[111]
ORF6	61	Membrane-associated protein in the ER and Golgi Apparatus, which disrupts immune signaling by inhibition of host cell mRNA export and production of host proteins through interaction with Rae1.[112]
ORF7a	122	Accessory protein that is an integral membrane protein, which binds to and inhibits the host protein Serine Incorporator 5 (SERINC5) that normally may become over-expressed to interfere with budding virus particle formation.[113]

ORF7b	44	Accessory protein that is an integral membrane protein in the Golgi Apparatus, which promotes production of IFN-beta, tumor necrosis factor-alpha (TNFα), IL-6, activation of IRF3, and TNFα-induced cell death.[114]
ORF8	121	Protein that may be transported to the ER and associate with major histocompatibility complex-I to down-regulate it, and can be secreted as a dimer from cells and serve as a mimetic of interleukin-17A (IL-17A) to stimulate IL-17A receptor signaling and production of inflammatory cytokines such as IL-1β, IL-6, IL-12, and TNF-α.[115]
ORF9b	97	Protein that associates with the host adapter protein TOM70 (a component of the mitochondrial translocase complex of the outer membrane), and suppresses Type I interferon-mediated antiviral responses.[116]
ORF9c	73	Transmembrane protein with unknown function that is highly related to NSP14 in bat SARS coronavirus and SARS-CoV-1.[117]
ORF10	38	Protein with unknown function, which interacts with a variety of cellular host proteins, but does not appear to be essential for viral infection or replication.[118]

The production of the structural proteins by ribosomes is near the membranous endoplasmic reticulum (ER) of cells. The ER is an extensive network of membranes in cells from which the Golgi Apparatus derives. The Golgi Apparatus allows for the transport of membrane lipid and proteins throughout the cell. In the case of the Spike protein, most of it is driven into the luminal side (as opposed to cytoplasmic side) of the ER following its biosynthesis, but it remains anchored in the ER membrane by its transmembrane domain and by covalent attachment of the fatty acid palmitate at multiple sites. The Spike, Membrane, Envelope, and Nucleocapsid proteins, and genomic RNA remain in close proximity within the ER following their production, and through the Golgi apparatus of cells, eventually get trafficked together via the Golgi Apparatus in vesicles to the cell surface, where the virus particles in these vesicles are released following fusion of the lipid bilayers of the vesicles with the lipid bilayer of the plasma membrane.

The traditional explanation of viral replication involves the production of new virus particles that infect more cells and continue to make new virus particles in a logarithmic fashion until the immune system turns the tide to control the infection. However, as will be discussed in Chapter 8, if the immune system initially fails to contain the virus and prevent the early spread of SARS-CoV-2, a loss of control

of immune cell activation can result in a devastating "cytokine storm," with the overproduction of immune modulatory proteins such as interleukins and interferons, which can make the clinical situation far worse.

2.7.5. SARS-CoV-2 Mutation to "Variants of Concern"

Canada-wide, since the first recorded wave of COVID-19 cases that peaked around May 6, 2020 (7-day daily average = 45.6 per million people (pmp)), there has been eight more waves. These 8 additional peaks occurred around January 13, 2021 (**Wave 2**: 7-day daily average = 210.9 pmp), April 19, 2021 (**Wave 3**: 7-day daily average = 227.0 pmp), September 22, 2021 (**Wave 4**: 7-day daily average = 221.6 pmp), January 9, 2022 (**Wave 5**: 7-day daily average = 1091.6 pmp), April 15, 2022 (**Wave 6**: 7-day average = 263.8 pmp), August 1, 2022 (**Wave 7**: 7-day daily average =123.8 pmp), October 22, 2022 (**Wave 8**: 7-day daily average =79.7 pmp), and December 26, 2022 (**Wave 9**: 7-day daily average =64.6 pmp).[119] There has been a steady decline of COVID-19 cases since the beginning of 2023, although there was a slight uptick in COVID-19 cases in the Fall of 2023 starting in September with the onset of the flu season. This remained lower in incidence than any of the earlier COVID-19 waves.

In Canada, as elsewhere, major initiatives to sequence the genomes of SARS-CoV-2 variants as well as human hosts were undertaken. With the CDN$40 million CanCOGeN project funded particularly by Genome Canada, over 433,475 viral samples and 7,171 human samples were fully sequenced at the genome level by April of 2022.[120] Such sequencing studies in Canada and many other countries have revealed just how quickly SARS-CoV-2 mutates; over 10,000 mutant forms of the SARS-CoV-2 virus have been sequenced and identified. However, interest has focused on what have been called variants of concern (VOC) or variants of interest, which have mutations that appear to increase the infectivity of the SARS-CoV-2, and in doing so have allowed these VOC to out-compete other variants and predominate for a time, until they are displaced by other VOC. Typically, SARS-CoV-2 mutants have lifetimes of about 4 months before they begin the fade from their previous prevalence.[121]

In Canada, each of these subsequent COVID-19 waves after the original Wuhan strain were largely defined as being dominated by one or more new VOC's: January 2021 **Wave 2** by B.1.160, B.1.438.1, B.1.2, B.1.1.176; April 19, 2021 **Wave 3** by B.1.1.7 (Alpha) and P.1.14 (Gamma); September 2021 **Wave 4** by AY.25.1 and AY.27 (Delta); January 2022 **Wave 5** by BA.1 (Omicron); April 2022 **Wave**

6 by BA.2 variants including BA.2 (Omicron); August 2022 **Wave 7** by BA.5 variants including BA.5.2 and BA.5.2.1 (Omicron); October 2022 **Wave 8** also by BA.5 variants including BA.5.2 and BA.5.2.1 (Omicron); December 2022 **Wave 9** by other BA.5 variants, BQ1, and BQ.1.1 (Omicron); and as of mid-September 2023 by EG.5 (Eris), EG.5.1, XBB.1 and XBB.2 (Omicron) variants.[122]

Early in the COVID-19 pandemic, certain VOC accounted for most cases within a wave. However, as the pandemic progressed, there has been a greater of diversity of competing VOC's. This phenomenon is likely due to an optimization of the mutations to increase the affinity of the SARS-CoV-2 Spike protein for the ACE2 protein on host cells, reduce its virulence so the host is less likely to be sick, and more readily go out and transmit the virus, and better avoidance of immune cell defenses. It should be appreciated that all of the VOC are still extremely similar in structure to the original Wuhan strain. For example, their Spike proteins are at least 96% identical in amino acid sequence. Some of the mutations in the Spike protein associated with VOC are shown in Figure 4. Interestingly, the Wuhan SARS-CoV-2 Spike protein has about a 10- to 20-fold greater affinity for ACE2 than SARS-CoV-1.[123, 124]

Figure 4. Location of mutations in the receptor binding domain (RBD) region of the SARS-CoV-2 Spike protein encoded by variants of concern. The original Wuhan sequence (UniProt ID P0DTC2) is provided with the single letter amino acid codes for each of 20 possible amino acids from residues 311 to 591, which encompasses the receptor binding domain that interacts with the ACE2 protein on host cells. Those amino acids that are known to be important for direct binding to ACE2 are bolded and underlined. Identical amino acids in the VOC are shown with dashes, and substituted amino acid residues are indicated. It is evident that many of the mutations are shared between the VOC, and they often occur at amino acid positions that are known to be critical for binding to ACE2.

Variant	311	321	331	341	351
Wuhan	GIYQTSNFRV	QPTESIVRFP	NITNLCPFGE	VFNATRFASV	YAWNRKRISN
Alpha/B.1.1.7	----------	----------	----------	----------	----------
Beta/B.1.351	----------	----------	----------	----------	----------
Gamma/P.1	----------	----------	----------	----------	----------
Delta/B.1.617.2	----------	----------	----------	----------	----------
Epsilon/B.1.427/B.1.429	----------	----------	----------	----------	----------
Omicron/BA.1.1.529	----------	----------	--------D-	----------	----------
Omicron/XBB.1.5	----------	----------	----------	----------	----------
Eris/EG.5.1	----------	----------	----------	----------	----------
	361	371	381	391	401
Wuhan	CVADYSVLYN	SASFSTFKCY	GVSPTKLNDL	CFTNVYADSF	VIRGDEVRQI
Alpha/B.1.1.7	----------	----------	----------	----------	----------
Beta/B.1.351	----------	----------	----------	----------	----------
Gamma/P.1	----------	----------	----------	----------	----------
Delta/B.1.617.2	----------	----------	----------	----------	----------
Lambda/C.37	----------	----------	----------	----------	----------
Omicron/BA.1.1.529	----------	L-P-F-----	----------	----------	----------
Omicron/XBB.1.5	----------	L-P-F-----	----------	----------	----------
Eris/EG.5.1	----------	L-P-F-----	----------	----------	----------
	411	421	431	441	451
Wuhan	APGQTGKIAD	YNYKLPDDFT	GCVIAWNSNN	LDSKVGGNYN	YLYRLFRKSN
Alpha/B.1.1.7	----------	----------	----------	----------	----------
Beta/B.1.351	------N---	----------	----------	----------	----------
Gamma/P.1	------T---	----------	----------	----------	----------
Delta/B.1.617.2	----------	----------	----------	----------	-R--------
Lambda/C.37	----------	----------	----------	----------	-Q--------
Omicron/BA.1.1.529	------N---	----------	---------K	-----S----	----------
Omicron/XBB.1.5	------N---	----------	---------K	-----S----	---------K
Eris/EG.5.1	------N---	----------	---------K	-----S----	-----L---K
	461	471	481	491	501
Wuhan	LKPFERDIST	EIYQAGSTPC	NGVEGFNCYF	PLQSYGFQPT	NGVGYQPYRV
Alpha/B.1.1.7	----------	----------	----------	----------	Y---------
Beta/B.1.351	----------	----------	---K------	----------	Y---------
Gamma/P.1	----------	----------	---K------	----------	Y---------
Delta/B.1.617.2	----------	-------K--	----------	----------	----------
Lambda/C.37	----------	----------	----------	----------	----------
Omicron/BA.1.1.529	----------	------NK--	---A------	--K--S-R--	Y---H-----
Omicron/XBB.1.5	----------	------NK--	---A-----S	--R--S-R--	Y---------
Eris/EG.5.1	----------	------NK--	---A-----S	--R--S-R--	Y---------
	511	521	531	541	
Wuhan	VVLSFELLHA	PATVCGPKKS	TNLVKNKCVN	FNFNGLTGTG	
Alpha/B.1.1.7	----------	----------	----------	----------	
Beta/B.1.351	----------	----------	----------	----------	
Gamma/P.1	----------	----------	----------	----------	
Delta/B.1.617.2	----------	----------	----------	----------	
Lambda/C.37	----------	----------	----------	----------	
Omicron/BA.1.1.529	----------	----------	----------	------K---	
Omicron/XBB.1.5	----------	----------	----------	------K---	
Eris/EG.5.1	----------	----------	----------	------K---	

By January 7, 2022, 84.2% of Canadians had been vaccinated for COVID-19 at least once, 77.9% at least twice and 31% three-times. However, this did not prevent the largest wave of COVID-19 cases, which at the time were dominated by the Omicron BA.1 and BA.2 VOC's. In November of 2021, it had been the Delta VOC that predominated. Within a month, Omicron BA.1 effectively outcompeted the Delta variant. Studies have indicated that Omicron BA.1 was 3- to 6-times more infectious than previous SARS-CoV-2 variants.[125] Despite almost an 850% increase in the total number of COVID-19 cases between the peaks of the fourth and fifth waves, there was only a 221% increase in total hospitalizations, a 29% increase in total ICU admissions and a 53% increase in total deaths. These data clearly demonstrate that Omicron BA.1 and BA.2 variants were much less severe than the Delta variant.

The duration of the illness for those with COVID-19 was also about half the length of time. The same relatively low rates of hospitalization, ICU admissions and deaths have been observed with the subsequent VOC's.

The Omicron BA.1 VOC was first identified in South Africa (although it appears to have originated in Europe), and there were very few deaths per capita in South Africa from this variant. Only about 40% of the South African population was vaccinated at least once by the end of 2021, and in 2023 about 50% were doubled or more vaccinated.[126] At the peak of the Omicron BA.1 wave in South Africa with 2.93 deaths per million people per day (7 day average), there was 4.29 deaths per million people per day (7 day average) in Canada in the same wave.[127] This might be partly explained by a lower average age in South Africa (median age is 27.6 years compared to 41 years in Canada). However, a very large portion (around 20%) of the South African population also have compromised immune systems with AIDS. Typical life expectancy in Canada is 81.75 years, compared to 65.25 years in South Africa. The average age of death from COVID-19 in Canada in 2020, pre-vaccination, was 83.8 years, whereas in 2019, the average age of death from all causes was 76.5 years.[128]

Since the first emergence of the Omicron VOC's, the incidence of COVID-19, hospitalization and deaths have remained low in Canada for over a year and a half. This is despite the multitude of over 30 other Omicron variants of SARS-CoV-2 (including BA.1, BA.5.1.27, BA.5.2.34, BA.5.5.1, BE.1.1.1, BE1.2, BE.9, BF.11, BF.7, BN.1.3, BN.1.3.1, BQ.1, BQ.1.1, BQ.1.2, BQ.1.3, BQ.1.5, BQ.1.8.2, BR.2.1, BW.1.1, CH.1.1, CK.1, CM.8.1, CV.1, DJ.1.1, BF7, XBB.1, XBB1.5, XBB1.16, XBB.2, EG.5 (Eris), EG.5.1, FL15.1) that have been accounting for COVID-19 cases in September, 2023. By the end of the third week in August 2023, EG.5 was responsible for 20.6% of all US cases of COVID-19, and the FL15.1 strain accounted for about 13.3% of US COVID-19 cases.[129] The substantially reduced progression to severe COVID-19 outcomes seen with the early Omicron variants as compared to the Delta variant was also described in a meta-analysis of the large, integrated healthcare system in Southern California.[130] The SARS-CoV-2 virus has continued to evolve to be as infectious and benign as it can be, such that none of the new variants really predominated in 2023 in Canada.

The high rate of mutation of SARS-CoV-2 is in part due to the poor fidelity of its RNA-dependent RNA polymerase to faithfully reproduce the complete genome of the virus without introducing mistakes*, i.e.*, mutations. There is also a phenomena of RNA recombination whereby simultaneous

infection of the same host cells by two or more related SARS-CoV-2 virus variants can produce new hybrid variants.[131] Many different RNA viruses can undergo mutation by recombination. The mechanism involves the viral RNA-dependent RNA polymerase detaching from one RNA template strand with the partially completed nascent RNA strand intact. It then attaching to another RNA template strand at the identical or a similar position and resuming elongation of the nascent RNA strand. Such jumping on and off different RNA templates can occur multiple times before the nascent RNA strand is fully completed.

Genome sequencing studies have revealed that about 2.7% of the SARS-CoV-2 genomes investigated have evidence of a recombination ancestry.[132] The highest rates of recombination in an RNA virus, as much as 25%, has been reported for mouse hepatitis virus.[133] The SARS-CoV-1[134] and MERS-CoV[135] viruses are believed to have emerged from RNA recombination events. Such a mechanism can provide for zoonotic transmission of coronaviruses and contribute to the species jump with other RNA viruses.

It has been suggested by Tanaka and Miyazawa (2023) that the extra mutations in the Omicron BA.1 variant are too many to be accounted for by natural mutation, and that Omicron variants were already present in 2020.[136] Compared to the original Wuhan strain designated 614G, there were at least 50 mutations identified in Omicron BA.1 variant, with 32 of these causing amino acid substitutions in the Spike protein, and half of these were in its receptor binding domain. There are twice as many mutations in the BA.1 variant of the Spike protein than any of the previous variants. BA.1 also features three mutations in the Membrane protein and six mutations in the Nucleocapsid protein compared to the Wuhan proteins.[137] Moreover, BA.2 has additional 8 unique mutations not found in BA.1 and is missing 13 mutations that are found in BA.1. In fact, all of the BA.1, BA.2 and BA.3 lineages appear to have arisen at about the same time, with additional Omicron variants later arising from different lineages. Thus, these newer Omicron variants did not simply come from a few additional mutations in earlier VOC's. Of the 50 mutations in Omicron variants, 26 were unique to Omicron, 10 were shared with Delta, and 6 were found in the Beta VOC.

Tanaka and Miyazawa (2023) carefully tracked the occurrence of the Spike mutations in the BA.1 and BA.2 strains and these authors came to the conclusion that these were genetically engineered.[136] Alternative hypotheses have been proposed that these variants first emerged by: 1) cryptic spread and

was already present earlier on but not picked up by the standard viral surveillance and sequencing; 2) they evolved in chronically infected COVID-19 patients, who were probably immunocompromised; and 3) zoonosis where Omicron accumulated in nonhuman hosts, such as a mouse, and then jumped into humans.[137] The detection of very similar sequences of the Spike protein isolated from places like Puerto Rico in 2020 supports the first explanation,[136] although the question arises why did Omicron variants not spread much sooner globally, since they are so infectious?

The second hypothesis is partly supported by the high rate of immunosuppression from HIV-infection in as much as 20% of the South African population.[138] But this also begs the question that if Omicron came to South Africa from elsewhere, why did it not spread quickly in Puerto Rico or Europe, where it had been detected previously?

The third hypothesis of a zoonosis origin such as a mouse is also problematic,[139] since the mutations in the Spike protein of Omicron would have optimized for a nonhuman species in which the ACE2 receptor for the Spike protein is likely to be slightly different from humans.

The possibility still remains that the early Omicron variants may have also resulted from genetic engineering and a release from a laboratory. Whether intentional or not, this release may have resulted in the development of a vaccine that permitted “natural” immunity with more infectious and benign SARS-CoV-2 variants.

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Chapter 3:

The Body's Defenses Against Infectious Pathogens

3.1. The Innate and Adaptive Immune Systems

With the constant threat of evolving and new infectious diseases, organisms have had to develop effective countermeasures. Every newborn baby is particularly vulnerable to pathogens, although mother's first milk, known as colostrum, is laden with protective antibodies and maternal immune cells that can confer significant immunity. As maternal protection wanes and the neonate is exposed to various environmental stimuli, hematopoietic (*i.e.,* blood forming) stem cells in the body actively give rise to an extensive arsenal of diverse cells and molecules that form the immune system. The composition and functioning of the immune system is complex, and involves hundreds of diverse immune response proteins that affect over 20 different types of immune cells. What follows is a brief introduction to one of the most amazing defense systems against infectious pathogens as well as cancer found in the bodies of humans and other animals.

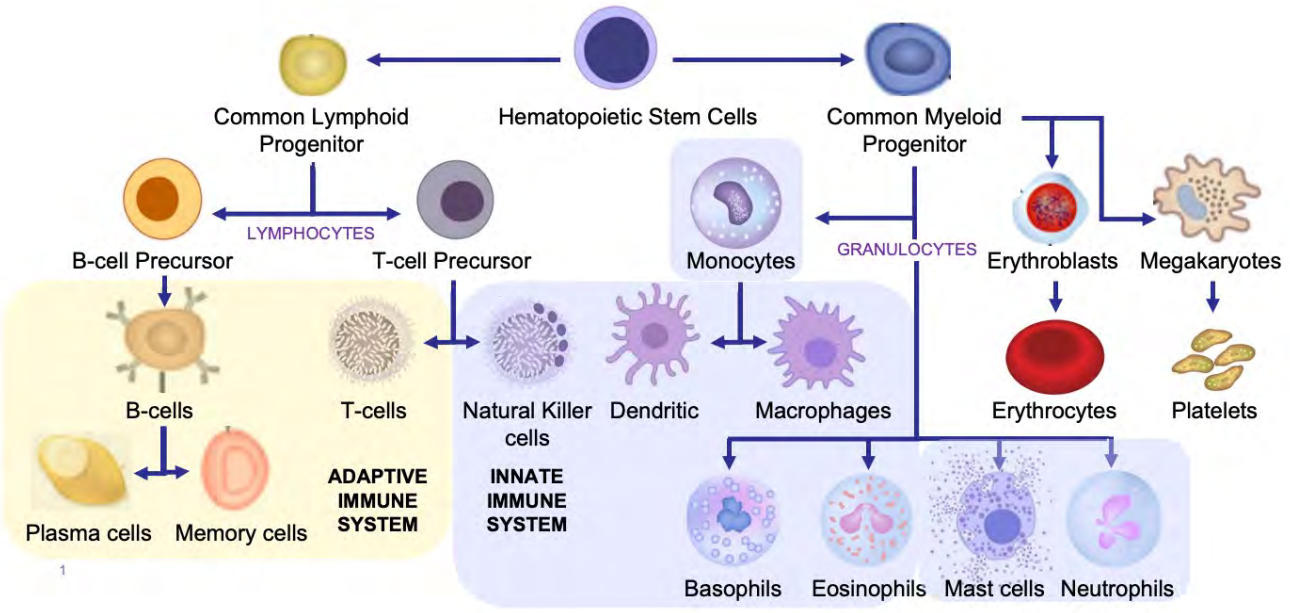
There are two main branches, which are distinguished as the innate and the adaptive immune systems. The cells of the innate immune systems are generally non-specific in their targeting. They develop very quickly within minutes to days following exposure to a danger signal and therefore are particularly useful for combating new pathogens. The innate immune system is especially strong in infants and children compared to adults. Over time, cells called lymphocytes of the adaptive immune system learn to recognize and remember foreign proteins and other structures described as antigens. The specific portions that are targeted on antigen are known as epitopes. The innate immune system, although still very active in adults, is less so due to its augmentation by the adaptive immune system. Nonetheless, these two complementary systems work as a finally tuned orchestra to provide host defense against the diverse foreign agents that will be encountered over a lifetime.

3.2. The Production of Hematopoietic Cells of the Immune System

Hematopoietic stem cells reside primarily in the red bone marrow, which is the core of the bone to generate many of the cells of the immune system and other blood cells depending on how they are stimulated with a variety of possible intercellular mediators known as cytokines. These include a wide range of chemokines, interleukins, interferons, and colony-stimulating factors. Dependent on which combination of cytokines engage the stem cells on specific cell surface receptors, these cells are programmed to undergo successive changes and differentiate into red blood cells (erythrocytes), platelets or different cell types of the immune system, collectively referred to as white blood cells or leukocytes. There is typically about one white blood cell for every 700 erythrocytes in the blood. The erythrocytes transport oxygen, carbon dioxide, and small molecules through the circulatory system. Much smaller platelets mediate the clotting of erythrocytes at sites of tissue damage to prevent loss of blood, and initiate healing through the release of growth factors such as platelet-derived growth factor and transforming growth factor-alpha (TGFα). Apart from acting as a growth factor to stimulate tissue regeneration, TGFα can also promote the formation of new blood capillaries.

There are many distinct leukocyte populations, particularly in the innate immune system (Figure 5). Whereas mammalian erythrocytes and platelets do not have nuclei, leukocytes are classified on the basis of their progenitor cell (myeloid or lymphoid), or on the morphology of their nucleus (mononuclear cells have rounded nuclei and polymorphonuclear cells have multilobed nuclei) and the presence or absence of granules in their cytoplasm. This results in two general groupings: 1) blood mononuclear cells (BMCs, also known as agranulocytes), which includes monocytes and lymphocytes; and 2) polymorphonuclear leukocytes (PMNs, also known as granulocytes). Granulocytes feature granules in their cytoplasm that are loaded with inflammatory and toxic factors, which are released from these cells when they are activated. For example, eosinophils contribute to attacking multicellular parasites, such as worms, through the release of cytokines, positively-charged peptides, and hydrolytic enzymes. Basophils release the anticoagulant heparin to reduce the rate of blood clotting and the vasodilator histamine to increase blood flow to tissues. Neutrophils are amongst the first recruits to a site of inflammation, where they attack and engulf viruses and other microbes.

Figure 5. Cells of the hematopoietic system.



At the early stages of differentiation into leukocyte sub-populations, the stem cells are prompted by specific cytokines to undergo transition into a variety of different lymphoid or myeloid cell lineages. From myeloid progenitor cells, erythrocytes and platelets are generated to comprise most blood cells, but granulocytes are also produced to form monocytes such as dendritic cells and macrophages, or other cells that produce substances that aid in the killing of foreign pathogenic cells as well as recruiting other leukocytes. The lymphoid precursor cells undergo maturation to form lymphocytes, of which B-cells (antibody-producing) and T-cells comprise the adaptive immune response. Other cells that are closely related to T-cells, such as Natural Killer cells, are effective in attacking cancer cells and certain microbe-infected cells. These cells types have some characteristics of both the innate and adaptive immune responses thereby helping to bridge coverage between these two systems to ensure no chinks exist in host defense armor.

The existence of cells associated with innate host defense was first reported in starfish larvae that were irritated with small citrus thorns in 1886 by Russian scientist Elie Metchnikoff.[140] The thorns were attacked and digested by macrophages, which are highly mobile, phagocytic cells. Since starfish have been on the Earth for over a billion years, this demonstrates just how ancient and critical immune systems are.

The development of B- and T-cells starts before birth *in utero*. In newborns, these lymphocytes are naive to the extra-uterine environment and undergo major transitions. The populations of B- and T-cells, for example, learn to differentiate between "self" and "foreign" or "non-self." If the immune system is unable to recognize the normal cells of the body as "self," then auto-immune disease could arise as these cells would target specific components of the body that are misjudged as foreign. The lymphocyte population also learns to ignore harmless molecules in food and the non-dangerous substances that are commonly and continuously encountered in the environment to avoid being constantly and unnecessarily activated; for example, this would include the non-dangerous substances encountered in the gut and airways. These processes of developing central and peripheral tolerance occur via several unique mechanisms before and after birth. The ability of the immune system to distinguish between an enormous range of harmless self and harmful non-self molecules is one of its truly unique features that is critical for survival.

Activation of the immune system is essentially a double-edged sword where a careful balance must be found between removing the foreign agent without harming the host in the process. For example, too much acute or prolonged activation of the immune system may cause severe inflammation and overt tissue damage to the host. Therefore, the immune system has a large number of regulatory mechanisms that detect when a pathogen is cleared and it is appropriate to turn down immune system activation. This is also the reason why any B- and T-cells that inappropriately recognize the body's normal cells, resident flora of bacteria and microbes as well as common substances in the environment, are committed to self-destruction early in development or are carefully regulated throughout life. The B- and T-cells remaining after this careful education process form a diverse pool of naïve lymphocytes that are sensitive to foreign pathogens. Selective stimulation of these naïve cells with antigens on the pathogen triggers their activation and successive divisions into a clonal army of identical cells that have high specificity for an antigenic epitope. As the amount of foreign antigen in the environment declines, such as the successful eradication of a pathogenic virus, the stimulated lymphocyte clones undergo programmed cell death or convert to an inactive resting state. During this process, memory lymphocytes also develop, which survive for various prolonged periods of times, in some cases even a lifetime following exposure to a foreign entity. These memory cells can rapidly reawaken from their slumber to re-engage more efficiently with the pathogen once again when presented with the same or very similar antigens on the pathogen. This allows much faster and more

effective immune responses than in their first encounter. This unique feature of long-term immunological memory is why recovery for a pathogenic infection often provides sustained protection to future encounters with that specific pathogen. This is referred to as naturally acquired immunity.

3.3. The Nature of Antibodies

The specific parts of the foreign antigens that T- and B-cells recognize are called epitopes. They can be very small, right down to just a few amino acids in unique combinations. Such epitopes should be distinct in structure from those found in the normal proteins of the body. Any T- and B-cells that would target “self antigens” are weeded out early in the development of the immune system. Antigens can be proteins, sugars, fats or nucleic acids.

As part of the humoral immune response, B-cells produce immunoglobulins, which are relatively large proteins that bind to specific epitopes on antigens. These antibodies are among the most common classes of globulin proteins found in the plasma of blood after albumin. Each B-cell initially produces a specific antibody that has affinity for a distinct epitope. Since the body has a broad repertoire of billions of different B-cells to recognize the various foreign antigens that it will encounter in a lifetime, at the start there can only be one of each unique antibody producing B-cell. However, in a process known as clonal expansion, engagement of a B-cell with an antigen that is recognized by that B-cell can induce its rapidly proliferation into an army of identical B-cell clones that target exactly the same epitopes on the antigen. Different B-cells may produce antibodies that bind to different epitopes on the same antigen, and this is referred to as a polyclonal antibody response. In short, the body does not have the capacity to hold large numbers of each clone, so it expands and contracts the number of clones as required. The pathogen might itself have many different proteins and other structures to which antibodies can bind. The binding of antibodies to a virus, bacteria or even the toxins produced by them, can block their functional interactions, such as preventing attachment to host receptors. Bound antibodies also attract other immune mediators such as complement proteins to support the attack against antibody-coated infectious pathogens.

The specificity of a single B-cell to produce an epitope-selective antibody has been exploited in the production of monoclonal antibodies. When a B-cell is chemically fused with a cancer cell, the resulting hybridoma cell can be immortalized to constantly grow, divide and keep producing identical

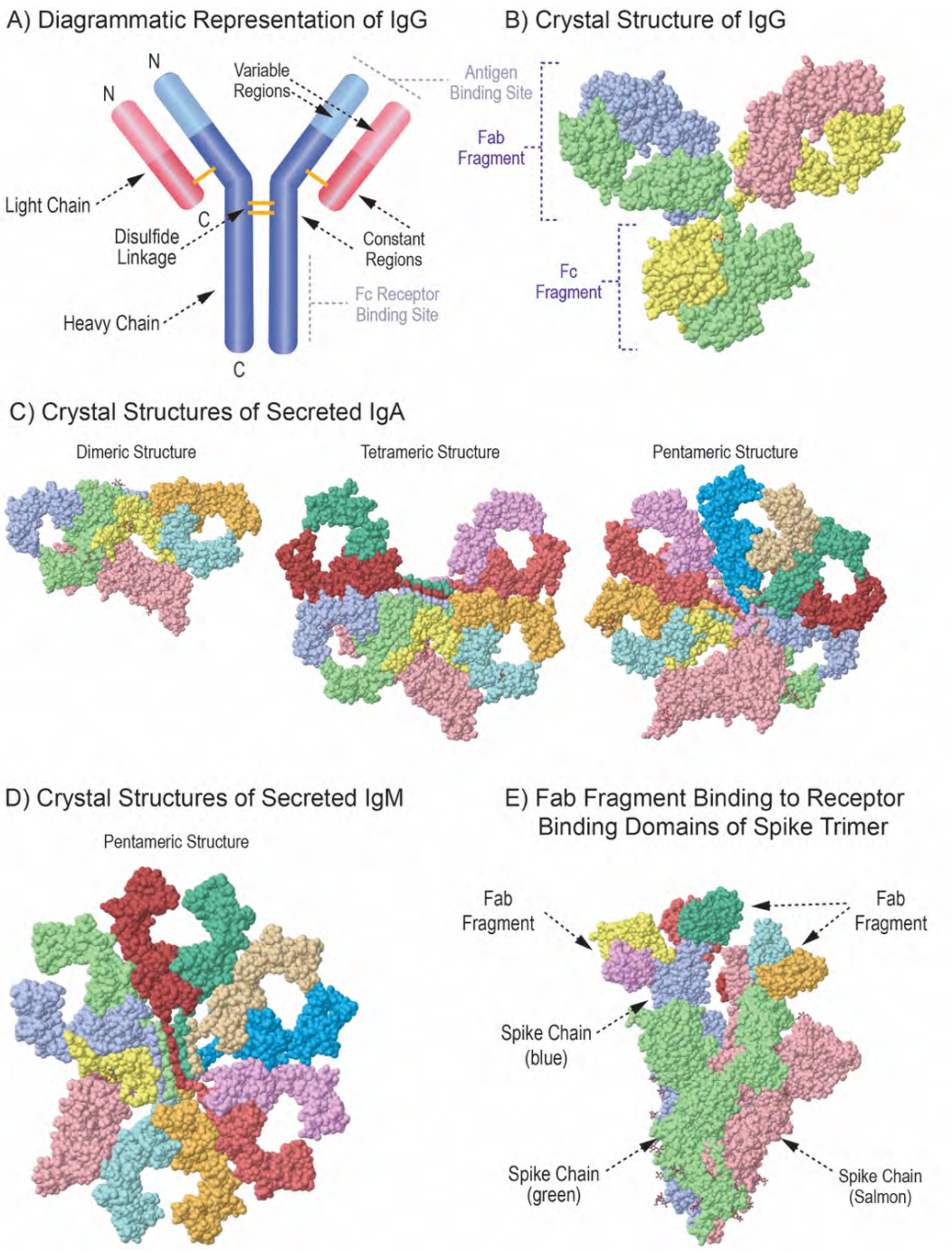
antibodies in future generations derived from that cell. This has been extremely useful for production of therapeutic antibodies that can specifically attack cancer cells or pathogens, and even for blocking the ability of a pathogen like the SARS-CoV-2 virus to bind to host receptors, thus preventing its entry into cells. However, minor changes in the structure of the SARS-CoV-2 Spike protein induced by immunological selection pressure that mediates host cell binding can also result in the loss of the efficacy of such highly specific antibodies. By contrast, mutations of the structure of a virus are less problematic for recognition by polyclonal antibodies as would be found in the blood of a person that has been infected with the virus. This is because the polyclonal antibodies work together to recognize a wide range of structures on the pathogen. For example, with regards to SARS-CoV-2, a set of antibodies will recognize its Spike protein, another set the Membrane protein and the Envelope protein and so on. Therefore, changes in the Spike protein will not impact broad-based naturally acquired immunity to the same degree as a focused vaccine-induced immunity to a single Spike structure. This is one of the reasons that naturally-acquired immunity is often considered the gold standard in vaccine design. T-cells will also play a role and will be discussed later.

Antibodies are amazingly durable proteins. There are different classes of antibodies that vary in their primary locations of action, ability to dock multiple antigens and stability (Figure 6). In the blood, the IgG class antibodies predominate, and these can survive for three weeks or more at 37°C, cruising at high speed through the 60,000 plus miles of the arteries, veins, and capillaries in the circulatory system as well as the lymphatic system. Kept at 4°C with antibiotics to prevent bacterial growth (bacteria like to eat proteins), these antibodies can retain their structure and binding properties for over a decade. In the nasopharynx, airway passages, lungs and lower digestive tract, secreted IgA and IgM class antibodies can last for about 5 to 6 days. These latter antibodies are the most useful for fighting a respiratory virus infection. There are also IgD and IgE class antibodies that tend to exist primarily in the gut.

All of the human antibodies are composed of two identical large (heavy) chains and two identical small (light) chains held together via disulfide atoms links as monomers. These interwoven protein chains take on a ”Y” shape where the bifurcating portion (called the Fab portion) features two separate, identical binding regions at its tips for recognition of an epitope. This region is very unique amongst different antibodies with differences in amino acid sequences, which define the specificity of an antibody. Due to the presence of two copies of epitope binding domains in each antibody, antibodies

are bivalent and can bridge two separate viruses simultaneously to cluster them into larger inactive complexes. The other end of the antibody, which is almost identical amongst antibodies of the same class, is known as the “Fc” portion and acts as a tail-piece. Many different cells of the innate immune systems have specific Fc receptors, and so they are directed to antibody-coated pathogens to facilitate their destruction. Antibodies of the IgD, IgE and IgG types are bivalent as they occur as only as monomers. However, IgA type antibodies can occur as dimers, tetramers and pentamers as well as monomers, whereas IgM antibodies exists in even larger complexes as pentamers or hexamers (Figure 6). This multimerization and other unique features of IgA and IgM class antibodies strengthens the mucosal antibody response to pathogenic microbes. They are able to better sequester viruses and bacteria for destruction by roving macrophages. However, IgG class antibodies are predominately generated by vaccines that are injected intramuscularly.

Figure 6. Structures of Immunoglobulins. (A) Diagrammatic representation of IgG. The X-ray crystallographic structures from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Base (PDB) various classes of immunoglobulin are shown for (B) IgG (PDB file: 1IGY), (C) dimeric, tetrameric and pentameric secreted IgA (PDB files: 6UE7; 6UE8; and 6UEA, respectively) and (D) pentameric IgM (PDB file: 7K0C). (E) Interaction of the Fab portion of anti-Spike RBD IgG antibodies with the Spike protein trimer complex (PDB file: 7TB8). For visualization purposes, the light and heavy chains of the immunoglobulins are shown in different colours as space filling representations of atoms on each of these macromolecules.



3.4. The Nature of T-cells

In circulating blood, about 80 to 90% of the lymphocytic cells are T-cells. Whereas monocytes account for only about 5 to 10% of the peripheral blood mononuclear cells (PBMCs), B-cell numbers vary from 5 to 10%, and dendritic cells represent only about 1-2%. The dendritic cells are important for processing and presenting antigens to T-cells. T-cells feature unique receptors for antigens (T-cell antigen receptors), which like antibodies have specific recognition of epitopes. However, these antigens generally must be presented by cell surface membrane receptors called major

histocompatibility (MHC) proteins on antigen-presenting cells including dendritic cells, macrophages, Langerhans cells and B-cells, and in the central nervous system by astrocytes and microglia (macrophages in the CNS), and by perivascular macrophages.

There are at least three major classes of T-cells that are distinguished based on whether they exhibit certain cellular complementarity determinant (CD) marker proteins on their surfaces:

1) CD3- and CD4-positive T-cells are helper cells that coordinate adaptive immunity through the activation and regulation of other immune cells, including B-cells (which are CD19-positive);

2) CD3- and CD8-positive T-cells can destroy damaged, pathogen-infected and cancerous cells; and

3) CD3-positive gamma (γ)-delta(δ)-positive T-cells.

The γδ T-cells are less common in humans but have their highest abundance in the gut mucosa where their unique features allow them to quickly recognize and respond to foreign antigens. To activate the killing function of CD8-positive T-cells on pathogen-infected cells, the antigenic epitopes must be presented on MHC class I molecules and recognized by a specific T-cell receptor. For this reason, CD8-positive T-cells primarily attack cells that are actively infected with a pathogen, but rarely a pathogen directly, which is the main job of the antibodies.

There are many other T-cell subsets with their unique set of CD markers, as well as related cells such as the CD56-positive and CD3-negative cells, known as Natural Killer (NK) cells, with spontaneous lytic activity to destroy cells. The NK cells have a large array of unique activating and inhibitory surface receptors, but not classic MHC molecules that allow them to detect and kill specific viruses and cancer cells. There are also various regulatory T-cells and NK-cells that ensure that these highly potent killing mechanisms are controlled so as not to harm the host.

In short, the immune system is an amazing set of cells and proteins educated to distinguish “self” from “non-self” so it can detect, remember and protect the host from cancers and every kind of foreign invader.

3.5. The Consequences of a Too Active Immune System

The immune system is highly active under conditions of infection, and many of the symptoms of disease are a consequence of its activation. For example, at higher temperatures, the immune system is more efficient, and many viruses can only survive within a defined temperature range, so a metabolically costly fever is induced to help protect the host. Redness and swelling at a site of infection reflects the protective inflammatory response. Overproduction of mucus and coughing is a strategy to restrict the spread of pathogens and clear it. Likewise, postnasal drip is a means of cleansing the nasal cavities of microbes by flushing them out. Unfortunately, these actions can also help the spread of pathogens, which is one of their strategies for survival. All of this can induce discomfort and takes a toll on the body but helps remove foreign invaders. This is especially undesirable when a benign allergen that is a common element in the environment such as pollens or peanuts inappropriately activates immune mechanisms.

Most of the time the host defense mechanisms work harmoniously to protect the host, but there are times when the immune system overreacts or fails to distinguish self from non-self. For instance, there can be too much or inappropriate immune activation where the production of antibodies, T-cells or other immune meditators can trigger autoimmunity, allergy, immunopathology, or other diseases. For example, while antibodies are highly specific, at very high concentrations they can cross-react with off-target proteins that are normally present in the body and this can induce inflammation and tissue damage. Also, if all B-cells produced antibodies at the same time, the viscosity of blood would be so great that it would flow poorly. Therefore, when individuals are infected and mount an effective immune response that successfully eliminates the pathogen, it is imperative that antibody levels naturally wane, but a degree of residual immune protection remain. Antibodies typically decline in blood once a pathogen is eradicated by the immune system over a period of weeks or months. Importantly, despite low antibody levels, the B-cells that produced these antibodies remain alive in a dormant state as memory B-cells that reside in tissues and circulate in blood ready to respond should the same invader return. Upon re-infection with the pathogen, these “hibernating” B-cells are individually stimulated to grow and divide to generate identical daughter cells that produce the same antibody with an improved capacity for attacking the invading pathogen. Plasma and memory B-cells are known to survive for decades and can produce more antibodies upon reinfection with the same pathogen.[141] Symptomatic disease occurs when the infectious pathogen can propagate faster than the

immune system can mount an effective response. However, upon re-infection, the immune system usually overcomes the pathogen in a few days with fewer symptoms and full recovery is usually achieved, once again demonstrating the power of naturally-acquired immunity.

3.6. Evading the Immune System

The immune system is the only body system with the ability to match pathogen diversity and deal with the plethora of strategies employed by foreign invaders. The mammalian immune system employs thousands of immune response genes as needed depending on the pathogenic encounter. Conversely, each type of pathogen has many fewer genes and therefore is more restricted in its arsenal. Nonetheless, each type of pathogen has developed strategies to subvert or even destroy the immune system. For example, the Human Immunodeficiency Virus (HIV) that causes AIDS selectively infects and destroys the CD4-positive T-helper cells until their numbers decline below functional levels. Since these cells are critical in coordinating the adaptive immune response, their loss eventually leads to a collapse of the immune system and allows this virus and other viruses to spread largely unimpeded.

Antibody-dependent enhancement (ADE) should also be mentioned here as another instance where the immune response may actually aid the pathogenic invader. This is a mechanism, sometimes referred to as immune enhancement or disease enhancement, by which the coating of the pathogen, such as a virus, with suboptimal antibodies actually helps the pathogen invade the host by binding to Fc or other receptors on the host cells. ADE can happen following vaccination or natural infection, particularly when non-neutralizing or sub-neutralizing concentrations of antibodies are elicited. ADE has often been observed with positive-strand RNA viruses such as those causing dengue, yellow fever and Zika, as well as betacoronaviruses. Prior to the COVID-19 pandemic, ADE was noted in rodents vaccinated against SARS-CoV-2. The more targeted the antibody response, the greater the risk of ADE. When there are few antibodies that are bound to a virus so that it is still functional, the antibodies can act as a bridge between the virus and the Fc receptor of immune cells. Once attached to the surface of these immune cells, the virus can enter their cytoplasm where the virus can undergo replication. Normally, the phagocytic cell would engulf the virus in a process called phagocytosis and demolish the virus in digestive vesicles called lysosomes. This potential to induce non-appropriate immune responses illustrates the critical importance of monitoring for ADE and related phenomena when

developing vaccines. The phenomena of ADE is of concern with COVID-19 vaccines that have focused solely on the Spike protein as an antigen.

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Chapter 4:

Tracking SARS-CoV-2 and the Immune Response

4.1. Contact Tracing

Contact tracing is described by the World Health Organization (WHO) as a public health tool for "identifying, assessing, and managing people who have been exposed to someone who has been infected" with any virus of concern.[142] The recent WHO posts on contact tracing are in regard to the COVID-19 virus and the later variants of the same. With contact tracing, in brief, the idea is that health professionals can in part prevent the spread of any infectious disease in a local population, in this case COVID-19, by first identifying a person infected with a disease early enough to prevent them from spreading the disease to others not yet infected. The means to prevent onward spread involves several interrelated parts: identify that the person has the actual disease; stop onward transmission by isolating or quarantining that person; and finally by tracing the immediate contacts of that person in the days leading up to either the onset of symptoms or by positive test for the causal disease agent. The key here is two-fold: timeliness of the diagnosis and the accuracy of the testing regime(s). It is also critical that the contact tracing is applied in the earliest stages of a pandemic. However, once the disease is rampant in the community as during a wave of infections, this strategy is ineffective. In the right circumstances, such as preventing the spread of Ebola virus, contact tracing can be effective. However, Ebola is not spread through casual contact, air, food or water, and only from someone who is symptomatic.

The Mayo Clinic posts instructions on contact tracing on their website.[143] According to the Mayo Clinic, they advise the following steps: 1) Identify those who have been diagnosed with a disease, *e.g.,* COVID-19 diagnosed in a clinic, hospital or laboratory; 2) Send the name of the person infected with SARS-CoV-2 based on signs and symptoms of disease, along with either PCR or the so-called "rapid antigen" tests, and send to the health department for that area; 3) The health authority will follow up with those named to trace "close contacts", that is someone who has been within 2 meters of the infected person for 15 or more minutes within 2 days of the infected person's diagnosis and may include family members, friends, co-workers, or others.

The follow-up by the health department asks the contacts questions about symptoms and may request that the contacts also be tested for COVID-19 by the above methods. The further follow up of the contacts is divided into those who test negative and/or cannot be tested for the disease versus those who do test positive. In the first case, the health department may request for the patients:

> "*Ask them to self-quarantine at home for 14 days after they were exposed; request that they keep social distance from others or even isolate themselves from family and pets, and use a separate bedroom and bathroom; request that they monitor their health and watch for any COVID-19 symptoms; ask them to check their temperature twice a day; ask them to let their doctor and health department know right away if they develop any symptoms; request that they send doctors and the health department daily health updates*." [143]

For those in the second category, *e.g.,* "*those who have symptoms and can't be tested, test positive for the COVID-19 virus, or develop symptoms,*" the health services requests for the patients:

> "*Ask them to self-isolate and recover at home if illness is mild. People with symptoms will likely be asked to isolate themselves from family and pets and use a separate bedroom and bathroom; ask them to seek medical care if they have any emergency warning signs, such as trouble breathing or persistent chest pain; give them specific instructions to monitor their symptoms and avoid spreading the COVID-19 virus to others*." [143]

In other words, the two follow-up actions of the health authorities are practically identical.

How well does contact tracing work in theory versus praxis? One view is that it is an effective tool to try to break the chain of transmission. The key issues are these: 1) Timeliness; and 2) the accuracy of the diagnostic tests.

While in principle, contact tracing could be useful as a way to break the infection cycle with newer victims, the success of this will depend on how rapidly the initial tracing is done to correctly identify if a person suspected of harboring the disease actually has it. The key issue here is indeed timing since if this is not done rapidly, the suspected person will have acquired many more potential contacts individually or through family and friends who can, in turn, infect others.[144] The symptoms of COVID-19 are very much the same as other common respiratory illness. Any symptoms, mild to severe, will

show considerable overlap with many infectious viral respiratory diseases, including other members of the coronavirus family, with influenza, with RSV, and a host of others. So, if symptoms alone will not suffice, what analytic tests can be performed to complement the symptoms and give an accurate diagnosis of disease?

There are presently only two types of tests that have really been adopted for identification of active SARS-CoV-2 infection. The first involves PCR tests (Chapter 4.2). The second is rapid antigen tests (Chapter 4.3). Serology tests for antibodies (Chapter 4.4) are far more accurate, but cannot discern when an infection occurred, and for this reason will not be addressed further in this section. The process of virus spread can be exponential after the "patient 0" is first identified, but not prevented from adding further potential victims.

The first problem arises due to the accuracy or likely inaccuracy of the diagnostic tests. Both PCR and rapid antigen tests may be highly inaccurate. For example, PCR performed at 38 thermal cycles (Ct) and above, which is commonly performed, will give over 90% false-positive results. The levels of active virus are evident at Ct's of 25 or less, but if higher Ct numbers are needed for detection, this is usually from dead virus or RNA fragments from the virus. Using thermal cycles above 25 generates false-positives for active virus, and the higher the Ct amplification number, the greater the error. PCR used at Ct of 35 or higher are essentially useless for quantitative estimates of disease status for individuals and populations. What this means in principle is that the contact tracers will be examining a host of people who do not actually have COVID-19 or had it and have since recovered. These people are unlikely to have the disease when tested and thus those they contacted immediately before the PCR are also not likely to have the active disease either unless they acquire it from another source. In other words, PCR used improperly may subject healthy individuals to restrictions that cause more harm than good.

Likewise, the accuracy of the rapid antigen tests is problematic since it can be insensitive and miss the early stages of a SARS-CoV-2 infection. Both the PCR and the rapid antigen tests should only be used to confirm the diagnosis of the disease in someone who has or recently had COVID-19-like symptoms. It remains unclear whether those that are without symptoms are actually infectious or have been infected. A prior infection with SARS-CoV-2 might be revealed by a serological test for antibodies, but those that test positive with this test will probably not be actively infectious any longer.

For these reasons, unless both timeliness and accuracy are ensured, contact tracing is mainly an exercise in "virtue signaling", without any actual ability to control disease spread, especially during an active wave of SARS-CoV-2 infections.

The assumption that contact tracing in COVID-19 will prevent the spread of infectious diseases is based on hypothetical situations or those based on very limited disease vectors with clear symptoms and accurate testing. Neither of these has been true for COVID-19. The claims made by the Mayo Clinic and others that contact tracing is effective also ignore the reality that any diminution of disease spread may more likely be due to natural, or other forms of acquired, herd immunity.

The Government of Canada website for the Public Health Agency of Canada, last updated on November 3, 2021, stated the following information:

> With respect to the "infectious period", "*The time period in which an individual with COVID-19 is infectious remains uncertain. A person may be infectious for up to 3 days before showing symptoms (pre-symptomatic infectiousness)*." [145]
>
> With respect to the 'incubation period", *"The incubation period ranges from 1 to 14 days. The median is 5 to 6 days between exposure and symptom onset. Most people (97.5%) develop symptoms within 11.5 days of exposure."* [145]
>
> With respect to to "reinfection", "*There is emerging evidence of <u>human re-infection with SARS-CoV-2</u>. This has been documented by individuals confirmed to have been infected by different strains of the virus. Further research is required to fully comprehend the relationship between positive <u>antibody tests</u> and any protection against re-infection*." [145]
>
> And, *"Currently, we do not know: whether the presence of antibodies indicates immunity to re-infection, and if it does, how long that potential immunity lasts; or the potential severity of subsequent infections"* (reformatted for clarity).[145]

None of this should give the public much assurance as written and could be roughly translation from Government of Canada-ese as: "*We don't really know if you have or had COVID-19, because the time frames are incredibly broad and our tests, which we are not really discussing, sort of don't work as advertised*."

This is similar to the Canada Communicable Disease Report (CCRD) issued on November 5, 2020 and also produced by the Public Health Agency of Canada:

> ***"Background:*** *COVID-19 cases need to be isolated long enough to prevent further transmission but no longer than needed. Determining the infectious period of COVID-19 is complicated by four factors: 1) people can be diagnosed when they are symptomatic, pre-symptomatic or asymptomatic, 2) the common diagnostic test, RT-PCR, is accurate for diagnosis as it is able to detect viral genetic material, but it cannot document when someone is no longer infectious because it cannot distinguish whether viral particles are still infectious or not, 3) cell culture is the best way to confirm whether infectious virus is present, but it takes time and requires specialized laboratory facilities, and 4) although transmission is primarily respiratory, virus has been found in feces and eye secretions."* [146]

In other words, all the concerns that CCRD knew in 2020 were clearly not communicated in any effective way to PHAC with the consequence that the government health authorities continued to do things that simply could not work to diagnose or control COVID-19. Even a non-government organization, such as the Mayo Clinic did not have a sound approach to the problem.[147] They proposed the same PCR methods (without specifying Ct to be used) and antibody tests, again, without any clear specificity for those tests that are most effective or used long after the symptoms of the disease have subsided and the person is no longer infectious.

For the above reasons, in both Canada and the US, the tactics used by health authorities during the pandemic essentially meant that they had no realistic ability to determine who was actually affected with COVID-19, nor if any of their control measures actually were effective. With this conclusion, should the public be surprised that COVID-19 policies in both countries largely seemed to be *ad hoc*, inconsistent, and highly ineffective?

4.2. PCR Tests for SARS-CoV-2

To establish whether a person has an active ongoing infection with SARS-CoV-2 and not another pathogen that produces similar symptoms to COVID-19, specific tests are necessary. Likewise, other tests are required to determine whether an individual has immunity from future infections with SARS-

CoV-2 and is protected from getting COVID-19 again. These specific tests have been feasible since the release of the genome sequence of the original Wuhan strain of SARS-CoV-2 in January 2020.

There are two major types of testing that are performed for determination if a person is actively infected with SARS-CoV-2. A Nucleic Acid Test (NAT), most commonly the Reverse Transcription - Polymerase Chain Reaction (RT-PCR)-based test, has been used for detection of the RNA component of the virus. It relies on amplification of the viral nucleic acid material through repeated heating and cooling cycles of separation and annealing of the nucleic acid strands, with a doubling of the genetic material with each thermal cycle. The other type of test is the rapid antigen test, which detects the presence of a viral protein.

The main issue with the RT-PCR test is that it often employs a high number of thermal cycles (see details below), which can generate a large percentage of false-positive results. Individuals can still test positive with the RT-PCR test two weeks after they have fully recovered from COVID-19 and are non-infectious. With the rapid antigen test, it is not possible to amplify up the viral protein material, so it suffers from a lack of sensitivity and can often generate false-negatives. Depending on the specificity of the antibody detection reagent used, it may also cross-react with related proteins that are found in other common cold coronaviruses related to SARS-CoV-2 and produce false-positives.

A PCR test is a commonly used molecular diagnostic tool in order to detect the presence of specific DNA or RNA in a sample. For the clinical detection of SARS-CoV-2, all clinical virology laboratories use reverse-transcriptase real-time PCR (RT-rtPCR) for the detection of SARS-CoV-2 viral RNA in nasopharyngeal swabs (NPS), mid-turbinate swabs (MTS), or saliva.[148] In this method, a reverse transcription step is first performed, which copies the genetic code of the viral RNA into DNA, which is much more stable than RNA. The PCR can then be performed, which involves using what are called ‘primers’ which are short pieces of DNA that are designed to bind to unique complementary sequences that are present in a viral genome. The primers are designed to bind at both ends of a segment of the viral genome. If the primers bind, an enzyme known as a ‘polymerase’ will use the viral genome as a template to extend the primers until the target gene segment has been completely copied. This works by varying the temperature of the sample. A high temperature is used to get double-stranded DNA to separate into single strands. Next, an ‘annealing’ temperature is used to allow the primers to bind to the single strands of DNA. Finally, a third temperature is used to promote ‘extension’ of the primers

until the targeted gene sequence has been copied. This constitutes a single cycle of the test. Multiple cycles are employed to increase the copies of the targeted gene segment exponentially, essentially doubling the amount of DNA with each thermal cycle. Oligonucleotides that are labeled with fluorescent dye (*e.g.*, fluorescein) are usually added to the incubated sample which incorporates into the targeted gene segment. If enough gene segments get amplified, a special machine can detect the amount of the fluorescent dye. The amount of dye usually correlates with the number of viral genomes in the clinical specimen. An important piece of information generated with the RT-PCR test is the 'cycle threshold' (Ct) value. The Ct value is the number of thermal cycles that the test had to be performed for the fluorescent signal to clearly exceed background levels.

While RT-PCR tests are based on a remarkable technology, they never should have been used as a stand-alone Gold Standard test for defining cases of COVID-19. In fact, it is wholly inappropriate to define the disease COVID-19, which is an illness with clear symptoms, based only on the presence of SARS-CoV-2 RNA as detected by the PCR test. A positive result with a PCR test does not mean that a person has COVID-19 and is able to transmit the disease. First of all, every laboratory conducting RT-PCR tests for the detection of SARS-CoV-2 should have determined an appropriate Ct cut-off through parallel testing of samples using the gold standard functional virology assay in which evidence of replication-competent, potentially infectious virus particles is obtained by looking for evidence of cytopathic effect (killing) in what are known as permissive cells (*i.e,* cells that are stripped of their antiviral properties so that viruses can readily infect them). This was done by Canada's National Microbiology Laboratory, with the Ct cut-off determined to be only 24, meaning that tests showing positive results at Ct values greater than 24 failed to demonstrate the presence of potentially infectious viral particles. Second of all, the presence of replication-competent viral particles in a sample does not necessarily equate to a case of COVID-19, which is a disease with symptoms. The latter can only be defined if an active infection is present in conjunction with signs and/or symptoms of illness, which would require assessment by a physician. Remarkably however, entities like Public Health Ontario categorized samples with Ct cut-offs of up to 38 cycles and, in some cases, in the absence of clinical data, as representing positive cases of COVID-19 with greater than 90% inaccuracy. This is highly ill advised, especially in the absence of publicly available data proving that the Ct cut-off was established using the Gold Standard functional virology assay. Consequently, overall cases of COVID-19 have likely been dramatically overestimated, and to an unknown degree. This inflation of the problem of COVID-

19 resulted in unnecessary pressure to force COVID-19 vaccines on public and private employees by governments and independent companies at the whim of their management.

As mentioned earlier, a main limitation with the RT-PCR test is that it is often used in a manner with a high number of thermal cycles, which can generate a large percentage of high-false positive results (*e.g.*, a 90% false-positive rate is typical with more than 35 cycles). Studies have shown that if more than 30 cycles of PCR amplification are required to detect the presence of SARS-CoV-2 RNA in a specimen sample, this is insufficient to actually propagate the virus in optimal cell culture conditions in a laboratory.[149] Unfortunately much of the results reported in the scientific literature for the presence of SARS-CoV-2 virus in clinical specimens is based on the use of 35 thermal cycles or greater. This is also true for the clinical Phase 3 trials that were used to test the efficacy of the COVID-19 vaccines. This problem undermines much of the public health data with respect to how many people were infected with SARS-CoV-2, as well as many clinical studies that sought to determine the effectiveness of a vaccine to prevent COVID-19. For example, a substack by Dr. Byram Bridle listed 48 of the most influential publications that have been cited by public health officials to mislabel asymptomatic people as sources of SARS-CoV-2 who cause COVID-19 to spread.[150]

It is also worth mentioning that PCR testing of sewage water became a common strategy to monitor community levels of SARS-CoV-2 infection. It should be appreciated that such an application of the PCR method is highly non-quantitative. Apart from the accuracy of the test at high Ct performance numbers, there can be large variations in the level of sewage water depending on the weather and season. At best, such measurements might be useful in a qualitative manner to identify the presence of new variants of SARS-CoV-2 relative to other variants.

4.3. Rapid Antigen Tests for SARS-CoV-2

To also determine the presence of virus, antigen tests can be performed. These are tests that, like the RT-PCR test, detect the presence of SARS-CoV-2 virus. Unlike PCR tests that monitor for the presence of SARS-CoV-2 viral mRNA, antigen tests detect the presence of target proteins within the virus particle. This relies on the availability of pre-made antibodies that are specific for binding to one or more of its viral proteins, most commonly the Spike or Nucleocapsid protein. Such antibodies may be generated in animals inoculated with whole or portions of the target viral proteins that are

artificially manufactured in cells and which are described as recombinant versions of the proteins. These recombinant proteins are believed to be essentially identical to the original viral proteins, although they may be subjected to minor modifications. A major difference between the genetic tests and the viral protein antigen tests is that there are no available means to amplify the number of viral protein molecules as there is with viral RNA molecules using the PCR method.

Many of the provinces in Canada recommended widespread use of rapid antigen tests, especially for those who did not receive at least two injections of a COVID-19 vaccine. One of the most used test kits is manufactured by Abbott Panbio.[151] In the province of Ontario, the government recommended this test only for asymptomatic (*i.e.,* apparently healthy) individuals. Remarkably, however, as indicated in the printed material provided by the Government of Ontario, the kits were only tested on and approved for use in symptomatic individuals. No evidence was provided that screening with the kit was effective for use in asymptomatic individuals. Finally, the printed materials accompanying the kit stated that a negative test result (expected when testing asymptomatic people) does not exclude that a person has been infected with SARS-CoV-2. However, by definition, an asymptomatic person cannot have COVID-19, because COVID-19 is a disease characterized by symptoms and signs of illness. Interestingly, the booklet accompanying the rapid antigen test kit that was approved by the government of Ontario contradicts their general messaging regarding RT-PCR testing for SARS-CoV-2. Whereas the Government of Ontario claimed that people who test positive with the RT-PCR test at cycle thresholds of up to 38 can transmit SARS-CoV-2, the rapid antigen test kit stated that people who test positive at cycle thresholds above 33 were not contagious.

The inability of the Abbott rapid antigen test to detect SARS-CoV-2 in asymptomatic people was confirmed in a study conducted by the Canadian Public Health Laboratory. The test kit was unable to detect SARS-CoV-2 in samples that tested positive with RT-PCR cycle thresholds greater than 22. People testing positive at cycle thresholds of 22 or less would clearly be sick (*i.e.,* symptomatic).[152]

Many Canadians, especially those who did not receive a COVID-19 vaccine, were forced to use these kits between two to five times per week to maintain their jobs, volunteer positions, *etc.*, often at their own expense. Each kit costed about CDN$16 directly from the manufacturer. Pharmacies charged CDN$40 (and up to CDN$99) per test. This resulted in substantial extra costs for working

people, and substantial profits for those in the testing business. To reiterate, these rapid antigen tests would usually be positive if someone had such a high viral load that they would clearly be symptomatic.

The requirement for asymptomatic working people to have a rapid antigen test (which was rarely positive) as part of their employment condition may have given the appearance that due diligence was being practiced with respect to public health. In reality, people wasted a lot of money and trips to pharmacies for something that could never reveal the information the kits were being promoted for (*i.e.*, early detection of infection). Meanwhile, the manufacturers made massive profits for something that had little public health value. People who did not receive a COVID-19 vaccine should not have been forced to conduct rapid antigen testing as a requirement to work. This is especially true, since in 2022 and 2023 in Canada, most reported COVID-19 cases were in double and triple vaccinated individuals, and many people already had natural immunity from infection with SARS-CoV-2.

4.4. Serological Tests for Antibodies Against SARS-CoV-2

Once the SARS-CoV-2 virus is cleared by the immune system of recovered COVID-19 survivors, evidence of immunity is established by the presence of antibodies in their serum and other body fluids such as saliva, or less commonly, by the presence of specific T lymphocytes in their blood.

The serological tests for antibody detection have the advantages that they are highly sensitive and can provide a measure of the immunity present in a previously infected individual, even years after the initial exposure to the virus. However, it is also possible to pick up immunoreactivities with antibodies produced against related viral proteins found in other coronaviruses. Historically, the PCR test was most used due to its accuracy and sensitivity, but antigen testing was more convenient and could even be performed in the home or workplace for rapid analyses of SARS-CoV-2 infection status. Relatively little serological antibody testing has been performed in Canada and it was primarily offered by just a few commercial companies.

Serological tests work by having a purified protein from a pathogen or peptides derived from the amino acid sequences of such proteins immobilized on a surface such a cellulose or nitrocellulose membrane, or glass or plastic slide. If an antibody present in a blood or saliva sample recognizes the protein or peptide as an antigen, then it will tightly bind to it. The binding of that antibody is then detected with a secondary antibody, which is an antibody that recognizes the Fc portion of the primary

antibody that is being tracked. For example, this could be an anti-human IgG antibody made in sheep. The secondary antibody is tagged with a visible dye or fluorescent dye, or an enzyme that generates a dye, which can be viewed on the surface of the antigen coated membrane or slide.

While rapid antigen testing for SARS-CoV-2 infection is strongly encouraged by public health authorities in Canada, testing for SARS-CoV-2 antibodies in serum or saliva samples has been discouraged by many of the same agencies, including the BC Centre for Disease Control.[153] Whereas over 40 million dollars was allocated by the Canadian federal government for just the genome sequencing of the SARS-CoV-2 isolates, for example, with the CanCOGeN Project,[154] little funding was provided in Canada for the development and application of antibody tests to determine the extent of natural immunity or immunity provided by the COVID-19 vaccines. A very small number of serological testing projects in Canada were funded by the COVID-19 Immunity Task Force (CITF).[155]

One project to evaluate antibody-based immunity was funded through the Angus Reid Group and conducted by the University of Toronto and was called Action to Beat Corona Virus (Ab-C).[156] Using over 22,000 dried blood spot samples provided by over 11,000 Canadians, the detectable antibodies in these samples that targeted the Spike and Nucleocapsid proteins were used to ascertain vaccine-induced and naturally-induced levels of immunity, respectively, against the virus. The Ab-C study has reported that by August 2021, only around 6% of tested Canadians had natural immunity.[157] These findings revealed that the study's SARS-CoV-2 antibody screening methodology markedly underestimated the degree of natural immunity in the Canadian population. For example, about 3.9% of Canadians who had COVID-19-like symptoms had tested positive for SARS-CoV-2 infection by PCR-based tests by this time.[158] Due to under-reporting of COVID-19 cases, recorded PCR results were already believed to underestimate actual SARS-CoV-2 infection rates by at least another 4-fold.[159] Moreover, at least 40% of SARS-CoV-2 infections are asymptomatic.[160] Consequently, the actual percentage of SARS-CoV-2-infected Canadians was substantially higher than the Ab-C study estimates.

In the Ab-C study recombinant versions of only the Spike and Nucleocapsid proteins were used for the testing of endogenous antibodies in the dried blood samples that bind to these antigens. This use of dried blood samples affords low sensitivity, and since antibody levels normally begin to drop in the months following the elimination of a viral infection, they may decline to below the threshold of

detection with these tests. Also, as will be elaborated on later, antibodies against the Nucleocapsid protein are often not detectable in the serum of convalescent, recovered COVID-19 patients.

Apart from the issue of the Nucleocapsid protein used as an antigen, fresh blood or serum samples can provide much better yields of active antibody than dried blood specimens. Serological tests, like those provided by LifeLabs with fresh blood samples,[161] tracked antibodies against the Nucleocapsid and Spike proteins. These tests utilize recombinant proteins that are expensive to manufacture, and are used at dilute concentrations in order to minimize costs, but at the sacrifice of sensitivity. LifeLabs has since discontinued its COVID-19 antibody testing service.

4.5. Antibody Neutralization Assays for Spike Binding

While the testing of SARS-CoV-2 Spike and Nucleocapsid protein antibodies was viewed by health authorities as having limited value to assess immunity against COVID-19 in the public, such information was considered highly relevant in evaluating the efficacy of vaccines to prevent COVID-19. In particular, the manufacturers of these vaccines and the health agencies were particularly fixated on the measurement of "neutralizing" antibodies against the Spike protein as surrogates for overall immunity to SARS-CoV-2. Due to the location of the Spike protein on the surface of the viral particle, and the importance of the receptor binding domain (RBD) of the Spike protein for attachment to the ACE2 protein on the surface of host cells, the ability of antibodies to block this binding was deemed to provide an assessment of the degree of immune protection afforded by such antibodies.

There were a few different strategies that were developed to test the degree of "neutralization" activity of antibodies against the Spike protein. The first was simply to evaluate whether antibodies in serum from patients that recovered from COVID-19 were able to block the ability of SARS-CoV-2 virus to infect and kill monkey or human cells in culture. However, this kind of testing was expensive since Level 3 or 4 Biosafety laboratories are required for proper handling of the SARS-CoV-2 virus. Consequently, alternative approaches were developed that relied on producing a surrogate virus that could express the SARS-CoV-2 Spike protein on its surface, which would allow this substitute virus to enter and kill animal or human cells that had been transfected with human ACE2. Lentiviruses were especially popular for this application, because as safe, non-pathogenic viruses, they are commonly used in biomedical research.[162] Pseudo-type lentiviruses that are non-replicative due to deletion of

necessary genes can be used safely in Biosafety Level 2 (BSL2) labs to create such constructs that are useful for neutralization assays. Such neutralization assays were instrumental in the original identification of therapeutic monoclonal antibody producing cells, whose antibodies could block SARS-CoV-2 infection in COVID-19 patients. The only difficulty was that the necessary precision binding of such antibodies to the receptor binding domain meant that minor changes in the amino acid structure of the target virus, as occurred with subsequent variants of SARS-CoV-2, rendered many of the early therapeutic monoclonal antibodies obsolete.

Another strategy to detect neutralizing antibodies was to use tests with recombinant ACE2 protein immobilized on enzyme-linked immunosorbent assay (ELISA) plates to check for the ability of serum samples with antibodies to block a dye-labeled recombinant Spike protein from binding to the ACE2. The presence of such neutralizing antibodies results in a reduction in detected signal due to the binding of these antibodies to the Spike protein in its receptor binding domain.

While such neutralizing antibodies would be a desirable outcome from immunization with a vaccine or the result of natural infection with the SARS-CoV-2 virus, it is important to appreciate that over 95% of the antibodies produced against the Spike protein do not target its RBD, but still provide immune protection, in part by guiding different classes of innate immune cells directly to the virus particles and to virus-infected cells that express Spike protein on their surface. Furthermore, T-cells also recognize epitopes throughout the Spike protein, which facilitates their killing of SARS-CoV-2-infected cells.

4.6. Results of the Kinexus Serological Tests for Natural Immunity to SARS-CoV-2

The clinical studies conducted by the Vancouver-based company Kinexus Bioinformatics Corporation have provided important insights into the adaptive antibody response to SARS-CoV-2 infection and COVID-19 vaccination. In the interests of full disclosure, I am the majority shareholder, the president, and the chief scientific officer of Kinexus.

In February 2020, Kinexus initiated a research program to determine if the company could identify the parts of the various proteins encoded by the genome of the SARS-CoV-2 that elicited strong immunoreactivities with antibodies in people who had recovered from COVID-19. With the availability

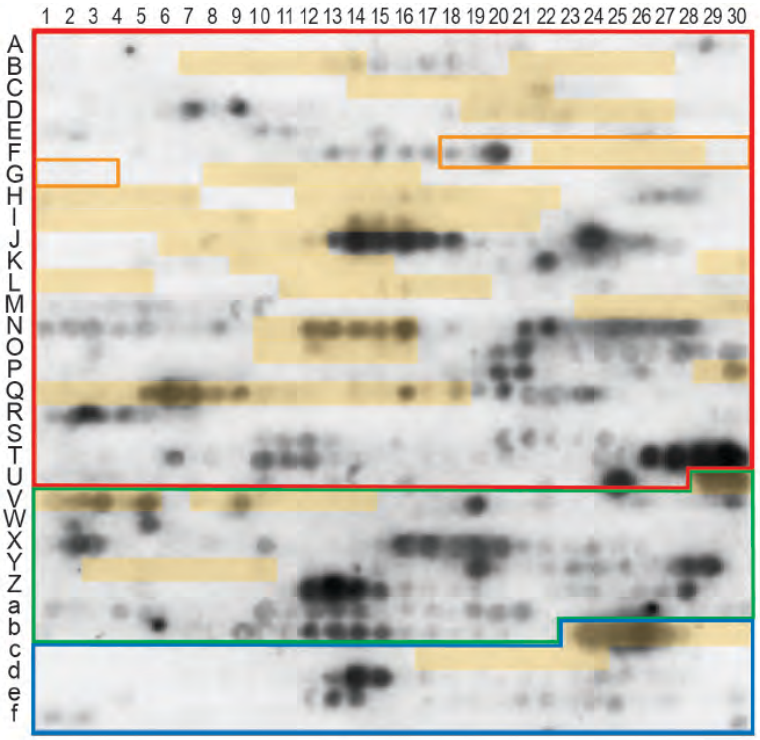
on January 10, 2020, of the full sequence of the SARS-CoV-2 genome, it was possible to predict the amino acid sequences of all 28 of the viral proteins encoded by its genes.

Using its automated peptide synthesis capability, Kinexus created cellulose membranes upon which overlapping 15 amino acid-long pieces of these viral proteins were tiled out as arrays of distinct peptide spots of defined composition. This permitted the detection of antibody epitopes as small as two amino acids long. Essentially, over 6000 distinct, but overlapping parts of all 28 predicted viral proteins were robotically synthesized over a series of cellulose membranes with replicate copies of each membrane. The concentrations of these peptides were at least 50-times higher than what could be achieved with recombinant versions of the same SARS-CoV-2 viral proteins. This permitted high sensitivity detection of antibodies that might specifically bind to these peptides at much lower concentrations than other serological tests. By testing serum samples from recovered COVID-19 patients separately with replicate copies of these SARS-CoV-2 peptide arrays, Kinexus identified over 400 viral peptides that generated strong immune responses with respect to antibody production following infection by SARS-CoV-2. Initially, from studies with serum samples from over 20 COVID-19 convalescent patients with protein spot membranes with 257 to 1,768 separately arrayed peptides, Kinexus reduced the number of best markers to 120 peptides. Figure 7 provides an image of the overlaid results from combined analyses with samples from 9 recovered COVID-19 patients with large 960 SARS-CoV-2 peptide SPOT membranes. With 120 of the most immunogenic peptides, the company further tested serum samples from another 450 recovered COVID-19 patients as well as healthy adults with no history of COVID-19 illness to identify 41 peptides that served as the most commonly targeted parts of 10 of the SARS-CoV-2 proteins. This permitted the creation of a 41-marker test that was the size of postage stamp. With these 41-marker peptide spot arrays, Kinexus then screened more serum or dried blood spot samples from over 4500 additional individuals that were COVID-19 confirmed or suspected as well as samples from healthy individuals with no prior history of COVID-19-like symptoms. This permitted exploration of the degree of natural and COVID-19-vaccine induced immunity in people primarily located in B.C. and Ontario.

The Kinexus SARS-CoV-2 antibody clinical study with the various SARS-CoV-2 peptide spot arrays revealed that almost everyone tested had a unique antibody response evident from very diverse spot patterns of immunoreactivities with selected SARS-CoV-2-based peptides between people. Also, when about a hundred of the study participants were retested nearly a year later, from when they were

initially screened following an earlier SARS-CoV-2 infection, the spot patterns were very similar and reproducible for the same person**.** Furthermore, the study found the presence of multiple antibodies against the SARS-CoV-2 protein that was clearly evident in people even 30 months after their initial infection with SARS-CoV-2, which was consistent with the establishment of lasting immune memory from natural infection.

Figure 7. Kinexus CDH/CDR SARS-CoV-2 SPOT array overlay of 9 images of separate serum sample results from different participants that recovered from COVID-19. Short overlapping peptides that cover the entire structures of the Spike (upper, red outline), Nucleocapsid (middle, green outlined) and Membrane (lower, blue outlined) proteins of the Wuhan strain, were produced on arrays that were probed with serum samples that contained antibodies from confirmed COVID-19 cases. Peptides from the Receptor Binding Domain (RBD) region of the Spike protein are boxed in orange. A dark spot indicated that this region of the targeted protein was immunogenic and elicited antibodies against this part of the virus protein. Evidently, the RBD region of the Spike protein was not particularly immunogenic in people who successfully recovered from COVID-19. Peptides that are expected to feature Omicron BA.1 mutations are highlighted in yellow shading. Apart from the D796Y and N969K mutations in the Omicron Spike protein, none of the other 32 mutations were in parts of this viral protein that elicited strong antibody responses.



Omicron Mutations	SPOT Array Locations
Spike	
A67V	B7-B13
Δ69-70	B8-B14
T95I	B21-B27
G142D	C14-C21
Δ143-145	C15-C22
Δ211	D19-D25
L212I	D19-D26
ins214EPE	D21-D27
G339D	F22-F28
S371L	G8-G14
S373P	G9-G15
S375F	G10-G16
K417N	H1-H7
N440K	H12-H18
G446S	H15-H22
S477N	I1-I7
T478K	I1-I8
E484A	I4-I11
Q493R	I9-I15
G496S	I10-I17
Q498R	I11-I18
N501Y	I13-I19
Y505H	I15-I21
T547K	J6-J12
D614G	K9-K15
H655Y	K29-L5

Omicron Mutations	SPOT Array Locations
Spike	
H655Y	K29-L5
N679K	L11-L17
P681H	L12-L19
N764K	M24-M30
D796Y	N10-N16
N856K	O10-O16
Q954H	P29-Q5
N969K	Q6-Q13,
L981F	Q12-Q18
Nucleocapsid	
P13L	U29-V5
Δ31-33	V7-V14
R203K	Y3-Y10
G204R	Y4-Y10
Membrane	
D3G	b23-b24
Q19E	b25-c1
A63T	c17-c24

Another important insight from the Kinexus clinical study was that following infection with the SARS-CoV-2 virus, each person's antibodies could collectively recognize hundreds of very different parts of the virus proteins. This is known as a polyclonal antibody response, and underlies the effectiveness of the immune system to combat mutated versions of the virus. Scores of different antibodies may be detected against different parts of the Spike protein alone with the serum from a single recovered COVID-19 patient. Another striking finding is that when the locations of the amino acid mutations in the Alpha, Beta, Delta and Omicron variants of SARS-CoV-2 are mapped, it turns out that these mutations rarely occur in the parts of the SARS-CoV-2 proteins that people usually make antibodies against. Therefore, most of the antibodies made against the original Wuhan strain of the virus should and do work effectively as well as against any of the variants, and *vice versa*. This is why the COVID-19 vaccines that were produced with the original Wuhan strain of the Spike protein could still produce protection from even the Omicron BA.4 and BA.5 strains of SARS-CoV-2, for at least for a few months. In fact, the bivalent vaccines with the Wuhan/Omicron BA.4/5 Spike RNA combination proved to be no better for eliciting antibody responses than the original Wuhan Spike RNA vaccines.

The Kinexus clinical study also revealed that the RBD region of the Spike protein was poorly immunogenic. Since all of the tested people with COVID-19 had fully recovered, this demonstrated that antibodies against the RBD, which would normally have the potential for being "neutralizing" antibodies in tests with lentiviruses, were not reliable markers of effective immunity against SARS-CoV-2.

Another significant finding from the Kinexus clinical study was that with over 2,900 people who were asymptomatic for COVID-19, over 90% of these individuals clearly possessed antibodies that could recognize SARS-CoV-2, with numbers and intensities of visible immunoreactive spots that were similar to that seen with PCR-test confirmed, recovered COVID-19 patients. This was already evident in a preliminary study that Kinexus conducted with the BC Children's and Women's Hospital that was published in the flagship journal of the American Society for Clinical Investigation, *JCI Insight*.[163] In this *JCI Insight* report, which included serum samples collected in Spring 2020 from 276 healthy, adult participants, half of whom were healthcare workers, about 90% of those tested had detectable antibodies that immunoreacted with many of the targets on the Kinexus 41-marker SARS-CoV-2 peptide spot array and also reacted with recombinant preparations of the Spike and Nucleocapsid proteins. The Kinexus SARS-CoV-2 antibody test results were cross-validated with another SARS-CoV-2

antibody test developed and marketed by the U.S. company MesoScale Diagnostics.[164] The Kinexus SARS-CoV-2 antibody tests are likely among the most sensitive and accurate serological antibody tests available. No other reported tests have detected antibodies against so many different SARS-CoV-2 proteins.

In the Majdoubi *et al.* (2021) *JCI* study, it was suggested that the high rate of detection of antibodies in the serum of healthy adults in the late Spring of 2020 was due to the presence of pre-existing antibodies.[163] This was subsequently tested by Kinexus with serum samples obtained from 30 people who had confirmed COVID-19 and strong antibody responses. The corresponding Spike protein amino acid sequences that were the most immunoreactive were tested against the equivalent, but slightly different amino acids sequences in SARS-CoV-1, MERS and four cold coronaviruses. While some of the antibody responses were clearly stronger with Spike peptides with SARS-CoV-2 sequences, they were often as strong as or stronger with the sequences derived from the other coronaviruses. This indicated that many of the antibodies that reacted with SARS-CoV-2 may have arisen from B-cells that were previously stimulated with other coronaviruses. Exposure of these individuals to SARS-CoV-2 likely re-activated memory and plasma B-cell that recognized Spike protein from past infections with one or more of the other coronaviruses. Since most of the participants from the Kinexus study were apparently asymptomatic for COVID-19, it would appear that their antibodies were sufficiently robust to provide effective protection against SARS-CoV-2.

In the Kinexus clinical study for SARS-CoV-2 antibody levels in those with PCR test-confirmed symptomatic COVID-19, despite clear detection of antibodies against the Spike and other proteins from this virus, Kinexus observed that nearly half of the participants had little or no detectable antibodies against the Nucleocapsid protein of the SARS-CoV-2 virus. There have also been cases of people who were hospitalized for COVID-19 but failed to have anti-Nucleocapsid antibodies in their blood when tested a couple of months later using the LifeLabs' serological test, which relied on whole recombinant Nucleocapsid protein as an antigen. Consequently, the absence of anti-Nucleocapsid antibodies is not a reliable measure that a person has not already been infected with SARS-CoV-2. The most robust and consistent antibodies that Kinexus identified were found to be generated against the Membrane protein of SARS-CoV-2 in those that have recovered from COVID-19. Since the Membrane protein is present in greater abundance on the surface of the SARS-CoV-2 particle than the Spike protein, this would have been a better marker of seroprevalence of SARS-CoV-2 infections than the Nucleocapsid protein, and possibly a more suitable target than the Spike protein for COVID-19 vaccine development.

While anti-Spike protein antibody detection could also be used to establish the seroprevalence of SARS-CoV-2 infections, once mass vaccination was underway, this antigen could no longer be used to distinguish between vaccine- and natural infection-induced immunity.

4.7. Seroprevalence to SARS-CoV-2 During the COVID-19 Pandemic in Canada

According to seroprevalence studies funded by the Canada COVID Immunity Task Force (CITF), in March of 2020, only 0.3% of tested Canadians had antibodies against the SARS-CoV-2 virus.[165] As mentioned Chapter 4.4, the Ab-C study determined that a year later in March 2021, only around 6.5% of tested Canadians had natural immunity.[157]

With CITF funding, the Canadian Blood Services, using highly sensitive Roche Elecsys anti-SARS-CoV-2 Spike protein antibody and anti-Nucleocapsid antibody tests, determined that 99.65% of 13,189 unique donors had anti-Spike antibodies, and 22.65% had anti-Nucleocapsid antibodies by mid-February 2022.[166] The anti-Spike antibodies could have been produced as a consequence of natural infection and/or COVID-19 vaccination. The seroprevalence level of the anti-Nucleocapsid antibodies, which could only arise from natural infection, was evident in 36.59% of blood donors between 17-24 years of age across Canada. Despite nearly all donors having vaccine related antibodies as of December 2021, with the emergence of the Omicron variants, by mid-February 2022, the infection related antibody rate was more than 4-times the monthly seroprevalence rate for the anti-Nucleocapsid antibodies observed for the year of 2021. Evidently, the vaccination of the donors was not protective against infection by SARS-CoV-2. By June 2023, more than 90% of blood donors in the 17–24 years of age group had anti-Nucleocapsid antibodies.[167] About 80% of the general Canadian population was found to have anti-Nucleocapsid protein antibodies by this date.

In a meta-analysis of Canadian seroprevalance studies from the Ab-C study group, Canadian Blood Services and others that was published in the *Canadian Medical Association Journal*, in November, 2021, there was over 95% seropositive prevalence of anti-Spike protein antibodies, but only 9% seropositive prevalence of anti-Nucleocapsid protein antibodies.[168] By March 15, 2023, 74% of Canadians were determined to have anti-Nucleocapsid antibodies, due to the rate of infections dramatically increasing during the Omicron period of the COVID-19 pandemic. It is also noteworthy that the rates of natural infection were higher amongst younger than older people during the course

of the pandemic. This is not surprising, in part because younger people are more socially outgoing and have more robust immune systems.

The Ab-C findings of low anti-Nucleocapsid protein antibody seropositivity during the first two years of the COVID-19 pandemic accounts for the lack of appreciation of the actual extent of natural immunity in the Canadian population by health authorities. Natural immunity was not factored into projected models of the COVID-19 pandemic, and policies such as implementation of vaccine passports also discounted natural immunity. By contrast, natural immunity was recognized in the issuing of vaccine passports in many European countries.

Were Canadian researchers and health authorities actually misled by these studies, which relied on a single marker for past SARS-CoV-2 infections*, i.e.,* anti-Nucleocapsid antibodies, and were most often performed with dried blood samples? Several other studies certainly challenge the notion that SARS-CoV-2 infections were low in Canada prior to the emergence of the Omicron variants.

Early studies performed by Ichor Blood Services in Alberta found that about 51% of the serum samples from unvaccinated people tested by August of 2021 had detectable Spike and Nucleocapsid antibodies that were comparable to levels to those that are found in PCR-confirmed COVID-19.[169] Subsequently, by December 23, 2021, Ichor Blood Services recorded around 89% positive SARS-CoV-2 Spike protein antibody results in unvaccinated people even in distant rural areas around La Crete in northern Alberta with much lower population densities than cities.[170] With such high rates of natural immunity in remote rural settings, it is reasonable to expect comparable or even higher rates sooner in urban, higher population density settings.

Over 1600 participants in the Kinexus clinical study of SARS-CoV-2 antibody prevalence in primarily the Vancouver area, who clearly tested positive for a previous SARS-CoV-2 infection and had COVID-19-like symptoms, first experienced these symptoms between November 1, 2019 and March 31, 2020.[171] Right from when Kinexus first started testing people in March 2020, consistently about 90% of those tested had antibodies that were immunoreactive with peptides patterned after hundreds of regions in the SARS-CoV-2 protein as partly documented in Figure 7. The number and intensity of immunoreactive antibodies against the smaller 41 marker tests that Kinexus conducted remained consistent with over 4000 people who tested positive with multiple markers throughout the course of

the 3-year study, very unlike the results from the CITF-funded studies mentioned earlier. The lack of Nucleocapsid immunoreactivity detected in the pre-Omicron period with these CITF-funded studies is likely due to the poor sensitivity of those tests that relied on a low concentration of recombinant Nucleocapsid protein, and less robust immune responses early in the pandemic for most people who were infected. With secondary Omicron infections, the antibody titers against this target were finally boosted to levels that became detectable in most people with the Nucleocapsid antibody-based tests supported by the CITF.

By early 2022, the majority of people in Canada and the US had been infected by SARS-CoV-2, and about a quarter of those had COVID-19 twice. In British Columbia, using a serological test for antibodies against the Spike and Nucleocapsid proteins of SARS-CoV-2, the BC Centre for Disease Control (BCCDC) reported that by August 2022, at least 70-80% of children ≤19 years, 60-70% of adults 20-59 years, but only ~40% of adults ≥60 years had been infected.[172] In the United States, seroprevalence studies found that about 75% of US children that were tested had infection-induced antibodies following Omicron infection, meaning that there was clearly widespread naturally-acquired immunity in this population by early 2022.[173, 174] Likewise, in England, SARS-CoV-2 antibody testing of unvaccinated school pupils from January to February 2022, showed that 62.4% of primary and 97% of secondary students were serologically positive for previous infection with the virus.[175]

4.8. T-Cell Tests Against SARS-CoV-2

In the adaptive immune response, humoral immunity with B-cells producing antibodies directed against the SARS-CoV-2 proteins is only part of the protection against the virus. T-cells are also important in thwarting the propagation of the virus by attacking and destroying the host cells that have been hijacked into becoming virus producing factories. Measuring the T-cell response is more time-consuming and expensive than serological testing studies. Firstly, the peripheral blood mononucleocyte fraction of blood cells are isolated by use of centrifugation of the blood with a density gradient that will separate them from the greater than 99% of the other blood cells, which are primarily red blood cells (erythrocytes). Commercial testing for this in Canada was difficult to obtain, but at least one company called Immunity Diagnostic Inc. (Immunity Dx) based in Vancouver, B.C. conducted a clinical study to evaluate the extent of natural T-cell immunity against the SARS-CoV-2 virus.[176]

Immunity Dx developed two methods to monitor the presence of T-cells that are immunoreactive with SARS-CoV-2 proteins. With both methods, synthetic peptides based on SARS-CoV-2 proteins or recombinant virus proteins were spotted onto membranes, and these were used to capture T-cells with antigen receptors that specifically recognized SARS-CoV-2 antigens. Following engagement of their T-cell antigen receptors, these T cells grew and propagated and were subsequently detected and quantified. The more T cells that were detected, the higher the levels of T cell immunity in the person from which the blood sample was obtained.

Dr. Ismael Samudio, the president of Immunity Dx, spearheaded a collaboration with Kinexus to evaluate whether clinical blood samples in some of the Kinexus clinical trial participants that were being tested for SARS-CoV-2 antibody levels also had T-cells that recognized the virus. In the blood samples from over 30 tested participants, there was perfect correlation between the level of antibody response and the degree of T-cell recognition of the same viral proteins. These findings indicated that monitoring SARS-CoV-2 antibody responses served as a good surrogate for overall immunity, including T cell immunity. It took about a week to perform the T-cell profiling of a participant's blood sample, and with the high costs of the reagents to perform each test, it was an expensive assay to perform. Ultimately, Immunity Dx had to close its business in 2022. At present, T-cell antigen testing is available through Ichor Blood Services, through a contract with the US Seattle-based company Adaptive Biotechnologies.[177]

4.9. The Natural Immune Response to SARS-CoV-2

As has been discussed in Chapter 3, the immune system has an effective combination of innate and adaptive immune responses to fight an infection by a virus like SARS-CoV-2. For a respiratory infection, the ability of the immune system to mount its defenses at the initial site of infection is critical. The innate immune response with phagocytic cells that consume foreign pathogens is instrumental in producing a robust follow-up adaptive immune response. Memory B-cells present in the tissues in the upper airways may become activated to produce antibodies if these cells have previously encountered the same or similar pathogens. With the whole pathogen, there are many different parts that provide for a broad spectrum of epitopes that can be targeted for antibody production. The more antibodies bound to the pathogen, the greater the opportunity to take it down by interfering with the pathogen's ability to bind to cells and by improving innate immune cell and T-cell recognition of the pathogen. In

the nose, mouth, throat and upper lungs, these antibodies are primarily of the IgA and IgM classes. Because these antibodies are multivalent, they are very effective for clumping the pathogen so that it can be more effectively eliminated in mucus-enriched snot and post-nasal drip, and by sneezing, coughing and ingestion. These antibodies will also facilitate better recognition of the pathogen by innate immune cells and T cells. Ultimately, the presentation of portions of the digested pathogen on innate immune cells along with major histocompatibility antigens in these cells triggers the activation of highly specific B-cells and T-cells with even greater affinity and at higher levels than prior to the infection. In a coordinated effort, this will effectively eliminate the pathogen, and set up the immune system for an even faster and more robust immune response in the future, usually without any disease symptoms.

COVID-19 vaccines were rapidly developed in an attempt to educate the adaptive immune system to prevent COVID-19 following exposure to SARS-CoV-2. In North America and Europe, the strategy was to employ totally new types of unproven genetic vaccines that were developed in a hurried fashion, and inadequately tested for efficacy and safety. The immune responses that were produced from these vaccines relied on production of antibodies of the IgG class, which are present at much lower concentrations in the upper airway passages and upper lungs than IgM and IgA antibodies. They also had less binding capacity for SARS-CoV-2 than the IgM and IgA antibodies. These vaccines required regular boosting due to their directed response to Spike protein only, mutation of the Spike protein in the evolving SARS-CoV-2 variants, and the poor establishment of immune memory.

The original Wuhan SARS-CoV-2 strain appears to have been much more virulent in causing death, that the variants of concerns that arose later. The early limited COVID-19 mortality data guided later public health responses and prompted the vast majority of unvaccinated recipient in Phase 3 clinical studies to quickly get vaccinated with a few months of the onset of these trials when they were unblinded. A private organization in the UK established the Control Group Cooperative with tens of thousands of unvaccinated individuals to ascertain the effectiveness of natural immunity.[178] In a survey of 18,497 unvaccinated members that reported their health status between September 2021 and February 2022 (during the Delta and Omicron BA.1 and BA.2 predominant periods of the COVID-19 pandemic), 25.1% had SARS-CoV-2-like symptoms (14.4% mild; 8.7% moderately severe; 2% severe; 1.4% hospitalized) and another 3% had confirmed SARS-CoV-2 infections, but were asymptomatic.[179] Because the survey findings were self-reported, there were not data for those that would have died

from COVID-19. However, these findings do indicate that the likelihood of hospitalization as a consequence of SARS-CoV-2 infection was only 0.4% during the 6-months study period, which encompassed one of the largest waves of COVID-19 cases during the COVID-19 pandemic. It is clear that natural immunity to the SARS-CoV-2 virus is robust, effective and long lasting.

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Chapter 5:

Evaluating the Efficacy and Safety of Vaccines

5.1. Pre-clinical and Clinical Studies

Some studies report on only one patient (case study) or a small sample of patients (clinical or case series). These studies offer some interest but are not considered high quality as there is no control group for comparison. For clinical studies that have control groups, the designs are case control studies (sometimes known as retrospective studies), cohort studies (usually prospective studies that compare two groups of patients but not randomized) and the gold standard randomized controlled trials (RCTs). The latter provides the best information as the two groups (treated and controlled) are balanced by randomization, and usually blinded to the trial participants and often administering physicians (double-blinded) to eliminate bias.

For the testing of a drug, vaccine or medical device, the underlying principles of the Scientific Method are rigorously applied. Because the stakes are much higher with human subjects, patient safety as well as the efficacy of the intervention are critical in the evaluation process. There is no point in introducing an intervention that causes more problems than the condition that needs to be treated. These tests are typically divided into pre-clinical studies in animals, and Phase 1, 2, 3 and 4 clinical studies in humans. Most government regulatory agencies require compelling results from Phase 3 human trials in order to permit the offering of a drug, vaccine or other medical treatment to the public. In the context of a pandemic crisis like COVID-19, the need for speed versus safety presented major challenges.

Typically, promising treatments are performed on at least two species of animals during pre-clinical studies. This is long before any human trials are normally considered and implemented. Rats and mice are usually the favored animals for experimentation, so there is a huge body of prior studies with these particular rodents that are available for comparative purposes. These are also relatively inexpensive for conducting studies that may require many individual animals for statistical purposes. Should the studies with rodents be promising, then further work may be conducted on larger animals such as dogs, pigs or monkeys. Particular animals may be selected, because they possess characteristics or propensities that are more similar to the particular human diseases under investigation that are to be treated.

Based on promising efficacy and safety in pre-clinical animal studies, a product manufacturer would normally register a proposed set of clinical trials with a government regulatory agency such as Health Canada or the US Food and Drug Administration (FDA) and then commence with Phase 1 human trials upon approval. In these small scale, short duration studies, the main objective is to establish safety of the intervention in healthy individuals. These usually involve small numbers, in the order of 20 to 100 people, tested over several months, to establish any toxicity issues.

In Phase 2 studies, the drug or other intervention is tested on diseased patients with different dosages to maximize the therapeutic effects and minimize any undesirable side-effects. Ideally for drugs, toxic dose concentrations are much higher than those that produce the desired therapeutic effects. Such drugs are described as having a high therapeutic index, and may be considered as effective and safe, at least in the short term. Several hundred people may be enrolled in a Phase 2 study.

Phase 3 studies are usually long and involve the enrolment of several thousands of people in multiple treatment centers, often in more than one country. These randomized controlled trials provide the best information, since they reduce bias by having two groups (treated and controlled), are balanced by randomization, and blinded to the participants and the testing doctors. These trials extend over 1 to 4 years. They ideally involve comparable numbers of carefully matched participants, the placebo controls, who have the disease condition, but are not treated with the intervention under evaluation. Clear evidence of significant clinical benefit from Phase 3 studies with no evidence of major side-effects will compel government regulatory agencies to permit the offer and marketing of the

product to the general public. However, further long-term safety testing data in Phase 4 clinical studies may be required to be ongoing for a few more years to allow continued approval. This may necessitate the manufacturer to provide the results from extended monitoring of the product for side-effects within the general population. This is known as "Post-Approval Research and Monitoring."

It should be appreciated that around 90% of promising therapeutics that enter into Phase 1 clinical studies fail to receive regulatory approval at the end of Phase 3 studies.[180] For most drugs that do succeed, the pre-clinical and clinical trials typically take between 10 to 15 years to complete, with clinical trials alone taking on average 6 to 10 years.[181] The typical cost for development of a successful drug, including the cost of the failures to get to a successful drug, is in the order of US$2 billion.[182] This is why new drugs are exceedingly expensive when they are first released on the market, along with high market advertising costs. However, the typical patent life of new drug is only a few years, since usually three-quarters of the 20-year patent protection life is gone by the time the new drug first reaches the market. Thereafter, any generic drug company can produce exactly the same compound much more cheaply without infringing on any patents related to the drug. However, drug manufacturers can reap several billions of dollars per year for the remaining duration of their patent without competition after regulatory approval.

The market for a drug is limited by the number of people who have the illness that it is designed to ameliorate. By contrast, vaccines are a prophylactic measure, where the market includes both healthy as well as diseased individuals. Thus, the potential markets for vaccines are an order of magnitude larger than traditional therapeutic drugs. For example, one of the most successful of all drugs in history, LIPITOR generated for Pfizer around US$10 billion annually in sales during the 14 years of its patent life.[183] By contrast, in its first year of sales, Pfizer received over US$37.8 billion in 2021 and once again the same amount in 2022 in revenues from their COVID-19 vaccine.[184, 185] This made the Pfizer COVID-19 vaccine the top selling pharmaceutical product in 2021, which grossed 78% more than its closest competitor, Abbvie's Humira, which is a monoclonal antibody drug used to treat rheumatoid arthritis and other autoimmune diseases.[186] In close third as the best-selling pharmaceutical product in 2021 was the Moderna COVID-19 vaccine, with about 48% of the proceeds achieved with the Pfizer COVID-19 vaccine.

In 2019, the revenue from the worldwide pharmaceutical market was about US$1.278 trillion.[187] In 2022, it climbed to US$1.482 trillion. Most of this increase came from COVID-19 vaccine sales.

Prior to the COVID-19 pandemic, the timeline for development of vaccines was typically 10 to 15 years, and in some instances, even longer.[188] Historically, the durations of Phase 1, 2 and 3 trials and the number of participants tested for each phase with vaccines is similar to what has been undertaken for drug trials. However, several of the COVID-19 vaccines were developed, tested, and approved for distribution to the general public in less than a year.

5.2. Post-approval Drug and Vaccine Safety Monitoring

Several governments have established databases whereby doctors, their patients and others may report adverse effects from the medications after their approval and release to the public. These databases were intended to provide warnings about products with safety issues that may not have been apparent from clinical studies, and which may have been underpowered with respect to the numbers of participants tested to detect rarer side-effects. These databases can also permit detection of bad batches of a particular drug or vaccine.

One of the largest databases is the Vaccine Adverse Event Reporting System (VAERS) established by the US Congress in 1990 and set up by the US Centers for Disease Control (CDC) and the FDA.[189] It is a voluntary reporting system that typically received reports of about 30,000 vaccine adverse events per years prior to the COVID-19 pandemic. While most reports of injury are less serious, between 10% to 15% of these describe hospitalization, life-threatening illness, disability or death. Although most filed reports are provided by doctors and healthcare professions, anyone can report an association between a vaccination and an adverse event. However, these reports are monitored and the CDC often follows up to investigate whether the vaccination may have actually caused the adverse event, since these associations may be coincidental in many cases. A forensic analysis of a large sample of VAERS death reports by Mclachlan *et al.* (2021) showed that most reports were submitted by health service employees and in only 14% of the COVID-19 cases could a vaccine reaction be ruled out as a contributing factor in their death.[190] The Harvard Pilgram Health Care study, which was prepared for the Agency of Healthcare Research and Quality section of the US Department of Health and Human

Services, indicated that less than 2% of actual injuries that may be produced from a vaccine are reported in VAERS.[191]

One of the other major adverse reporting databases for medical products is VigiAccess, which was set up by the World Health Organization (WHO) in 2015.[192] It records adverse drug reactions (ADRs) and adverse events following immunization (AEFIs) that are reported to national pharmacovigilance centers or national drug regulatory authorities. The latter are members of the WHO Programme for International Drug Monitoring (PIDM), which was created earlier in 1968. Like the VAERS, VigiAccess warns users that a high association of side-effects with particular drugs or vaccines does not necessarily indicate a causal relationship. Unlike VAERS, individual cases reports cannot be viewed in VigiAccess due to strict data protection laws and agreements between PIDM members and WHO.

The European Medicines Agency created the EudraVigilance system in 2001 for the European Union medicine regulatory network to manage and analyze information on suspected adverse reactions to medicines and vaccines that have been authorized in the European Economic Area (EEA).[193] The data in EudraVigilance are provided by EMA authorization holders and sponsors of clinical trials, who must report and evaluate adverse medicinal product reactions during their development and following their marketing authorization in the EEA.

In the United Kingdom, the Yellow Card scheme provides for the reporting of suspected side-effects to drugs, vaccines and medical devices to the UK Medicines and Healthcare Products Regulatory Agency (MHRA).[194] This scheme collects and monitors information on suspected safety concerns involving healthcare products, which are filed by the public and healthcare professionals. It serves to provide an early warning that the safety of a product may require further investigation by the MHRA. A forensic analysis of a random sampling of 57 death reports in the Yellow Card system in the 1980's showed that at least 40 were true positives (77%) while none of the remaining could be proved to be false positives.[195]

The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) specifically tracks reports of possible vaccine-injury, and it is managed by Health Canada and the Public Health Agency of Canada (PHAC).[196] CAEFISS collects information from provincial and territorial health

authorities that is passively reported to local public health units primarily by nurses, physicians and pharmacists, as well from federal authorities that provide immunization within their jurisdiction. Data into CAEFISS is also provided by the Canada Vigilance Program (CVP) within the Health Products and Food Branch (HPFB) of Health Canada, which tracks reports filed by market authorization holders for vaccines to the Marketed Health Products Directorate (MHPD) CVP whenever there are serious adverse events following immunization. The Advisory Committee on Causality Assessment (ACCA) reviews the reports of adverse events following immunization received through these national surveillance systems and assesses whether an event was likely to be causally linked to a vaccine using strict criteria developed by WHO.

One of the reasons why the VAERS was set up and so important in the US is the very limited liability that vaccine manufacturers have for their products as compared with pharmaceutical drugs. This stems back to increased litigation against vaccine manufacturers in the US in the mid-1970's, and a reluctance of the pharmaceutical industry to produce new vaccines against infectious diseases, which caused a vaccine shortage at that time. The US Congress responded by passing the National Childhood Vaccine Injury Act (NCVIA) in 1986. This included the establishment of the National Vaccine Injury Compensation Program (VICP) to compensate those injured by vaccines on a "no fault" basis.[197, 198] In 2005, the US Public Readiness and Emergency Preparedness Act was invoked, which empowered the Health and Human Services Secretary to provide legal protection to companies that manufacture or distribute critical medical supplies, including drugs and vaccines, unless there is "willful misconduct" by the company. This was first declared for countermeasures against COVID-19 on March 17, 2020 and was to be in effect until the COVID-19 pandemic was no longer declared as an emergency or by October 1, 2024 at the latest.[199] On May 11, 2023, the US Federal COVID-19 Public Health Emergency declaration was terminated.[200]

Ultimately, a great deal of expense and effort has been expended in establishing and maintaining these vaccine adverse event reporting systems. It is widely accepted that less than 10% of all vaccine adverse reactions are reported to systems like VAERS.[201] Nevertheless, as shall be shown later in Chapter 13, they have documented to date unprecedented levels of signals for COVID-19 vaccine injuries and deaths that are magnitudes higher than any prior approved vaccine or drug to date. Despite this, most of these vaccine adverse event reporting systems still claim that the risks of vaccine injury are outweighed by the risks of severe disease from COVID-19.

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This is Exhibit “D” referred to in the
Expert Report of Steven Pelech

Modeling Mischief and Other Data Crimes

Prepared by Christopher A. Shaw, Stefan Eberspaecher, Claudia Chaufan and Steven Pelech

[This represents an unpublished manuscript for a chapter in an upcoming book from the Canadian Citizens Care Alliance. It is based in part of a published report on the CCCA website entitled "Counterfactuals of effects of vaccination and public health measures on COVID-19 cases in Canada: What could have happened? [1]]

Table of Contents

1. What is Modeling and What is It Used For?

Modeling is a complex and challenging task, even for those skilled in mathematics. But what exactly is a model, when should it be used, and how can it be misused? When it comes to predictive modeling for pandemics, the goal is not to predict the future with certainty, but rather to gain insights into potential outcomes so that planning can be performed accordingly.

Models are not perfect representations of the real world and as such, will always be incomplete. The future is inherently unpredictable, as others from Yogi Berra to Karl Popper, have convincingly argued.[2] This does not mean that is just difficult to predict; in reality, accurately predicting the future is impossible. The more randomness there is within a system, the more unpredictable the future becomes.[3] While closed systems like a casino card game can be

predicted with high accuracy, the real world involves super-complex, interconnected systems where predicting outcomes becomes exceedingly challenging. Modeling a pandemic is a perfect example of such a problem.

Given the inherent unpredictability of the future, why should modeling complex systems be attempted at all. However, modeling a pandemic can be beneficial for several reasons:

1. Scenario Planning and Resource Allocation: A well-designed model provides a range of possible outcomes or scenarios. Decision-makers can explore various interventions and their potential effects on outcomes, helping them plan for different possibilities. Modeling extreme outcomes helps allocate resources effectively, such as hospital beds or ventilators, to handle potential crises.

2. Public Communication: Predictive models can communicate the potential risks and severity of a pandemic to the public, raising awareness and encouraging preparedness. However, it is crucial to be mindful of the limitations of models when communicating with the public, possibilities should never be represented as immutable certainties.

3. Identifying Key Drivers: Models can identify previously overlooked factors that drive the spread of a disease, but it is essential to approach the model's output with humility and sensitivity.

When a model's outcomes fail to represent actual events, this can be a cue that some component is missing from the model. The search for the missing pieces, can result in discovery of very important, previously unconsidered factors. For example, when the volume of plastics in the oceans was observed to be far lower than what was expected, this led researchers down a path that ultimately revealed that polystyrene, rather than persisting in the oceans for millennia, was photochemically degrading into organic carbon and carbon dioxide.[4] Instead, a primarily media-driven selection bias for the most extreme consequences resulted in our single-minded obsession with apocalyptic extremes. It is essential to approach modeling with humility, acknowledge its limitations, and as 18th century British mathematician Thomas Bayes taught us, be open to reevaluating decisions based on new information and outcomes.

2. Pitfalls of the Precautionary Principle

The precautionary principle, having been invoked near constantly throughout the pandemic, is worth looking at in greater detail. This principle, a way of thinking that has historically kept our ancestors alive, safe from the consequences of fat-tailed distributions, immediate and tangible threats, served its purpose well when the costs of avoiding dangers were relatively low and easily manageable. Avoiding freezing waters or staying clear of potentially hostile neighbors often required only minimal effort or inconvenience.

However, in today's complex and interconnected world, the exercise of power by authorities has grown immensely, and the consequences of decisions made based solely on precautionary measures can be far-reaching and severe. In some cases, the measures taken to prevent perceived threats might result in more harm than the threat itself.

Does this mean the precautionary principle should be abandoned altogether? Not necessarily. The precautionary principle can still be a valuable tool, but it must be applied thoughtfully and comprehensively. Rather than using it unidirectionally, merely to avoid the recognized threats, it should also be employed to evaluate the potential effects of interventions and actions taken to address these threats; anything less is naïve.

During the COVID-19 pandemic, precautionary measures were implemented to curb the spread of the virus and protect public health. While these measures at the time were believed by many public health officials to be essential and assumed to be effective in mitigating the immediate impact, they also had significant consequences on economies, mental health, and social well-being.

Throughout the recent pandemic, the precautionary principle was frequently used as weapon of condescension to silence any who might suggest moderation in our interventions. Yet those critics were blind to the irony that they were not applying the principle in a thorough manner. To truly harness the power of the precautionary principle, decision-makers should use it as a guide to model and assess the broader implications (*i.e.,* harms) of interventions before implementing them. This proactive approach allows for a more balanced decision-making

process, considering both the immediate dangers and the potential costs and benefits of the proposed actions.

For a moment, consider a scenario where there is considerable uncertainty regarding both the risks associated with a recognized threat and the potential risks of implementing interventions. In such a situation, the question is how to proceed? While decision-makers must carefully assess all variables, the principle of "*premium no nocere*" (*i.e*., "first, do no harm") should be invoked. Systems theory offers valuable insights here; when dealing with complex problems (also known as "Wicked problems"), unforeseen adverse effects can be minimized by refraining from intervention altogether. Introducing new variables into intricate systems can lead to a multitude of issues that abstaining from intervention would not pose. Unfortunately, present political systems tend to reward assertive leaders who are perceived as "taking action," a concept commonly referred to as "interventionism."

3. Transparency is Not Optional

Early on in the COVID-19 pandemic, worst-case scenario models of COVID-19 hospitalization and deaths rates were used to drive public health policy. Only later did it become evident that these models were actually quite simplistic and riddled with fatal flaws. They were also extremely inaccurate. Several publicized models, like the ones popularized by Dr. Neil Ferguson of Imperial College in London in the UK, were proprietary and akin to black boxes, concealing their inner workings.[5] Dr. Ferguson's models wildly projected exaggerated COVID-19 deaths during the February to May 4, 2020, period in the absence of lockdowns and his prescribed non-pharmaceutical interventions to be in the range of 400,000 to 610,000 in the UK, when the actual number of deaths was 28,734.[6] For almost all of the first year of the COVID-19 pandemic, there were no COVID-19 vaccines for the public. Dr. Ferguson and his colleagues forecasted 7 billion SARS-CoV-2 infections and around 40 million deaths world-wide by the end of 2020 if drastic measures were not implemented and the virus was left unchecked.[7] These estimates of morbidity were wildly over-estimated. As of October 15, 2023, over 3 and a half years into the COVID-19 pandemic, there has been some 771 million confirmed COVID-19 cases, although the actual number of SARS-CoV-2 infections is probably closer to 7 billion, and the

cumulative deaths with COVID-19 were reported to be just under 7 million.[8] The serological prevalence of SARS-CoV-2 infections in Canada and many other countries around the world has been near 90%, yet the death toll was vastly smaller than predicted by the Fergusson model. Unfortunately, such estimates were initially treated as near-factual representations and used to guide public policy in the UK and abroad.

Canada's counterpart to Dr. Ferguson as a purveyor of doom and gloom with projected COVID-19 casualties without enforcement of strict mandates was Professor David Fisman at the University of Toronto's Dalla Lana School of Public Health. His flawed COVID-19 pandemic modeling was reported in the *Canadian Medical Association Journal* article entitled "Impact of Population Mixing between Vaccinated and Unvaccinated Subpopulations on Infectious Disease Dynamics: Implications for SARS-CoV-2 Transmission."[9] The publication promoted the concept that the spread of SARS-CoV-2 was primarily from the unvaccinated to the COVID-19 vaccinated, which was widely disseminated in the popular press. This article also received widespread critical commentary, including many calls for retraction of the article directly to the journal.[10, 11, 12] A whole book has been written about the problems associated with Dr. Fisman's work.[13] Some of the major issues with the modeling included:

a. Using relative risk reduction rather than absolute risk reduction with the COVID-19 vaccines;

b. Over-inflating the effectiveness of COVID-19 vaccines and ignoring evidence of negative efficacy with booster shots;[14, 15]

c. Falsely assuming that the protection from COVID-19 vaccination did not wane;

d. Falsely assuming that vaccinated people do not get infected, do not get sick, and do not transmit SARS-CoV-2. Real-world data shown on the Ontario Public Health website on March 31, 2022 showed that 70% of hospitalized COVID-19 cases at the time were fully vaccinated for COVID-19.[16] There are no data that support the notion that vaccinated individuals with COVID-19 do not transmit SARS-CoV-2 with viral loads that are different from unvaccinated individuals;

e. Underestimating the percentage of the population that has been infected with SARS-CoV-2 as under 20% even after the Delta and Omicron waves of the virus sweeping through Canada. This should have been more like 80% or higher,[17] and which if used as a parameter instead of 20% would have completely flipped the conclusions of the model, *i.e*., the unvaccinated were protecting the vaccinated from spread of COVID-19;
f. Almost completely ignoring the protection conferred by natural immunity;
g. Ignoring any safety issues related to COVID-19 vaccination; and
h. It does not help that Dr. Fisman was highly conflicted as a consultant on advisory boards related to influenza and SARS-CoV-2 vaccines for Pfizer, AstraZeneca, Seqirus and Sanofi-Pasteur.

Prior to his resignation as an active member of its modeling group, Dr. Fisman also played a key role in the Ontario Science Table, which prominently advised the Ontario provincial government on policy during COVID-19 pandemic.[18] In the end, even Dr. Fisman *et al.* (2022) stated that "*the simplicity of our model is …. a weakness, because it does not precisely simulate a real-world pandemic process in all its complexity.*" [9] So while they concluded, "*we found that the choices made by people who forgo vaccination contribute disproportionately to risk among those who do get vaccinated*," this is clearly conjecture since no real-world observations with people were used to test their study. Thus, although the title of the publication implied that there was actual mixing of populations in the study, this did not actually transpire.

Regretfully, Dr. Fisman's dubious COVID-19 pandemic modeling is not unique in Canada. Modeling performed by the Public Health Agency of Canada (PHAC) has also been roundly criticized for being overly simplistic, relying on outdated assumptions and flawed reasoning.[1] Secrecy should have no place in this context. If models are used to guide society's actions and potentially impose risks, complete transparency is essential, and the entire model must be subject to critical discussion. Unlike his earlier modeling work, including with the Ontario Science Table, at least Dr. Fisman made his more recent COVID-19 pandemic modeling more open to analysis, which exposed many of its problems as outlined above.[9]

Modeling, like science, is an iterative process that thrives on evaluation and correction. An authoritarian approach to science is inherently flawed. Throughout the pandemic, numerous examples emerged where insightful individuals from disparate fields, such as or physics and geology, identified problems within the domain of epidemiology missed by others.[19, 20] Ethical considerations aside, allowing open discourse is the only way to prevent echo chambers from leading society into catastrophic scenarios. For this, transparency is indispensable.

4. Safe from Criticism

Another effect of the use of sophisticated mathematical modeling should be considered. One that has not been mentioned earlier, and in fact may be disingenuous in nature. Even highly skilled individuals may find themselves perplexed when confronted by such complexity. Understanding the inner workings of a model requires time and effort, and in some cases, access to the model itself has been denied leaving one to wonder in amazement about the veracity of the outcomes presented. What if this lack of transparency is intentional rather than accidental? Some critics of Dr. Fisman's modeling work considered it as flagrant propaganda that fuels fear, incites hatred and contempt of the unvaccinated minority, and supports authoritarian, forced vaccination and segregation policies.

It is possible to use models for somewhat nefarious purposes - to protect one's actions from criticism. Just like mentioning "immunochemistry" at a party is likely to result in you standing by yourself, complex math causes many to disengage immediately. It is possible that models have been used precisely for this purpose - shielding decision-makers from criticism and, at times, crafting a plausible counter narrative to present themselves in a positive light, as further discussed in the next subsection.

5. Application of Predictive and Retrospective COVID-19 Pandemic Modeling

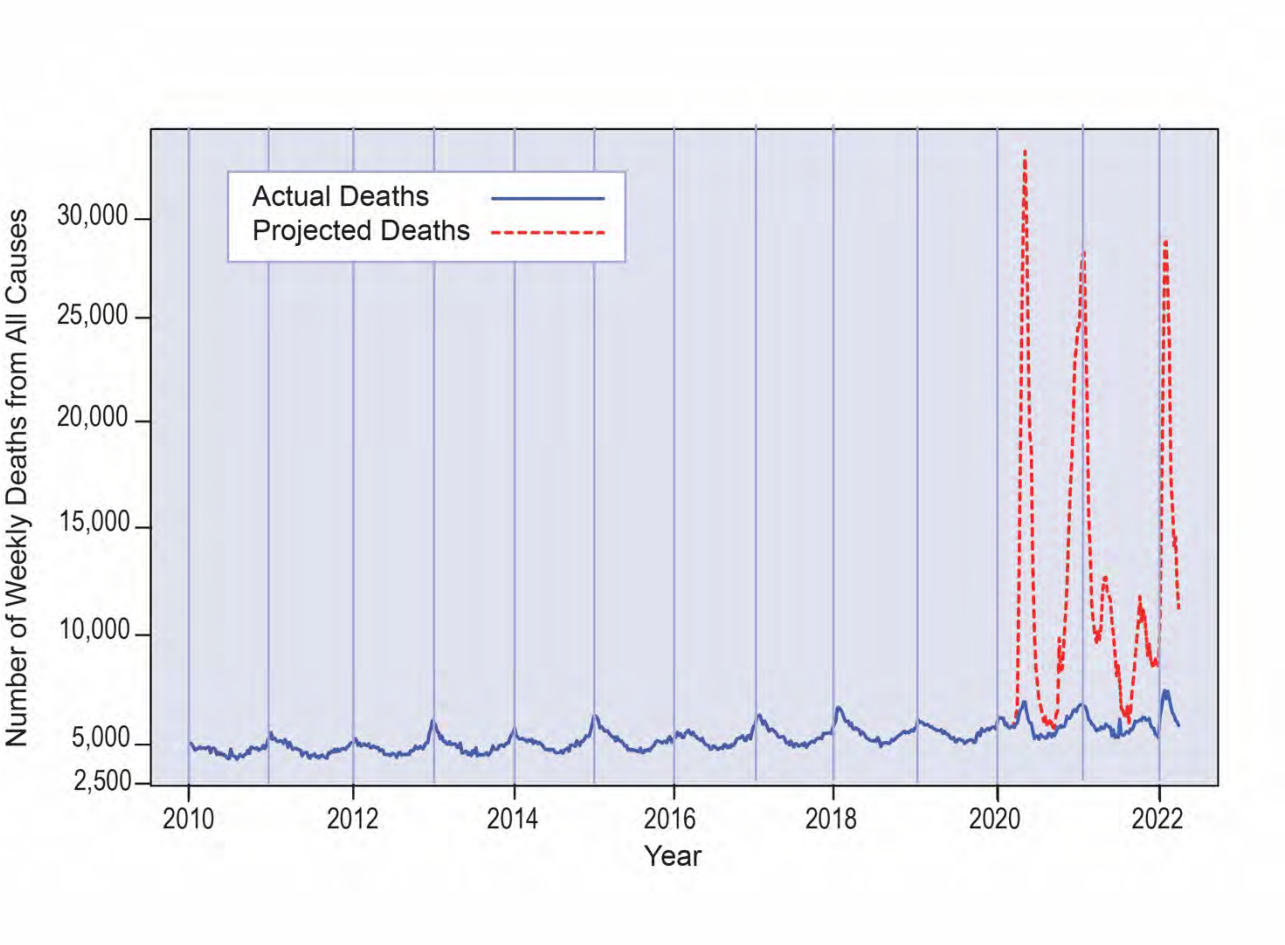
After three years into the COVID-19 pandemic, the Public Health Agency of Canada – including Canada's Chief Public Health Officer Dr. Teresa Tam – published a study in a Canadian public health journal declaring that pandemic-inspired restrictions substantially reduced the impact of COVID-19 in Canada.[21] *"*Counterfactuals of Effects of Vaccination and Public Health

Measures on COVID-19 Cases in Canada: What Could Have Happened*?"* asked the Canadian public to believe an imagined story about what *might* have happened had Canada's public health measures not been implemented. However, what has resulted is a counterfactual narrative of a *fantasized Canada* that was quite divorced from reality.

This article by Ogden *et al.*[21] garnered heavy criticism from Dr. Richard Shabas, the former Chief Medical Officer in Ontario from 1987 to 1997, and his colleagues.[22] The response from the article's authors has made it obvious that they are victims of common modeling pitfalls that have compromised their objectivity, thus adversely affecting the quality of their model and its output.[23] Instead of relying on modeling forecasts, the authors resorted to "back-casting" to state "what might have happened" or "what could have been" had governments not acted as they did. Giving credence to such questionable results occurs all too often when sensational outcomes are observed. Unfortunately for any modeling study, the historical path – the one involving no interventions – was foreclosed the moment official pandemic responses began.[24] This meant that neither the authors, nor anyone else, could ever observe the spontaneous and uninhibited nature of Canada's reactions to COVID-19.

The most dramatic claim in the Ogden *et al*. article was that, without social restrictions and vaccines, up to 800,000 COVID-19 related deaths *could have* occurred. Figure 1 below shows 12 years of all-cause mortality data in Canada (blue line), with the authors' "worst case" outcome superimposed (red line). Two things make the authors' assertion incompatible with any reasonable view: 1) there was no obvious increase in all-cause mortality between 2020-21 that is aberrantly different from historical trends (blue line); and 2) the death count of "up to 800,000 people" (red line) surpasses the number of Canadians killed in the 1918 influenza pandemic and two World Wars – *combined*., even when adjusting for population growth. It begs the question: could an infection with survival rate greater than 99% really have been the single-most devastating health event in a century?

Figure 1. Actual and predicted all-cause mortality in Canada. Predicted all-cause mortality, mostly from COVID-19 by Ogden *et al.* (2022) is shown in the dotted, red line.[23]



All models are unrealistic to a degree (and this is not a "fatal flaw"). However, models are only as good as the assumptions upon which they are based. Unfortunately, the authors underestimated the acquisition, extent, and durability of natural immunity while conveniently overestimating the duration of vaccine-acquired immunity. Furthermore, they have based their results on assumptions that underestimate the number of people who had already been exposed to SARS-Cov2 in late 2019 and early 2020. However, due to the over-simplicity of their models, including a complete failure to account for network structures, they overestimated the rate of viral transmission during the period being modeled. It appears that the authors wanted to have it both ways.

Ogden *et al.* (2022) [23] also assume that the spread of infection varied relative to the stringency of closures and other social restrictions: when these were strict, transmission was low; when they were relaxed, transmission increased. However, there is evidence that these measures did not work "as advertised." In many provinces, their effect might have plateaued by April 2020.[25] Stricter measures did not translate into proportionately slower spread. Unfortunately, this did not prevent the authors from forcing their model to respond as if these measures had been effective. In the authors' "worst case" scenario, large amounts of infection and disease are – conveniently – a foregone conclusion unless suppressed by top-down government edicts. The natural tendency of a population to automatically avoid a contagion was never considered.[26]

The authors' least-subtle omission was the failure to disclose personal conflicts of interest. While scientists from Canada's public health agency might claim they only provide guidance on sub-national pandemic responses, the interests of many federal health agencies are certainly evident. The purchase of COVID-19 vaccines by the federal government preceded their approval by Health Canada,[27] and some of the most restrictive measures imposed on Canadians (such as vaccine requirements for commercial travel) came from the federal level. As it happens, four of the authors were directly employed by the federal government and, as such, were not disinterested evaluators of their employers mandated pandemic policies. All this leads one to wonder: was their article a genuine evidence-based analysis of government policies? Or, rather, a blatant attempt to justify these policies? To their credit, the authors admit that Canada's response to the pandemic was imperfect, and that its unintended consequences need to be investigated. It will truly be a measure of the honesty and integrity Canada's public health agency and their provincial partners if the latter is ever realized.

6. Birds in a Cage and Better Modeling

How did these models prove to be so wrong? In part, this has been attributed to how little was known about the SARS-CoV-2 virus early in the pandemic. However, based on previous encounters with coronaviruses and other respiratory viruses, prior experience should have

provided better guidance. For example, in 2003 SARS-CoV-1 disappeared within a year of its discovery without the availability of specific vaccines or other specific medications for the virus.

Dr. B.F. Skinner, the behavioral psychologist, demonstrated that he could induce birds to perform elaborate rituals when they falsely believed that these actions would lead to a rewarding stimulus, such as food.[28] This psychological concept is known as superstition. Regrettably, higher species of animals are also susceptible to such behaviors. One of the most undesirable effects of modeling is its potential to solidify the belief in causality when a spurious association is observed. While the true aim of properly conducted science is to enhance humanity's knowledge base and improve predictive capacity, modeling can lead decision-makers to believe that their actions resulted in positive outcomes, contributing to the accumulation of anti-knowledge at a civilizational level. Decision makers equipped with copious amounts of anti-knowledge are far more likely to make poor decisions in future crises.

As pointed out by others,[29] it is unlikely that society will completely abandon modeling, even if it were convincingly demonstrated to be deceptive. Human fascination with technology and knowledge has benefited civilization for millennia, and it would be unrealistic to expect that it would be forsaken now. However, by adopting more cautious approaches to modeling complex systems, critically appraising outcomes, and maintaining humility in our conclusions, the likelihood of disasters in the future can be reduced. It would be very worthwhile to track the success of predictions and hold modelers accountable for their work. When modelers have a skin in the game, they may approach their conclusions with greater humility and exercise more caution in potentially unleashing chaos upon a traumatized society.

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