

**IN THE HIGH COURT OF NEW ZEALAND
WELLINGTON REGISTRY**

**I TE KŌTI MATUA O AOTEAROA
TE WHANGANUI-A-TARA ROHE**

CIV-2022-485-013

UNDER the Judicial Review Procedure Act 2016

IN THE MATTER of an application for judicial review of a
decision made under the Medicines Act 1981

BETWEEN **DCB**
First to Eighth Applicants

AND **THE MINISTER OF HEALTH**
First Respondent

AND **THE GROUP MANAGER OF THE NEW
ZEALAND MEDICAL DEVICES SAFETY
AUTHORITY (MEDSAFE)**
Second Respondent

AND **THE COVID-19 RESPONSE MINISTER**
Third Respondent

**FIRST AFFIDAVIT OF BYRAM BRIDLE IN SUPPORT OF
APPLICATION FOR JUDICIAL REVIEW**

Dated 25 January 2022

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AFFIDAVIT OF BYRAM W. BRIDLE

I, **Byram W. Bridle**, Associate Professor, solemnly, sincerely, and truly declare and affirm:

Introduction

1. I am an Associate Professor of Viral Immunology in the Department of Pathobiology in the University of Guelph in Ontario, Canada. The University of Guelph is a comprehensive public research university in Guelph, Ontario, Canada. It was established in 1964 after the amalgamation of the Ontario Agricultural College (1874), the MacDonald Institute (1903), and the Ontario Veterinary College (1922), and has since grown to an institution of almost 30,000 students. **Annexed** and marked "**BRI-1**" is a copy of my Curriculum Vitae (CV) which demonstrates my academic and scientific achievements.
2. I offer to assist the Court by drawing on my training, research, and experience generally and particularly during the current SARS-CoV-2 pandemic. I research vaccine development for the prevention of infectious diseases and to treat cancers in humans. I have studied and am able to give expert evidence about the human body's immune response to viruses. I am familiar with up-to-date research about this pandemic in the fields of immunology, virology, and public health. I train research fellows in the field of vaccinology. I received funding from the Ontario Government (from the Covid-19 Rapid Research Fund) and the Government of Canada (Pandemic Response Challenge Programme, National Research Council of Canada) in relation to the development of vaccines against coronaviruses. I hold no commercial interests in this activity. I hold numerous grants for research in cancer and viral immunology.
3. I was certified as an expert witness for scientific matters related to COVID-19 in the Ontario Supreme Court of Justice, Canada.

4. I can understand and interpret relevant data and research for the assistance of the Court, drawing on my professional training and experience. I have been provided with and read the Code of Conduct for Experts under the New Zealand High Court Rules: I agree to abide by the Code of Conduct.
5. I am advised that the New Zealand Minister of Health has granted provisional consent under the Medicines Act 1981 for the use of the Pfizer (Comirnaty) vaccine in 5-11-year-old children.¹ I have been asked to provide my expert opinion on whether this decision is reasonable and justified based on the data and science currently available.
6. In my evidence, I will outline the molecular basis for Covid-19, the immune response to the virus known as SARS-CoV-2, and the scientific understanding of the way the virus propagates between people. I will outline the rationale behind the use of the Pfizer mRNA vaccines. I conclude by finding that no scientific basis exists to justify the use of vaccine mandates to reduce the transmission of SARS-CoV-2. I will also give evidence that the Pfizer mRNA vaccine causes significant side-effects, which for many adults and young people are likely to be worse than infection with the virus itself. I will also explain why I believe that many individuals do not need to be vaccinated, since they have naturally acquired robust immunity to the virus. I conclude that otherwise healthy 5-11-year-old children face greater risks of adverse events from the vaccine than they do from SARS-CoV-2.
7. I have also summarised the scientific evidence in more depth that supports my belief that Covid-19 vaccines should not be mandated in a recent report I have completed which is **annexed** and marked “**BRI-2**”. In that report, I outline several facts related to covid-19 vaccines

¹ <https://www.beehive.govt.nz/release/government-confirms-covid-19-vaccinations-protect-tamariki>

which have direct relevance to the issue of vaccine mandates. In particular, I draw the Court's attention to the following:

- a. I have correctly identified safety concerns with Canada's Covid-19 vaccine program, including concerns related to blood clotting and heart inflammation. In response, the AstraZeneca vaccine was withdrawn from the Canadian programme and the Moderna vaccine was suspended for males aged 18 to 24 years (pages 4 and 5 of "**BRI-2**").
- b. The harm from SARS-CoV-2 has been overestimated (page 6 of "**BRI-2**").
- c. Molecular testing using the quantitative reverse transcriptase-polymerase chain reaction (PCR) for Covid-19 is inaccurate and frequently leads to false-positive results (pages 10 to 14 of "**BRI-2**").
- d. Asymptomatic transmission of SARS-CoV-2 is negligible (pages 14 to 18 of "**BRI-2**").
- e. Natural immunity to SARS-CoV-2 after infection protects against further transmission of the virus (page 19 of "**BRI-2**").
- f. Long term, SARS-CoV-2 and its variants will become endemic, and natural immunity will be important to reducing spread of the virus. Elimination of the virus is not possible (pages 19 to 21 of "**BRI-2**").
- g. How Covid-19 vaccines work (pages 31 to 35 of "**BRI-2**").
- h. The evidence for increased harm caused by the Covid-19 vaccines (pages 35 to 47, pages 96 to 102 [neurological risks] of "**BRI-2**").
- i. Covid-19 vaccines are particularly likely to cause side-effects in those with pre-existing immunity to the virus, and in North America, exposure to the virus is underestimated (pages 50, 86 to 96 of "**BRI-2**").

- j. Exaggeration of the risk of Covid-19 and an under-appreciation of safety concerns for pregnant women and their offspring from Covid-19 vaccines (pages 56 to 86 of “**BRI-2**”).
- k. Evidence for rapid waning immunity from the Pfizer and AstraZeneca vaccines (page 47 of “**BRI-2**”).
- l. Early treatment options and dietary supplements that would provide alternatives to the use of vaccines to reduce harm from Covid-19 (pages 103 to 105 and 121 to 127 of “**BRI-2**”).
- m. Evidence of an oppressive environment for scientists who question the use of lockdowns and safety of Covid-19 vaccines (pages 106 to 114 of “**BRI-2**”).

Covid-19 – a viral disease

- 8. Covid-19 is a disease that develops in a subset of individuals infected with the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). In most cases people do not develop disease and may remain asymptomatic or develop mild to moderate symptoms. In a relatively few cases, although not insignificant in number, largely being elderly or vulnerable people suffering from other significant medical conditions, the virus can cause serious disease if left untreated, and in some cases notwithstanding early treatment, including pneumonia, inflammation causing bleeding, clotting, neurological impairment, and other long-lasting symptoms.
- 9. Covid-19 is a real and serious disease; but it is also comparable to other respiratory diseases that can develop in vulnerable populations, such as from strains of influenza virus and other coronaviruses (for example Middle Eastern respiratory syndrome-coronavirus [MERS-CoV]). Some common colds are also due to coronaviruses, so it is the case that components of this virus have been seen by the immune system in the bulk of any population. It is not like a virus entering a naïve population

which has been cut-off from parts of the world where similar viruses historically circulated. In “**BRI-2**” page 6, I discuss in more detail the evidence of a more realistic assessment of the threat from Covid-19, compared to what is often portrayed in the media.

The Human Immune System

10. The human immune system is complex and intricate. It protects people from before birth to death, although it becomes more dysfunctional as we become older (a process known as immunosenescence). The operating parts of the immune system must distinguish non-dangerous self from dangerous non-self, pathogens from non-pathogens. Pathogens range from sub-microscopic viruses like SARS-Cov-2, which hijack our cellular machinery to make copies of themselves, through to bacteria, which may not be too different in size from our own cells, to fungi, which can be larger than our own cells, protozoa and multi-cellular parasites.
11. We live with viruses: our immune system is primed to rapidly recognise viral pathogens based on our innate immune system, as well as based on past exposure of our adaptive immune system (*e.g.* B cells that make antibodies and T cells) to similar viruses. Again, SARS-CoV-2 is in a family of coronaviruses which almost everyone will have been exposed and have some degree of immunity to.
12. The human immune system has multiple components. Every healthy person has pattern recognition receptors that respond to features common to pathogens. This triggers rapid innate immune responses against viruses. An example of a major anti-viral mechanism within the innate arm of an immune response is:
 - a. **Natural killer cells**, also known as NK cells or large granular lymphocytes (LGL), are a type of *cytotoxic lymphocyte* critical to the *innate immune system* and represent 5–20% of all circulating

lymphocytes in humans. The role of NK cells is analogous to that of *cytotoxic T cells* in the vertebrate *adaptive immune response*. NK cells provide rapid responses to *virus*-infected cells and other intracellular pathogens acting within hours and up to three days after *infection*.

13. In turn, the innate immune system induces adaptive immune responses. The primary features of adaptive immune responses, simplified are:
- a. **Antibodies:** they are proteins made by our immune system (specifically, B cells) to bind to and direct attacks upon an invading infectious agent; they are very large and are mainly excluded from the inside of our cells.
 - b. **T cells**, which are a type of *lymphocyte* (they are the main type of cell found in *lymph* nodes). A lymphocyte is a type of *white blood cell* in the *immune system*. T cells are one of the important *white blood cells* of the immune system and they play a central role in the *adaptive immune response*. T cells can be distinguished from other lymphocytes by the presence of a *T-cell receptor* (TCR) on their *cell surface*.
 - c. **B cells**, also known as B lymphocytes, are a type of *white blood cell* of the *lymphocyte* subtype. B cells produce *antibody* molecules; these antibodies are inserted into the plasma membrane where they serve as a part of *B-cell receptors*. When a naïve or memory B cell is activated by an antigen, it proliferates and differentiates into an antibody-secreting effector cell, known as a plasmablast or plasma cell. Additionally, B cells *present antigens* (they are also classified as professional *antigen-presenting cells* (APCs)) and secrete *cytokines*, which signal inflammation is occurring.
 - d. **Immunological memory**, is a key feature of the adaptive immune system. Upon re-exposure to the same pathogen or a part of a novel pathogen that is shared with one that caused a previous infection, the antibody and T cell responses are much more rapid and of much greater magnitude. The speed and robustness of this

so-called secondary immune response is the reason that many people do not experience disease or only a mild version of it upon re-exposure to a pathogen. Naturally acquired immunological memory typically lasts a very long time, often for the duration of person's lifetime.

14. This is how the innate human immune system works, in simplified terms. Once a host identifies that there is a foreign invader, so-called 'professional antigen presenting cells' take up some of the virus particles and dismember them within subcellular compartments. This process cuts the virus up into scores of small pieces of various sizes and displays some of these pieces on the surface of the cell. Each cut-up piece of virus protein is shown to the T cells (also the B cells, which manufacture antibodies) of the immune system and a match is almost always found. Before we are born, through a molecular shuffling of the genes that encode the antigen-binding site in each of our billions of T and B cells, a huge and varied repertoire of cells, capable of recognizing everything to which our bodies will ever be exposed, is formed.
15. It is to this very large library of T-cells that the cells bearing the cut-up pieces of the invading respiratory virus are shown. The process in healthy people takes a few days to complete, but once it is done, a few dozen, perfectly matched T-cells (and B-cells) have been identified and these are instructed to multiply, making many copies of themselves. While this is simplified, specifically targeted white blood cells are now at large in the host and these set about clearing the viral infection, wherever it is. If this repertoire is formed because of natural infection and some vaccines, generally immunity to almost every part of the invader is acquired.

Traditional Versus mRNA-Based Vaccines

16. Immunity to an infectious pathogen can often, but not always, be conferred by exposure to a well-designed vaccine. Traditional vaccines

trace their modern era origins to the work of Edward Jenner, who noticed that milkmaids had smooth skin because, unlike most others, had never been made ill by smallpox. Jenner hypothesized that this was because the milkmaids were uniformly infected by the clinically much milder cowpox, a related but different virus. His famous experiment, where he successfully protected a boy by deliberately infecting him first with cowpox and, weeks later, with smallpox, marked the start of the field of vaccination (from *vacca*, a cow). Classical vaccines, as in Jenner's experiment, take an infectious agent and after basic formulation, inject it into the host. The essential mechanism of traditional vaccines is to present to the human immune system the entire infectious agent. This is crucial if the breadth of acquired immunity conferred is to be maximized.

17. This breadth of immunity which follows natural infection can never be improved by a vaccine. At best, it might be matched by a very well-designed vaccine. But not every vaccine gets close to conferring the full breadth of immune protection obtained by infection. The Covid-19 vaccines are a case in point. Though most of the commercially available vaccines use new technology (either DNA with a virus vector, like the AstraZeneca and Johnson & Johnson products or encapsulated mRNA, like the Moderna and Pfizer/BioNTech products), every one of them encodes only a portion of the SARS-CoV-2 virus, the so-called spike protein. It follows that the extent of the immunity conferred by Covid-19 vaccines is limited primarily to an antibody response to this spike protein (because that is all the immune system is seeing of the virus), and this has been shown in the real-world.² By contrast, immunological studies of those who have recovered from infection show that T cell immunity to all components of the virus has been acquired.³ Optimum host protection requires an immune response to multiple components of the virus.

²<https://link.springer.com/article/10.1007/s10654-021-00808-7>

³<https://immunology.sciencemag.org/content/6/58/eabf7550.full>

18. One of the consequences of the natural immune response cutting the virus up into many pieces and then assembling a repertoire of white blood cells capable of responding to dozens of such pieces is the adaptability of this acquired immune response. Termed multi-locus immunity, this means that if a virus like SARS-CoV-2 was to infect the host, the fact that it was a new virus does not mean that we are susceptible. On the contrary, many of the small pieces into which the virus is cut are identical between different, but related, coronaviruses and as a result, the host can be partially immune to that virus also, notwithstanding that the host had never seen this new virus before.⁴
19. The process was demonstrated by the results of some experiments conducted in 2020 on volunteers who had survived infection by the original SARS virus in 2003. There were two significant findings: first, all those infected in 2003 had retained vigorous immunity 17 years later. When presented in a lab with pieces of the original SARS virus, blood-derived T cells from the volunteers demonstrated prompt and profound responses, confirming immunological memory was thorough, robust, and durable. Through the process described above, all the volunteers' T-cells also showed vigorous immune responses to SARS-CoV-2, a virus to which they'd never been exposed.⁵ This indicates that immunity from other coronaviruses is likely to protect from SARS-CoV-2 infection.

Approval of the Pfizer Vaccine and its Technology

20. The Pfizer Covid-19 vaccine was granted Provisional Consent until 3 November 2021 in New Zealand,⁶ which has since been extended. I understand that provisional consents are restricted to two years with the possibility of renewal. This has enabled approval of the vaccines while Phase 3 clinical trials are yet to be completed. I observe that the

⁴<https://www.science.org/doi/10.1126/science.abf6648>

⁵<https://www.nature.com/articles/s41586-020-2550-z>.

⁶New Zealand Gazette 21 June 2021.

Gazette approval requires Pfizer to submit additional information on certain dates, including periodic update safety reports and about the efficacy of boosters. I have not been informed about compliance by Pfizer with the reporting requirements in the approval.

21. The Pfizer vaccine relies on technology that, prior to the Covid-19 pandemic, was not previously used in humans, except in small scale clinical trials (such as a clinical trial of a rabies mRNA vaccine).⁷ Phase three clinical studies are still being conducted: these studies involve following-up for two years, following vaccine recipients after the administration of the second dose. The long-term effects of use of the vaccines depends on the collection of data over a longer time. Therefore, the approval in New Zealand and overseas has been provisional. Such an approval with vaccines, particularly if used on such a large scale is unusual and carries with it real risks, some of which are not quantifiable from early trial evidence. Of concern, Pfizer's clinical trial has been compromised by unblinding and crossing over of the placebo arm, thereby abrogating the availability of an unvaccinated control group. Further, Pfizer's own six-month clinical trial update highlighted troubling findings, including greater all-cause mortality and a higher rate of severe adverse events in the vaccinated group as compared to those who were unvaccinated. I discuss this in "**BRI-2**" pages 50 to 56.
22. The provisional approval of the Pfizer vaccine underlines the importance of ensuring that recipients of the vaccine give fully informed consent, given the uncertain safety profile of the product. I discuss this aspect more fully below.
23. The backbone of the Pfizer vaccine is a lipid nanoparticle, which is a small bubble of fat. Inside the nanoparticle is a messenger ribonucleic acid (mRNA), which is a tiny piece of genetic material that provides the instructions for the recipient's cells to manufacture a modified

⁷Pardi, N, Hiogan, MJ, Porter, FW & Weissman, D, *mRNA COVID-19 vaccines – a new era in vaccinology*, Nature Reviews Drug Discovery 17, 261-279 (2019).

version of the SARS-CoV-2 spike protein. When these nanoparticles are injected into the body, they are intended to fuse with cells with which they come into contact. When this happens, the mRNA migrates from the lipid nanoparticle into the cell and the cellular machinery then uses the mRNA blueprint to manufacture the modified version of the SARS-CoV-2 spike protein. When this is detected by the immune system, antibodies are activated. This signalling to the immune system may involve a degree of inflammation which can cause localized injury to normal tissue. The Pfizer vaccine cannot of itself infect people with SARS-CoV-2.

24. The vaccines of this mRNA type were authorized for emergency use in many developed countries. When these vaccines were first developed there was a control group. Under pressure of public health agencies, desiring to vaccinate their populations, Pfizer unblinded the control group. Therefore, there is no longer a placebo group against which the longer-term study of the Pfizer vaccine may be undertaken. This undermines the rigorous nature of the safety assessment needed for a new medicine of this type, since the study can no longer be well controlled. Much more reliance must be placed on passive surveillance. This is challenging because there is now uncertainty as to both the numerator (the number of vaccine-related adverse events) and the denominator (the number that is typical for that event to arise, referred to as the background incidence of the event). It becomes difficult to prove definitively that any adverse event is caused by rather than just associated with the vaccine when there is only a passive surveillance system.
25. A serious difficulty with passive adverse event reporting systems is one of under-reporting of adverse events. Indeed, I was involved in highlighting the risk of blood clotting and myocarditis that were not immediately identified in early trials (pages 4 and 5 of “**BRI-2**”). Unless an adverse event requires medical attention or hospitalization, or leads to death, it may well go unreported. People are often discouraged from

reporting adverse events if they come up for example because this may be seen to undermine public health authorities messaging about vaccination, then also the physicians may be inclined to assume that the event is not related to vaccination and will be dissuaded from classifying it as an adverse event. In Canada, adverse event reporting by medical professionals has been pre-screened and is sometimes rejected by these authorities. This will make for inaccurate post-approval assessment of these vaccines. I discuss the evidence for the harm of the vaccines more fully in pages 35 to 47, and pages 96 to 102 [risks to the nervous system] of “**BRI-2**”.

How do mRNA Vaccines Work?

26. I discuss this in more detail in pages 32 to 35 of “**BRI-2**”. The spike protein gives the SARS-CoV-2 virus its crown-like appearance (it looks like a corona). This protein allows the virus to attach to human cells and infect them. If antibodies can bind to block all the spike proteins on the surface of the virus, then the virus cannot infect its subject. This takes some time to occur after an infection is acquired. How long it may take will depend on the viral load acquired, the responsiveness of the person’s immune system and the efficacy of the vaccine at that point in time (as to this aspect, it is largely a function of how long ago the second dose was administered). A person with pre-existing naturally acquired immunity will be able to respond to the infection very rapidly; within hours.
27. The binding of antibodies to even a part of the virus may tag it for attack by other cells of their immune system. The objective of vaccination is to manufacture sufficient spike protein to trigger a robust antibody response against the spike protein should we be infected in the future.
28. Importantly, the primary efficacy of this vaccine builds an immune response against the development of disease in the lower respiratory

tract. The Pfizer vaccine therefore has, at best, modest effectiveness in reducing the degree of infection in the upper respiratory tract. While at the peak period after vaccination these vaccines show a robust effect in the lower respiratory tract, they are not durable in this respect.⁸ Individuals may respond differently to vaccines, depending on the state of their immune system and the variable quality in the vaccine dose received. In contrast, naturally acquired immunity confers robust and long-lasting protection in both the upper and lower respiratory tract by virtue of natural exposure to SARS-CoV-2 being via this route.

29. The SARS-CoV-2 undergoes random mutations and some such variants become dominant, such as 'Delta' and 'Omicron'. These variants may escape the immunity provided by vaccines which were designed before such variants existed. Studies of the Delta variant of SARS-CoV-2 show that vaccinated and unvaccinated people carry similar viral loads in the upper respiratory tract.⁹ Moreover, the immune system is suppressed in the two weeks which follow vaccination, making the vaccinated person vulnerable to infection and disease in this period, and which may cause complications for the worsening of underlying diseases including cancers.
30. The Pfizer vaccine is diluted with a saline solution before administration. Errors in preparation of these vaccines in dilution can occur if the manufacturer's guidelines as to injection are not followed. Also, careful injection technique must be followed to minimize accidental intravenous delivery. In these cases, avoidable side-effects may arise.
31. The mRNA vaccines will wane in effectiveness as variants emerge, particularly if there are changes to the spike protein,¹⁰ as appears to be the case with the Omicron variant.

⁸<https://www.medrxiv.org/content/10.1101/2021.08.03.21261496v1>

⁹<https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v4.full.pdf>

¹⁰<https://www.nature.com/articles/s41579-021-00573-0>

32. The protection provided by the Pfizer vaccine is short lived (for further discussion see page 47 of “**BRI-2**”). It offers significantly reduced protection from about three to four months until six months, when efficacy wanes substantially, from more than 90% after vaccination to 0% after 8 months.¹¹ This means, for example, that many health care and border workers in New Zealand who I understand were the first to receive the vaccine back in April 2021 will not be protected now. Pfizer is marketing boosters to maintain effectiveness.¹² This has implications for community immunity as I discuss below, but in brief unless a community is vaccinated within a small window of time, waning protection amongst that community will occur at different intervals, making some members of that community vulnerable to infection and disease as the vaccine’s efficacy wanes; this is because the members of any given population will have been vaccinated at varying points in time.

Transmission of SARS-CoV-2

33. It is settled science that these new mRNA vaccines, including the Pfizer vaccine, do not provide sterilizing immunity.¹³ Unlike vaccines against non-respiratory diseases, such as polio and measles, these vaccines are designed to prevent severe disease, but not transmission. This means that it is not possible to quantify with any precision how long any given vaccinated person might remain contagious after infection, or the level of risk of transmission of the virus they may pose to those around them. Evidence for the vaccine effectiveness in cohort studies, shows a rapid waning of protection at eight months post vaccination.¹⁴
34. Accordingly, it is not sound public health policy to assume that vaccination will equate to a person not being infected or contagious:

¹¹https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3949410

<https://www.medrxiv.org/content/10.1101/2021.10.13.21264966v1.full.pdf>

¹²<https://www.nejm.org/doi/full/10.1056/NEJMoa2114255>

¹³Krammer F. SARS-CoV-2 vaccines in development. *Nature*. 2020 Oct;586(7830):516-27.

¹⁴https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3949410

they pose a similar risk of transmission once infected as does an unvaccinated person (if a child, they will if unvaccinated generally pose substantially *less* risk).¹⁵ A young person with a healthy immune system can develop a rapid immune response to infection and pose a very low risk of transmitting the disease to others.¹⁶ This is even so with the Delta variant.¹⁷ On the other hand, a vaccinated person who is either no longer mounting a robust immune response, because the vaccine induced antibodies are waning, or because their immune response to the vaccination was sluggish, particularly if they have a weak immune system, or the dose was diluted, may be at greater risk of transmitting the virus than an unvaccinated healthy person. Statistical analysis of data which examines the relationship between levels of vaccination and cases of Covid-19 in 68 countries shows that countries with higher per capita vaccination levels do not, on average, result in lower Covid-19 case incidence.¹⁸ In fact a trend emerged suggesting the opposite may be happening.

35. It is a serious public health error to assume that vaccination will afford widespread community protection to those who are vulnerable to disease and death if infected with SARS-CoV-2, in the absence of other public health measures being applied. Any given individual, vaccinated or not, for these reasons may transmit the virus to a vulnerable person. The errors are as follows:

- a. There is an implicit assumption among public health authorities that community immunity can be built largely out of a mass vaccination program, deploying vaccines like the Pfizer mRNA vaccine. This assumption is not scientifically sound.

¹⁵<https://www.medrxiv.org/content/10.1101/2021.09.28.21264262v1>

<https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8485578/pdf/eurosurv-26-39-3.pdf>

¹⁶<https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8437699/pdf/main.pdf>

¹⁷<https://www.medrxiv.org/content/10.1101/2021.07.29.21261317v1.full.pdf>

¹⁸Subramanian SV, Kumar A. Increases in COVID-19 are unrelated to levels of vaccination across 68 countries and 2947 counties in the United States. *European Journal of Epidemiology* 2021 doi: 10.1007/s10654-021-00808-7

- b. The points I have made above about the limits to the protections offered by the Pfizer vaccine mean that, at best, vaccination with the Pfizer vaccine can only be a part of building community immunity.
 - c. It is my expert opinion that naturally acquired immunity will remain the key ingredient to building robust community immunity. This is particularly so since, as I will outline below, the immune response to vaccination is not as strong as the immune response triggered by natural infection (with or without prior vaccination).
36. Unless public health authorities clearly point out the limited protections offered by the Pfizer and similar vaccines, vulnerable vaccinated persons may well put themselves at risk under a false assumption that they have strong protection from infection and disease. Highly vaccinated populations are still experiencing significant rates of hospitalization and death among vaccinated people.¹⁹
37. Not everyone who is vaccinated will develop many spike proteins and the quality of the vaccines can vary from batch to batch. Therefore, citing pharmaceutical companies' research of the efficacy of these vaccines, and the perceived effectiveness amongst a trialled group, is an unsafe basis upon which to deliver public health messaging. Other factors such as the age of the vaccinated person, the body mass and overall health can affect the effectiveness of any vaccine of this type.

Vaccinating children and the young

38. The stated purpose of vaccinating children, youth, and young adults of childbearing age is to protect them from infection and reduce the risk of them transmitting SARS-CoV-2 to adults, particularly the aged and

¹⁹<https://www.timesofisrael.com/health-ministry-chief-says-coronavirus-spread-reaching-record-heights/>

infirm. The first point to recall is that the Pfizer vaccine does not induce sterilizing immunity; therefore, public health authorities do not exempt vaccinated people from all lockdown policies and encourage them, and require them in many countries, to physically distance (this is being seen in countries where the Delta variant is rampant, such as Israel and Singapore).²⁰ With new variants on the horizon, there are issues with significantly reduced vaccine induced immunity. I discuss the flawed nature of the evidence justifying Covid-19 vaccine use in more detail in “**BRI-2**” page 38.

39. Moreover, given that the natural immune response amongst children and young people remains robust to the Delta variant,²¹ the risk of side effects that the Pfizer vaccine poses to children and the young (discussed below) suggests it is not in the health interests of children and young people to be vaccinated, as overwhelmingly they are not at any risk of disease from this virus.²² A recent study in the United States showed that the risk of myocarditis after vaccination in teenagers was 3.7 to 6.1 times higher than the risk of hospitalisation due to Covid-19, even under conditions of moderate and high Covid-19 incidence.²³
40. This means that mandating vaccination in education settings has little scientific justification in relation to the protection of children and young people, or in relation to reducing the risk they present of spreading the disease.

²⁰<https://www.timesofisrael.com/health-ministry-chief-says-coronavirus-spread-reaching-record-heights/>

<https://www.straitstimes.com/singapore/more-covid-19-patients-in-singapore-reported-to-have-died-in-october-than-18-months-prior>

²¹<https://www.medrxiv.org/content/10.1101/2021.10.06.21264467v1>

²²<https://www.gov.uk/government/news/jcvi-issues-updated-advice-on-covid-19-vaccination-of-children-aged-12-to-15>

²³<https://www.medrxiv.org/content/10.1101/2021.08.30.21262866v1.full.pdf>

Side-Effects of the Pfizer Vaccine

41. The spike protein itself, which is an integral part of the vaccine can lead to vascular side effects and harm in and of itself, by harming the lining of blood vessels.²⁴ This has been demonstrated in laboratory studies.
42. New Zealand's medicines regulator, MedSafe, has listed the side effects of the Pfizer vaccine, as shown in the MedSafe publication annexed and marked "**BRI-3**". There is a reporting system of adverse events and side effects in New Zealand, known as CARM.²⁵ The New Zealand data shows similar side effects and adverse events identified in other countries.²⁶ I go into more detail about the side effects of the vaccines in pages 35 to 47, pages 96 to 102 [neurological risks] of "**BRI-2**". These side effects contraindicate the vaccine for some people: this is a judgement that a health professional ought to make in the context of a consultation with a patient over informed consent, with the history of the patient in front of them. For this reason, lining up people for mass vaccination in mobile clinics is not a safe method of administration of the Pfizer vaccine.
43. Guidance for health practitioners and vaccinators has been produced by the Ministry of Health. I annex and mark "**BRI-4**" a copy of this Guidance which I have been provided with. It is very important for the scientifically sound long-term assessment of the safety of the Pfizer vaccine that this Guidance is scrupulously followed.
44. The short-term clinical trials of the Pfizer vaccine in adolescents and children aged over 5 were insufficient to ensure long term side effects were seen and evaluated. This uncertainty contributed to the Joint Council on Vaccination and Immunisation in England initially recommending against vaccinating children. Given that children and

²⁴<https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8091897/>

²⁵<https://www.medsafe.govt.nz/Profs/PUarticles/ADRreport.htm>

²⁶<https://www.medsafe.govt.nz/Profs/PUarticles/ADRreport.htm>

<https://trialsitenews.com/wp-content/uploads/2021/06/Yellow-Card-Letter.pdf>

young people already have robust natural immune responses to this virus, have almost zero mortality, and are generally not particularly contagious there is little merit in vaccinating them and risking unknown long term side effects, let alone those short-term ones already observed. Elevated rates of myocarditis in boys following the second dose is a particular concern, in view of the potential for long term disablement and mortality. I note South Korea has moved to drop the second dose for children due to this fully emerged complication. Any form of compulsion to vaccinate this group (let alone adults) is unethical and has no place in a modern public health system.

45. I observe that the Ministry of Health, Labour and Welfare in Japan expressly disavows mandatory vaccination, emphasizes informed consent, and dissuades discrimination based on vaccination status.²⁷ This Japanese ministry advises as follows, which in my opinion is a sound public health approach to vaccination:

“Although we encourage all citizens to receive the COVID-19 vaccination, it is not compulsory or mandatory. Vaccination will be given only with the consent of the person to be vaccinated after the information provided. Please get vaccinated of your own decision, understanding both the effectiveness in preventing infectious diseases and the risk of side effects. No vaccination will be given without consent. Please do not force anyone in your workplace or those who around you to be vaccinated, and do not discriminate against those who have not been vaccinated.”

46. Pfizer note the following on page 37 of their fact sheet (annexed and marked “BRI-5”): “Serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.1% of placebo recipients.” Much larger numbers of adolescents and children would have to be studied to provide conclusive evidence of long-term safety: the limited data suggests that the risk of serious adverse events

²⁷ <https://www.mhlw.go.jp/stf/covid-19/vaccine.html>.

may have been 0.3% (four-fold) higher in the vaccinated group over the short term. The small number in the study makes drawing any conclusions from it unsafe; in that event, caution should be exercised, and the vaccine ought not to be given to this group given the low risk they face from infection with this virus.

47. Adverse events of special interest are apparently being monitored, although the thoroughness is questionable, and it is dependent upon the reliability of health practitioners and the vaccinated reporting them accurately, or at all. For example, the European Medicines Agency has compiled a list of important medical events (IMEs) which are always to be classified as serious (the IME list).²⁸ The IMEs that are most frequently reported following Covid-19 vaccination include (in descending order):
- a. Fainting.
 - b. Blood clot in the lungs.
 - c. Anaphylactic reaction.
 - d. Deep vein thrombosis.
 - e. Pneumonia
 - f. Low blood platelet counts (thrombocytopenia).
 - g. Blood clots or bleeding in the brain
 - h. Hallucinations.
 - i. Cerebral stroke.
 - j. Loss of consciousness.
 - k. Myocarditis and pericarditis.

²⁸<https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/safety-covid-19-vaccines>

48. Any number of these can give rise to serious health complications or death. Nor is it predictable who will suffer from them, although there is evidence that young men are suffering from myocarditis or pericarditis in significantly increased numbers.²⁹ One study has reported that the incidence of myocarditis in vaccinated Israeli teenage men aged 16 to 29 was 13.6-fold higher compared to historical background rates.³⁰ Trials in children have been too small to detect rarer adverse effects.³¹
49. The number of reporting events in several jurisdictions is substantially higher than other vaccines.³² This substantial increase suggests that serious consideration ought to be given to a full review of the frequency of such reports and what they imply for the safety of the Pfizer and similar vaccines, particularly given the emergency or provisional approvals that have been given by regulatory agencies worldwide.
50. Pfizer recently published results from six months of follow-up in their ongoing phase 2/3 clinical trial.³³ The results shown in the supplementary material appended to their paper provided a risk-benefit analysis that suggested the vaccine should never have received regulatory authorization in Canada. Numerous other concerns were identified, including substantial conflicts of interest among the study authors.
51. I, along with a team of colleagues, conducted detailed analysis of Pfizer's report and I produced the background and base information

²⁹<https://www.medrxiv.org/content/10.1101/2021.08.30.21262866v1>

³⁰<https://www.nejm.org/doi/full/10.1056/NEJMoa2109730>

³¹<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-biontech-announce-positive-topline-results-pivotal#:~:text=The%20study%20is%20evaluating%20the,6%20months%20to%202%20years.>

³²<http://www.mailaz.com/COVID-19/PDF%20Documents/2021-05-IPAK%20-%20Report%20on%20VAERS%20of%20COVID-19.pdf>

³³ Thomas SJ, *et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. *N Engl J Med.* 2021 Nov 4;385(19):1761-1773. doi: 10.1056/NEJMoa2110345. Epub 2021 Sep 15. PMID: 34525277; PMCID: PMC8461570.

which was thoroughly reviewed and reported upon in a recent analytical video.³⁴ This presentation accurately reflects my analysis and concerns.

The Limitations of Vaccination as a Public Health Strategy in this Declared Pandemic

52. While New Zealand Government messaging says that the Pfizer vaccine is “safe and effective”, this is simplistic and misleading. The data shows that the Pfizer vaccine is neither sterilizing nor durable; it’s efficacy in reducing rates of infection is questionable and not statistically or scientifically supported by reliable data. The efficacy of the Pfizer vaccine in reducing the onset of disease or death fades after a number of months following the second dose, meaning that boosters are often rolled out.³⁵ The administration of boosters has not yet been established to provide durable immunity, which is partly because there has been no long-term testing and evaluation of this vaccine. It is uncertain how many boosters might be required, how effective they might be, what harm might eventuate (especially from a reactive “mix and match” approach being posited by some countries, including Canada) or whether a wholly new vaccine might be needed to deal with future variants of this virus.
53. My evidence shows that using vaccination can only be one part of a public health response to this epidemic, which is primarily reliant on a robust and thorough immune response by activation of all components of the human immune system: something the Pfizer vaccine does not do. The new mRNA vaccines do not activate the full immune response: activation of that response depends upon individuals being infected and mounting a full immune response to natural infection, including activation of a diverse array of T-cells, B-cells, and natural killer cells which I have described above. Moreover, it is unclear the degree to

³⁴ <https://www.canadiancovidcarealliance.org/media-resources/the-pfizer-inoculations-for-covid-19-more-harm-than-good-2/>

³⁵<https://www.medrxiv.org/content/10.1101/2021.10.13.21264966v1.full.pdf>

which the vaccines may suppress the development of that full immune response following infection. If a full immune response was activated there would be no need for boosters unless a person had compromised immunological function. This aspect of these vaccines requires urgent study.

Disproportionate Number of Omicron Cases Amongst the Vaccinated

54. Transmission of the Delta variant is not substantially affected by vaccination, evidenced by the ongoing roll-out of booster or multiple booster vaccines in many countries.³⁶
55. However, there is now a greater concern with Omicron amongst the vaccinated. There is compelling evidence that there are a disproportionate number of cases of infection with the Omicron variant among 'vaccinated' individuals compared to those being defined as 'unvaccinated' as is evident in the data published in Canada. This is evident with data published by Ontario Public Health.³⁷ Specifically, Figure 1 shows that, as of December 24, 2021, Covid-19 cases are predominantly occurring among the 'fully vaccinated'.

³⁶<https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v4.full.pdf>

³⁷ <https://covid-19.ontario.ca/data>

Figure 1 – COVID-19 cases by vaccination status

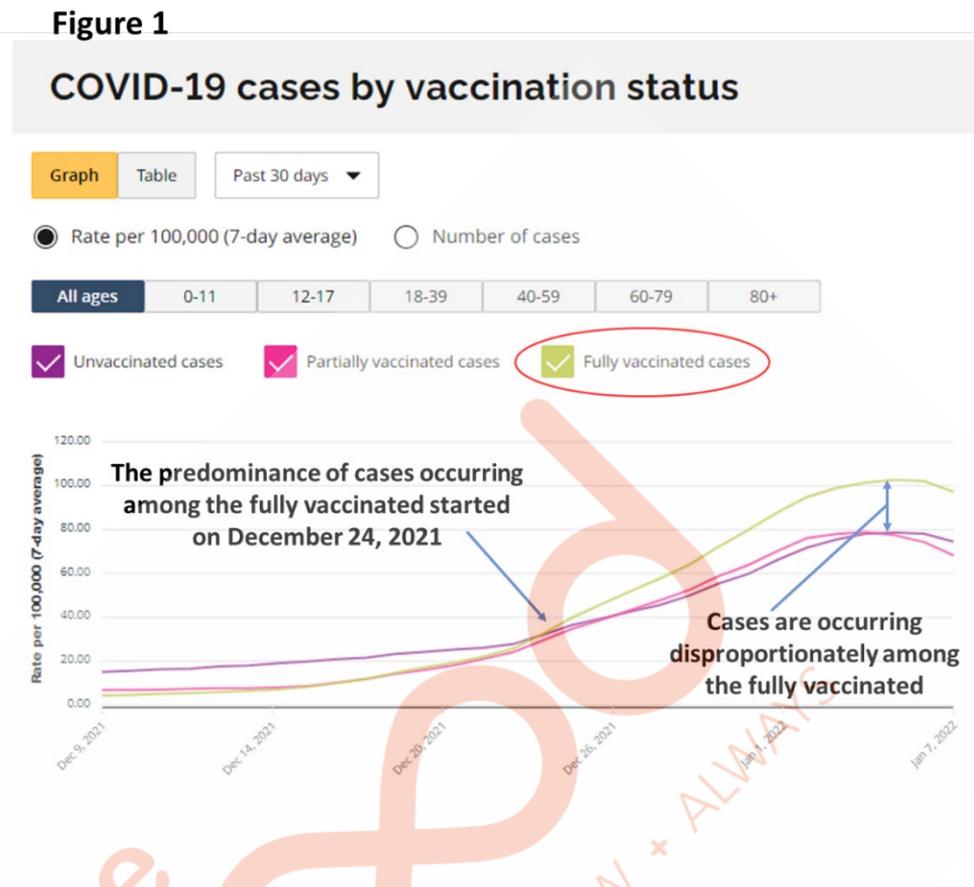


Figure 2 shows the same data as figure 1 but in the context of total case numbers as opposed to a proportion of each sub-population.

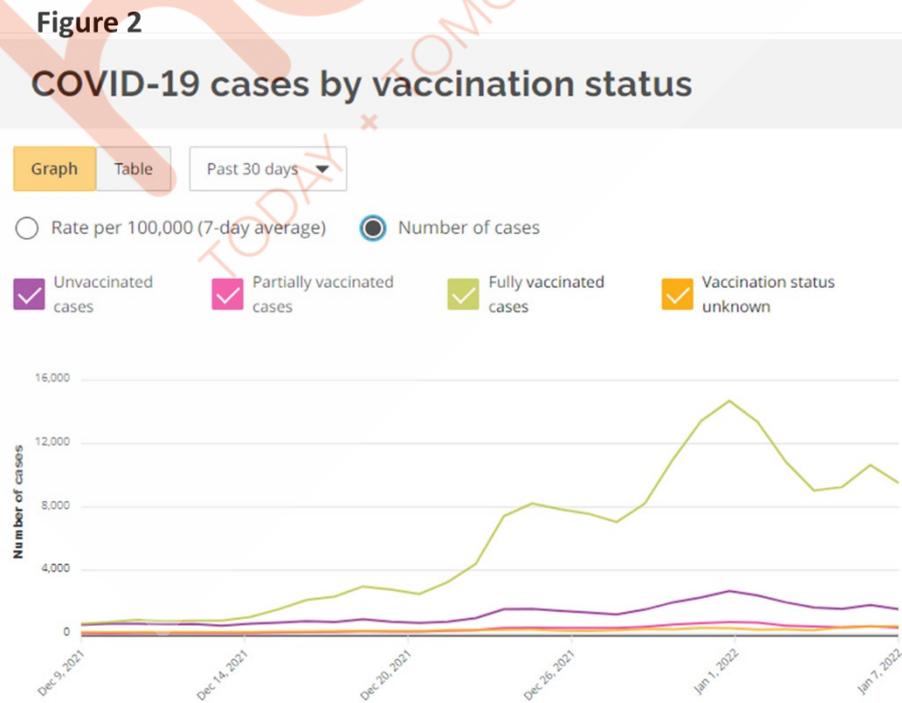
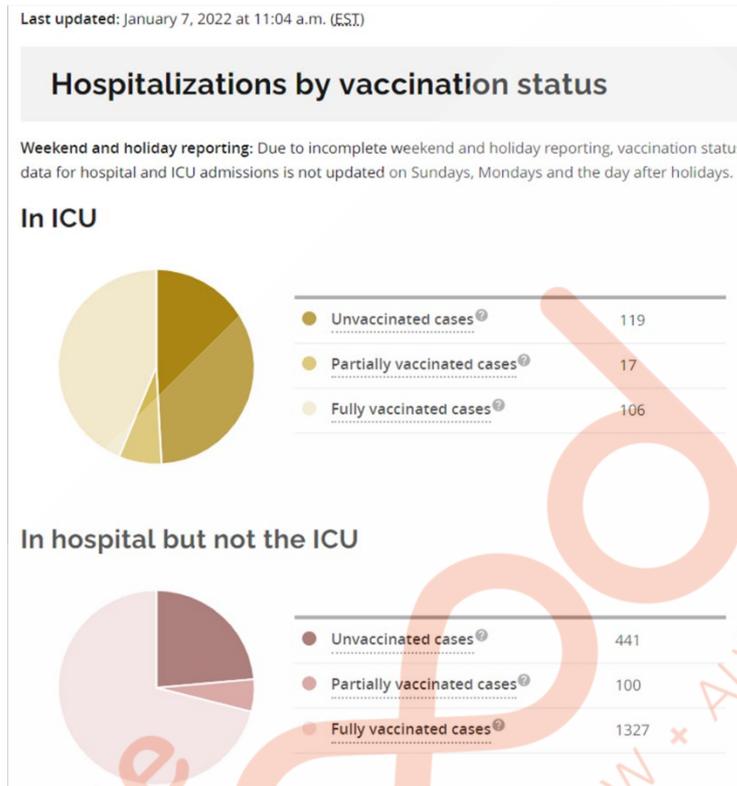


Figure 3 shows that most of the people in hospitals, including ICUs, due to Covid-19 are individuals that were ‘vaccinated’.

Figure 3



**51% of Covid-19 cas
ICU are individuals w
fully or partially vac**

**76% of hospitalizatio
Covid-19 are individu
were fully or partially v**

56. Further, national public health data shown on another dashboard demonstrate an uncoupling of cases of Covid-19 and associated deaths.³⁸ Specifically, Figure 4 shows the daily cases of Covid-19 throughout the declared pandemic in Ontario (uppermost graph). The multiple sequential waves of cases can be clearly visualized. The middle graph shows the number of daily deaths attributed to Covid-19 throughout the declared pandemic in Ontario. With each subsequent wave of cases the absolute numbers of daily deaths have steadily decreased despite more recent waves swamping earlier ones in terms of case counts. In short, the worst outcome of Covid-19, which is death, has progressively become uncoupled from the waves of cases. Although the current wave that is dominated by the Omicron variant is record-setting in terms of cases, the numbers of deaths remain

³⁸ <https://art-bd.shinyapps.io/covid19canada/> (last accessed on December 29, 2021)

relatively close to the baseline. At present, Covid-19 is not the deadly pathogen that is being promoted in public messaging and the focus on publicizing case numbers without defining their severity (or lack thereof) leads to an overestimation of danger. The lower graph shows the daily administration of Covid-19 vaccine doses scaled to the same timeline as the upper two graphs. Note that the third-to-last wave of cases (upper graph) was well on its way to resolving prior to most Ontarians being vaccinated. Also, the second-to-last and current, record-shattering wave of cases occurred despite most Ontarians being vaccinated. This is a clear sign that the current Covid-19 vaccines have failed to accomplish the goal of preventing the spread of SARS-CoV-2 and are unable to stop new waves of cases from occurring.

, the hood
TODAY * TOMORROW * ALWAYS

Figure 4 shows that most of the people in hospitals, including ICUs, due to Covid-19 are individuals that were ‘vaccinated’.

Figure 4



There has been an uncoupling of cases and deaths. Covid-19 is dangerous for most people

Vaccination does not correlate with protection.

The third-to-last wave of cases (upper graph) was well on its way to resolving prior to most Ontarians being vaccinated. Also, the second-to-last and current, record-shattering wave of cases occurred despite most Ontarians being vaccinated.

57. Figure 5 shows the proportion of adult admissions into intensive care units (ICUs) in Ontario that are attributable to Covid-19.³⁹ Note that ICUs are not at capacity, nor have they been for the duration of the declared pandemic. And for beds that are occupied, only a minority are represented by patients that tested positive for Covid-19. The current record-setting wave of cases of Covid-19 is not overwhelming

³⁹ <https://covid-19.ontario.ca/data/hospitalizations#hospitalizationsByICUBed> (last accessed on January 8, 2022)

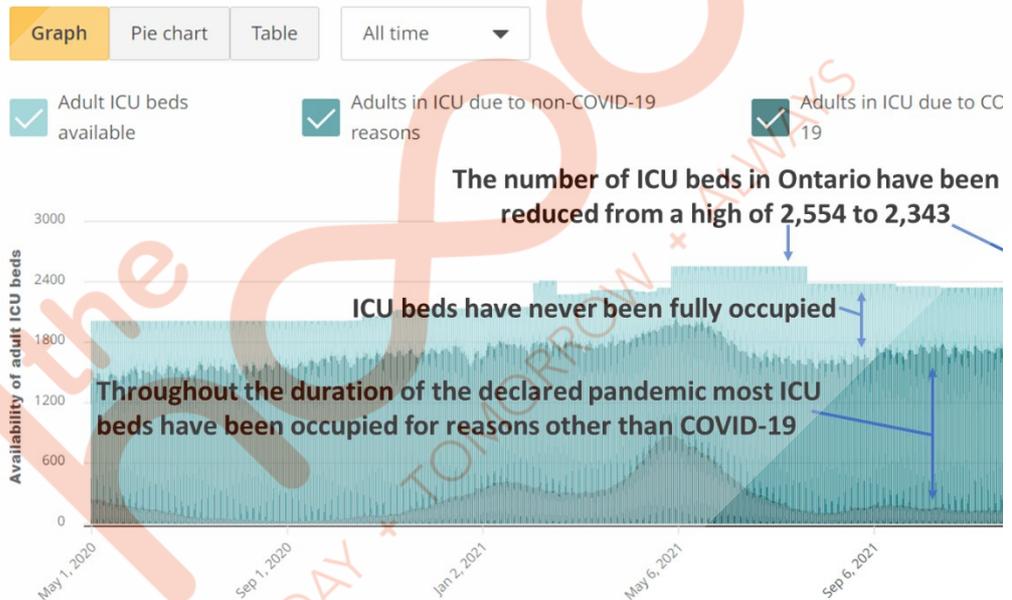
Ontario’s ICU capacities. Further evidence of this is the fact that the total number of beds available in Ontario have been reduced from the peak number in the summer of 2021.

Figure 5 shows the proportion of adult admissions into intensive care units (ICUs) in Ontario that are attributable to Covid-19

Figure 5

Availability of adult ICU beds

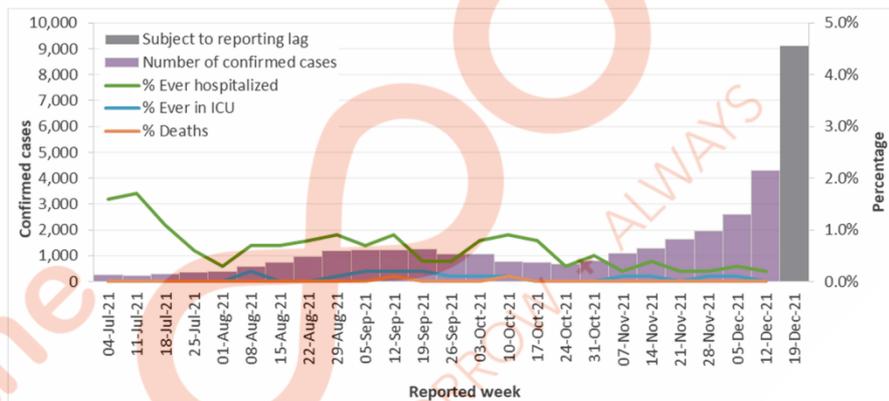
The data points show the daily number of adult ICU beds occupied (both COVID-related and non-COVID-related) and the number of available adult ICU beds.



Finally, Figure 6 alleviates concerns about the severity of Covid-19 in children.⁴⁰ Despite undefined ‘cases’ of Covid-19 spiking among children, hospitalizations have steadily declined and are near zero percent. Also, admission of children with Covid-19 into ICUs and deaths associated with this disease have steadily remained very close to or at zero percent. Covid-19 is not a serious issue for most children.

Figure 6 alleviates concerns about the severity of COVID-19 in children

Figure 6 Severity of illness indicators among confirmed cases of COVID-19 in children by public health unit reported week: Ontario, July 4, 2021 to December 25, 2021



58. Overall, the data shown in these six figures demonstrate that Covid-19 is not a so-called ‘pandemic of the unvaccinated’. Nor can it currently be considered particularly deadly. Instead, current public health data show that Covid-19 is disproportionately being diagnosed in the fully vaccinated population. Indeed, outbreaks of Covid-19 have become commonplace among workplaces in which all or almost all individuals are vaccinated against Covid-19. Clearly, the Covid-19 vaccines being used in Canada have failed to control the disease and are outdated in the context of the currently dominant circulating variants of SARS-CoV-2. However, if the current variants were simply evading vaccine-

⁴⁰ Public Health Ontario, Enhanced Epidemiological Summary COVID-19 in Children, Education and Child Care Settings: Focus on December 12, 2021 to December 25, 2021

induced immunity, one would expect to see evidence of no protection. In fact, as shown in Figure 1, Covid-19 is occurring disproportionately among the vaccinated. And this is despite a bias in testing the unvaccinated (*e.g.*, many workplaces only require regular testing for unvaccinated individuals). There could be a couple of reasons why infections are occurring at a higher rate in the vaccinated. It is possible that the behaviours of some vaccinated people have become riskier in the context of public health due to faith in erroneous public messaging that declared the vaccines to be highly effective at preventing breakthrough infections. A much worse alternative would be the possibility of vaccine-enhanced disease.⁴¹ It has been shown that vaccination against Covid-19 can alter the quality of immune responses against SARS-CoV-2.⁴² If this were to result in an inappropriate type of immune response, it could promote infection. Unfortunately, in the absence of long-term safety data for these vaccines this possibility can neither be confirmed nor refuted.

Conclusion

59. In summary:

- a. There is no sound scientific basis to require mandatory vaccination for the healthy, children or the young, or for those adults around them to be vaccinated.
- b. Nor is it a rational public health purpose for the prevention of transmission of the virus in the community since the vaccines at best may partly reduce the rate of transmission over a short-lived time window:⁴² The data on this does not support such a policy.
- c. The Delta variant of SARS-CoV-2 infects the upper respiratory tract of vaccinated people with similar viral loads as unvaccinated

⁴¹ Ricke DO. Front Immunol. 2021 Feb 24;12:640093. doi: 10.3389/fimmu.2021.640093. PMID: 33717193; PMCID: PMC7943455.

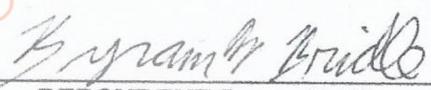
⁴²<https://www.medrxiv.org/content/10.1101/2021.08.03.21261496v1>

people,⁴³ meaning that differentiation of rates of transmission between these groups is not scientifically established.

- d. Transmission of the Delta variant is not substantially affected by vaccination, evidenced by the ongoing roll-out of booster or multiple booster vaccines in many countries, including Canada, which is now administering fourth doses to some individuals in the span of less than one year. Worse, is the compelling evidence that there are a disproportionate number of cases of infection with the Omicron variant among 'vaccinated' individuals compared to those being defined as 'unvaccinated' as is evident in the data published in Canada. The risk of side effects is real, particularly for young people, and the longer terms health risks are not known since there have been no long-term trials of the Pfizer and other mRNA coronavirus vaccines.

Declared Remotely by the Depondant,
 stated as being located in GUELPH,
 Ontario, Canada before me at the city of
CHESLEY, in the Province of Ontario
 on this day of January 25, 2022, in accord-
 ance with O.Reg 431/20, Administering
 Declaration Remotely

 P05826
 Commissioner for Taking Affidavits
 (or as may be)


 DEPONENT **Byram Bridle**

⁴³<https://www.medrxiv.org/content/10.1101/2021.09.28.21264262v1>

EXHIBIT NOTE
This is the attachment marked "B21-1" referred to in the
Affidavit/Declaration of BYRAM BRIDLE
Sworn/Affirmed/Declared at GUELPH, ONT
this 25 day of JANUARY 2022 before me:
Signature [Signature] P05826



Protected when completed

Date Submitted: 2021-11-11 15:27:47
Confirmation Number: 1389773
Template: Full CV

Dr. Byram W. Bridle

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

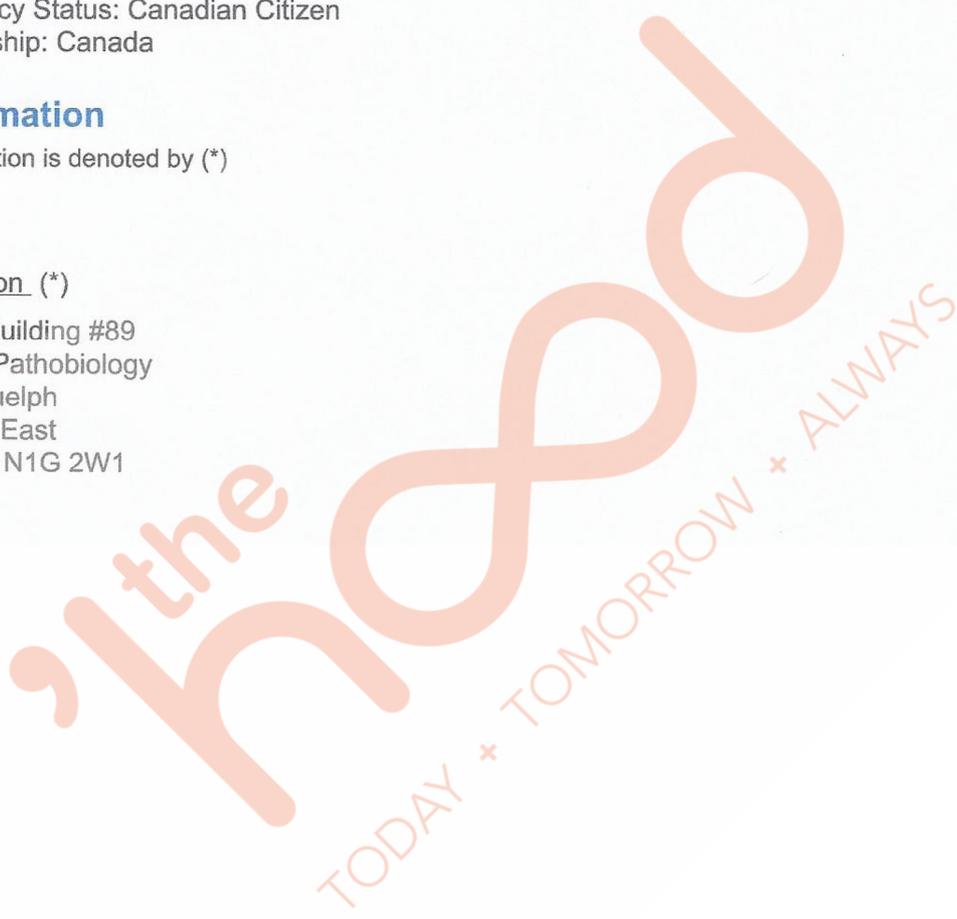
Contact Information

The primary information is denoted by (*)

Address

Primary Affiliation (*)

Room #4834, Building #89
Department of Pathobiology
University of Guelph
50 Stone Road East
Guelph Ontario N1G 2W1
Canada



Dr. Byram Bridle

Language Skills

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

Degrees

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

Credentials

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

2012/1 - 2017/12 Assistant Professor, University of Guelph
Named to the Regular Graduate Faculty in the Department of Pathobiology by the Board of Graduate Studies, University of Guelph.
Research Disciplines: Immunology
Areas of Research: Vaccine and Cancer, Immunotherapy, Vaccination, Virus, Cerebral Tumors, Leukemia, Lymphoma, Auto-Immune Diseases
Fields of Application: Biomedical Aspects of Human Health

Recognitions

- 2021/5 Recognized as an outstanding reviewer for the Canadian Institutes of Health Research
Canadian Institutes of Health Research
Distinction
CIHR's Review Quality Assurance (RQA) Process recognizes outstanding contributions to peer review. Through feedback and observations from Committee Chairs, Scientific Officers and CIHR staff, the RQA process captures contributions that exemplify the very best of peer reviewers. It is my pleasure to inform you that you are among a select group of reviewers who have been identified through this process as an Outstanding reviewer in recognition of your exemplary contribution to peer review for the Fall 2020 Project Grant competition. Among the 1107 reviewers that participated in the competition, only 12.6% obtained this recognition. On behalf of CIHR and the College of Reviewers, thank you for your selfless generosity volunteering your time and expertise and for your commitment to excellence in peer review. Your institution will be informed of your achievement as part of the College of Reviewers' Institution Activity Report planned to be sent to your institution's Vice-President.
- 2020/11 Invited to be a member of the Canadian Institutes of Health Research College of Reviewers (Canadian dollar)
Canadian Institutes of Health Research
Honor
"On behalf of the Canadian Institutes of Health Research (CIHR), we are very pleased to invite you to become a member of the College of Reviewers (College). This invitation is made in recognition of your accomplished career, demonstrated track record of excellence, and dedication to peer review."
- 2020/11 Identified as an outstanding reviewer for the Canadian Institutes of Health Research
Canadian Institutes of Health Research
Distinction
CIHR's Review Quality Assurance (RQA) Process recognizes outstanding contributions to peer review. Through feedback and observations from Committee Chairs, Scientific Officers and CIHR staff, the RQA process captures contributions that exemplify the very best of peer reviewers, such as providing reviews that exceeded expectations, completing additional tasks on short notice, and participating constructively in discussions about applications that were not assigned to them. It is my pleasure to inform you that you are among a select group of reviewers who have been identified through this process as an outstanding reviewer in recognition of your exemplary contribution to peer review during the fall 2019 Project Grant competition. On behalf of CIHR, thank you for your selfless generosity volunteering your time and expertise and for your commitment to excellence in peer review. Feel free to inform the Vice-President of Research or equivalent at your institution on this achievement.

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

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

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

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

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

User Profile

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

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

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

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

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

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

Disciplines Trained In: Immunology, Virology

Research Disciplines: Immunology, Virology

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

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

Employment

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

2012/1 - 2017/12

Assistant Professor

Pathobiology, Ontario Veterinary College, University of Guelph

Full-time, Assistant Professor

Tenure Status: Tenure Track

A tenure-track early career faculty position, specializing in viral immunology. Responsible for training highly qualified personnel, managing a research program, teaching undergraduate, Doctor of Veterinary Medicine and graduate students, and providing community service.

Research Disciplines: Immunology, Virology

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

Fields of Application: Biomedical Aspects of Human Health

2005/9 - 2011/12

Post-doctoral fellow

Pathology and Molecular Medicine, Medicine, McMaster University

Full-time

Tenure Status: Non Tenure Track

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

Research Disciplines: Immunology, Virology

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

Fields of Application: Biomedical Aspects of Human Health

2000/1 - 2005/10

Research Assistant

Pathobiology, Ontario Veterinary College, University of Guelph

Full-time

Tenure Status: Non Tenure Track

PhD research project. Advisor: Dr. Bonnie Mallard Collaboration between the University of Guelph and University of Western Ontario. Developed strategies to suppress and modulate rat immune responses against porcine cells in support of xenotransplantation research.

Research Disciplines: Immunology

Areas of Research: Transplantation and Graft Rejection

Fields of Application: Biomedical Aspects of Human Health

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

1993/5 - 1993/8 Undergraduate Research Assistant
Food Science, Ontario Veterinary College, University of Guelph
Full-time
Tenure Status: Non Tenure Track
Studying the viscoelastic properties of acid milk gels using a nametre. Supervisor: Dr. Arthur Hill
Research Disciplines: Biology and Related Sciences
Areas of Research: Nutraceuticals and Functional Foods
Fields of Application: Industrial Manufacturing and Production

Affiliations

The primary affiliation is denoted by (*)

(*) 2018/1 Associate Professor, Pathobiology, University of Guelph
2012/1 - 2017/12 Assistant Professor, Pathobiology, University of Guelph
A tenure-track early career faculty specializing in viral immunology. Responsible for educating students, managing a research program that results in publishing independent academic work in scholarly peer-reviewed journals and providing community service.

Leaves of Absence and Impact on Research

2021/1 - 2021/12 Sabbatical, University of Guelph
I was granted a research leave. This allowed me to focus on research-related activities, including service to the research community during the declared COVID-19 pandemic. To accomplish this, I was relieved of all teaching and local service activities for a period of one year.

Research Funding History

Awarded [n=41]

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

Funding Sources:

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

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

Principal Applicant : James J. Petrik

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

Funding Sources:

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

Principal Applicant : Sierra Vanderkamp

- 2021/9 - 2023/8
Principal Applicant Heat- and Cold-Adaptation of Oncolytic Rhabdoviruses to Improve Their Clinical Utility, Grant, Operating
- 2020/7 - 2023/6
Co-applicant Characterization of Innate Lymphoid Cells in Canine Blood, Grant
Funding Sources:
OVC Pet Trust
Operating Grant
Total Funding - 16,100
Portion of Funding Received - 0
Funding Competitive?: Yes
Co-applicant : Dr. Samuel Hocker;
Principal Investigator : Dr. Khalil Karimi
- 2020/7 - 2023/6
Co-applicant The use of SPECTRA OPTIA, Apheresis System from TERUMO, in Veterinary Medicine, Grant
Funding Sources:
OVC Pet Trust
Equipment Grant
Total Funding - 40,000
Portion of Funding Received - 0
Funding Competitive?: Yes
Principal Investigator : Dr. Alice Defarges
- 2020/9 - 2022/8
Principal Investigator OVC MSc Scholarship, Scholarship
Funding Sources:
2020/9 - 2022/8 Ontario Veterinary College (OVC)
MSc Graduate Scholarship
Total Funding - 30,000 (Canadian dollar)
Principal Applicant : Lily Chan
- 2020/9 - 2022/8
Principal Applicant Advancing a Promising Infected Cancer Cell Vaccine Platform into the Translational Research Pipeline, Grant
Funding Sources:
Cancer Research Society (The)
Operating Grant
Total Funding - 120,000
Portion of Funding Received - 120,000
Funding Competitive?: Yes
Co-applicant : Dr. Sarah K. Wootton
- 2017/7 - 2022/6
Co-applicant Vascular Normalization as a Mechanism to Increase Oncolytic Virus Spread and Efficacy (a sub-project within a Program Project Grant that was awarded by the Terry Fox Research Institute to the Canadian Oncolytic Virus Consortium [\$7,396,160]), Grant
Funding Sources:
2017/7 - 2022/3 Terry Fox Research Institute (TFRI)
Program Project Grant
Total Funding - 314,460 (Canadian dollar)
Portion of Funding Received - 314,460
Funding Competitive?: Yes
- 2020/3 - 2022/3 Developing Prophylactic Virus-Vectored Vaccines for COVID-19, Grant

- Principal Applicant **Funding Sources:**
Ontario Ministry of Colleges and Universities
COVID-19 Rapid Research Fund
Total Funding - 231,888
Portion of Funding Received - 231,888
Funding Competitive?: Yes
- Co-investigator : Dr. Leonardo Susta; Dr. Sarah K. Wootton
- 2019/3 - 2022/2
Co-applicant AAV Gene Therapy for the Treatment of Surfactant Protein B Deficiency, Grant
Funding Sources:
2019/3 - 2024/2 Canadian Institutes of Health Research (CIHR)
Project Grant
Total Funding - 620,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes
- Co-applicant : Bernard Thébaud; Martin Kang;
Collaborator : Jeffrey Whitsett; Laura van Lieshout; Lawrence Nogee;
Principal Applicant : Sarah K. Wootton
- 2020/12 - 2021/12
Principal Investigator Translational Development of an Avian Orthoavulavirus-1-Vectored Vaccine for COVID-19, Grant
Funding Sources:
National Research Council Canada (NRC) (Ottawa, ON)
Pandemic Response Challenge Program
Total Funding - 444,000
Portion of Funding Received - 319,000
Funding Competitive?: Yes
- Co-investigator : Leonardo Susta; Sarah K. Wootton
- 2019/9 - 2021/8
Principal Investigator Nora Cebotarev Memorial Graduate Scholarship (student stipend funding), Scholarship
Funding Sources:
2019/9 - 2021/8 University of Guelph
Nora Cebotarev Memorial Graduate Scholarship
Total Funding - 25,000 (Canadian dollar)
- Principal Applicant : Jessica Minott
- 2020/9 - 2021/8
Principal Investigator Ontario Graduate Scholarship (student stipend funding), Scholarship
Funding Sources:
2020/9 - 2021/8 Ontario Ministry of Colleges and Universities
Total Funding - 15,000 (Canadian dollar)
- Principal Applicant : Jessica Minott
- 2021/5 - 2021/8
Principal Investigator Andrea Leger Dunbar Summer Studentship (student salary funding), Scholarship
Funding Sources:
2021/5 - 2021/8 Ontario Veterinary College (OVC)
Andrea Leger Dunbar Summer Studentship
Total Funding - 9,000 (Canadian dollar)
- Principal Applicant : Christina Napoleoni

- 2018/7 - 2021/6
Principal Investigator Developing Biotherapies for the Treatment of Canine Cancers, Grant
- Funding Sources:**
2018/1 - 2022/12 Private Donation
private donation
Total Funding - 1,500 (Canadian dollar)
Portion of Funding Received - 1,500
Funding Competitive?: No
- 2018/6 - 2021/5
Co-applicant PD-1 Expression on Blood Leukocytes in Dogs with Bladder Cancer, Grant
- Funding Sources:**
2018/4 - 2021/3 Pet Trust Fund (The)
Operating Grant
Total Funding - 27,584 (Canadian dollar)
Portion of Funding Received - 6,896
Funding Competitive?: Yes
- Co-applicant : Anthony Mutsaers;
Principal Applicant : Samuel Hocker
- 2018/1 - 2021/1
Co-investigator Oncolytic Viral Vaccine Therapy of Feline Mammary Carcinoma, Grant
- Funding Sources:**
2018/1 - 2021/1 Pet Trust Fund (The)
Operating Grant
Total Funding - 7,668 (Canadian dollar)
Portion of Funding Received - 1,534
Funding Competitive?: Yes
- Co-applicant : Michelle Oblak; Robert Foster;
Co-investigator : Geoffrey Wood;
Principal Applicant : J. Paul Woods
- 2020/3 - 2021/1
Co-investigator Developing Prophylactic Virus-Vectored Vaccines for COVID-19, Grant
- Funding Sources:**
University of Guelph, Ontario Veterinary College and Department of Pathobiology
Seed funding for COVID-19 research
Total Funding - 20,000
Portion of Funding Received - 20,000
Funding Competitive?: Yes
- Co-investigator : Dr. Sarah K. Wootton;
Principal Applicant : Dr. Leonardo Susta
- 2020/5 - 2020/8
Principal Investigator NSERC Undergraduate Student Research Assistantship (student salary funding), Scholarship
- Funding Sources:**
2020/5 - 2020/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Research Assistantship
Total Funding - 4,500 (Canadian dollar)
- Principal Applicant : Lily Chan

- 2018/9 - 2020/8
Principal Applicant
- Treatment of Osteosarcoma Lung Metastases with an Infected Cancer Cell Vaccine, Grant
- Funding Sources:**
- 2018/9 - 2021/8 Cancer Research Society (The)
Operating Grant
Total Funding - 60,000 (Canadian dollar)
Portion of Funding Received - 60,000
Funding Competitive?: Yes
- 2018/9 - 2021/8 Canadian Institutes of Health Research (CIHR)
CRS Operating Grant (jointly funded)
Total Funding - 62,086 (Canadian dollar)
Portion of Funding Received - 62,086
Funding Competitive?: Yes
- Co-applicant : Sarah K. Wootton
- 2018/9 - 2020/8
Principal Applicant
- Combining Oncolytic Virotherapy and Epigenetic Modifiers to Treat Acute Leukemias, Grant
- Funding Sources:**
- 2019/8 - 2021/7 Canadian Institutes of Health Research (CIHR)
CCS-RI Innovation Grant (jointly funded)
Total Funding - 100,000 (Canadian dollar)
Portion of Funding Received - 100,000
Funding Competitive?: Yes
- 2018/8 - 2021/7 Canadian Cancer Society Research Institute (CCSRI)
Innovation Grant
Total Funding - 105,215 (Canadian dollar)
Portion of Funding Received - 105,215
Funding Competitive?: Yes
- 2017/9 - 2020/8
Principal Investigator
- Enhancing Immunogenic Cancer Cell Death Through the Novel Combination of Oncolytic Viruses and Photodynamic Therapy (student stipend support), Scholarship
- Funding Sources:**
- 2017/9 - 2020/8 Canadian Institutes of Health Research (CIHR)
Vanier Scholarship
Total Funding - 150,000 (Canadian dollar)
Portion of Funding Received - 33,000
Funding Competitive?: Yes
- Principal Applicant : Ashley Ross;
Principal Investigator : Sarah Wootton
- 2020/5 - 2020/8
Principal Investigator
- Andrea Leger Dunbar Summer Studentship (student salary funding), Scholarship
- Funding Sources:**
- 2020/5 - 2020/8 University of Guelph
Andrea Leger Dunbar Summer Studentship
Total Funding - 9,000 (Canadian dollar)
- Principal Applicant : Kiersten Hanada
- 2019/9 - 2020/8
Principal Investigator
- Ellen Nilsen Memorial Graduate Scholarship (student stipend funding), Scholarship

Funding Sources:

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

Principal Applicant : Jessica Minott

2018/9 - 2020/8 Combining Oncolytic Viruses with Epigenetic Modifiers to Treat Acute Myeloid Leukemias
Principal Investigator (student stipend support), Scholarship

Funding Sources:

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

Principal Applicant : Elaine Klafuric

2020/5 - 2020/8 BioCanRx Summer Studentship (student salary funding), Scholarship
Principal Investigator

Funding Sources:

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

Principal Applicant : Lily Chan

2017/7 - 2020/6 Developing Biotherapies for the Treatment of Canine Cancers, Grant
Principal Investigator

Funding Sources:

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

2017/7 - 2020/6 Synthesis of a Novel Oncolytic Newcastle Disease Virus to Support the Treatment of
Co-applicant Companion Animal Cancer Patients, Grant

Funding Sources:

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

Co-applicant : Sarah Wootton;

Principal Applicant : Leonardo Susta

2018/1 - 2019/12 The Role of Interleukin-17-Producing Cells in the Pathophysiology of Canine Immune
Co-investigator Mediated Hemolytic Anemia, Grant

Funding Sources:

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

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

Principal Applicant : Shauna Blois

2019/5 - 2019/8 Undergraduate Research Assistantship (student salary funding), Scholarship
Principal Investigator

Funding Sources:

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

Principal Applicant : Lily Chan

2017/9 - 2019/8 Vascular Normalization as a Mechanism to Increase Uptake and Efficacy of Oncolytic
Co-applicant Viruses and Vaccine-Induced Effector Cells for the Treatment of Advanced Stage Ovarian
Cancer, Grant

Funding Sources:

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

Co-applicant : Sarah Wootton;

Principal Applicant : James Petrik

2018/9 - 2019/4 The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic
Principal Investigator Virotherapy (student stipend support), Scholarship

Funding Sources:

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

Principal Applicant : Jacob van Vloten;

Principal Investigator : Sarah K. Wootton

2014/4 - 2019/3 Developing Novel Cancer Biotherapies: Infrastructure to Support Translational Research
Principal Applicant in Companion Animals, Grant

Funding Sources:

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

2013/4 - 2019/3 Type I Interferon Receptor Signalling as a Master Switch for the Negative Regulation of
Principal Applicant Cytokine Networks, Grant

Funding by Year:

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

2015/4 - 2019/3 Development of Cutting-Edge Biotherapies for the Treatment of Cancers, Grant
 Principal Applicant

Funding Sources:

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

2016/3 - 2019/2 Developing Biotherapies for the Treatment of Canine Cancers, Grant
 Principal Investigator

Funding Sources:

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

2016/1 - 2019/1 Construction and Validation of Viral-Vectored Vaccines to Induce Robust Tumour-Specific
 Principal Applicant T Cell Responses in Dogs with Oral Melanomas, Grant

Funding Sources:

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

2016/7 - 2018/12 Accelerated Clinical Development of Synthetic Antibody Immuno-Modulators Through
 Co-applicant Companion Animal Trials (the "total funding" represents the amount awarded to B. Bridle;
 the award for both applicants was \$708,893), Grant

Funding Sources:

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

Principal Applicant : Jason Moffat

2016/9 - 2018/12 The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic
 Principal Investigator Virotherapy (student stipend support), Scholarship

Funding Sources:

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

Principal Applicant : Jacob van Vloten;

Principal Investigator : Sarah K. Wootton

2015/9 - 2018/8
Principal Investigator Art Rouse Cancer Biology Graduate Stipend (student stipend support), Scholarship

Funding Sources:

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

Principal Applicant : Robert Mould (PhD student)

2016/9 - 2018/8
Principal Investigator Sex Disparity in Innate Immune Responses to Viral Infection: the Role of Type I Interferon (student stipend support), Scholarship

Funding Sources:

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

Principal Applicant : Katrina Allison (MSc student)

Completed [n=39]

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

Funding Sources:

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

Co-investigator : Jessica Minott

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

Funding Sources:

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

Principal Applicant : Elaine Klafuric

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

Funding Sources:

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

Principal Applicant : Samantha Holtz

2015/6 - 2018/4
Co-applicant

Development of a Vaccine to Protect Against Toxoplasma gondii Infection in Sheep, Grant

Funding Sources:

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

Co-applicant : John Barta; Paula Menzies;

Principal Applicant : Sarah K. Wootton

2017/5 - 2017/8
Principal Investigator

Assessing the Impact of an Acidic Tumour Microenvironment on the Efficacy of Oncolytic Viruses (student salary support), Scholarship

Funding Sources:

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

Principal Applicant : Julia Saturno

2016/9 - 2017/8
Principal Investigator

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

Funding Sources:

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

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

Principal Investigator : Sarah K. Wootton

2017/5 - 2017/8
Principal Investigator

Enhancing Dendritic Cell-Based Anti-Cancer Vaccines Through Adaptation to a Hypoxic Microenvironment (student salary support), Scholarship

Funding Sources:

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

Principal Applicant : Mankerat Singh;

Principal Investigator : Khalil Karimi

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

Funding Sources:

2014/9 - 2017/8 Ontario Veterinary College
PhD Scholarship
Total Funding - 42,000 (Canadian dollar)
Portion of Funding Received - 42,000
Funding Competitive?: Yes

Principal Applicant : Megan Whaley (PhD student)

2016/9 - 2017/8
Principal Investigator Augmentation of a Canine Melanoma Vaccine with Immunomodulatory Antibodies (student stipend support), Scholarship

Funding Sources:

2016/9 - 2017/8 Canadian Institutes of Health Research (CIHR)
Canada Graduate Scholarship - Master's
Total Funding - 17,500 (Canadian dollar)
Portion of Funding Received - 17,500
Funding Competitive?: Yes

Principal Applicant : Wing Ka "Amanda" AuYeung (MSc student)

2016/9 - 2017/8
Co-applicant Support for Development of Novel Cancer Biotherapies, Grant

Funding Sources:

2016/9 - 2016/12 Private donation
Private donation
Total Funding - 25,000 (Canadian dollar)
Portion of Funding Received - 8,333
Funding Competitive?: No

Co-applicant : James Petrik;

Principal Applicant : Sarah Wootton

2014/6 - 2017/6
Principal Applicant Assessment of Canine Melanoma Samples from the Ontario Veterinary College- Companion Animal Tumour Bank for Expression of Antigens that can be Targeted with an Oncolytic Cancer Vaccine, Grant

Funding Sources:

2014/6 - 2015/5 Pet Trust Fund (The)
Operating Grant
Total Funding - 11,593 (Canadian dollar)
Portion of Funding Received - 11,593
Funding Competitive?: Yes

2016/1 - 2016/12
Co-applicant Support for Development of Novel Cancer Biotherapies, Grant

Funding Sources:

2016/1 - 2016/12 Private donation
Private donation
Total Funding - 50,000 (Canadian dollar)
Portion of Funding Received - 16,667
Funding Competitive?: No

Co-applicant : James Petrik;

Principal Applicant : Sarah Wootton

2015/9 - 2016/8
Principal Investigator Augmentation of a Canine Melanoma Vaccine with Immunomodulatory Antibodies (student stipend support), Scholarship

Funding Sources:

2015/9 - 2016/8 Pet Trust Foundation
OVC Pet Trust Scholar Program
Total Funding - 35,000 (Canadian dollar)
Portion of Funding Received - 18,500
Funding Competitive?: Yes

Principal Applicant : Wing Ka "Amanda" Au Yeung (MSc student)

2016/5 - 2016/8
Principal Applicant Evaluating the Impact of Oxygen Level, Temperature and pH on the Oncolytic Potential of Viruses and Epigenetic Modifiers in Canine Osteosarcoma Cells (student salary support), Scholarship

Funding Sources:

2016/5 - 2016/8 Zoetis Canada
Summer Student Research Fund
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 8,000
Funding Competitive?: Yes

Co-applicant : Manali Desai (summer research assistant)

2016/5 - 2016/8
Principal Investigator Type I Interferon Signalling as a Master Switch for the Negative Regulation of a Broad Array of Cytokines (student salary support), Scholarship

Funding Sources:

2016/5 - 2016/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Student Research Award
Total Funding - 4,400 (Canadian dollar)
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Principal Applicant : Katrina Allison (summer research assistant)

2016/5 - 2016/8
Principal Applicant Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas (student salary support), Scholarship

Funding Sources:

2016/5 - 2016/8 Merial
Summer Research Assistantship
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 8,000
Funding Competitive?: Yes

Co-applicant : Julia Saturno (summer research assistant)

2015/9 - 2016/8
Principal Investigator The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy (student stipend support), Scholarship

Funding Sources:

2015/9 - 2016/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Graduate Scholarship
Total Funding - 21,000 (Canadian dollar)
Portion of Funding Received - 10,500
Funding Competitive?: Yes

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

Principal Investigator : Sarah K. Wootton

2014/9 - 2016/8
Principal Applicant

Evaluation of Adjunct Oncolytic Immunotherapy in a Canine Lymphoma Clinical Trial, Grant

Funding Sources:

2014/6 - 2016/5 Cancer Research Society (The)
Operating Grant
Total Funding - 120,000 (Canadian dollar)
Portion of Funding Received - 120,000
Funding Competitive?: Yes

Co-applicant : J. Paul Woods

2014/8 - 2016/6
Co-applicant

Oncolytic Viral Vaccine Therapy of Breast Carcinoma, Grant

Funding Sources:

2014/6 - 2016/5 Canadian Breast Cancer Foundation (CBCF)
Research Project Grant Program
Total Funding - 298,416 (Canadian dollar)
Portion of Funding Received - 59,472
Funding Competitive?: Yes

Co-applicant : J. Paul Woods;

Principal Applicant : Brian D. Lichy

2015/7 - 2016/6
Co-applicant

Accelerated Clinical Development of Synthetic Antibody Immuno-Modulators Through Companion Animal Trials, Grant

Funding Sources:

2015/7 - 2016/6 National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx)
Enabling Grant
Total Funding - 143,716 (Canadian dollar)
Portion of Funding Received - 32,100
Funding Competitive?: Yes

Principal Applicant : Jason Moffat

2014/9 - 2015/8
Principal Investigator

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

Funding Sources:

2014/9 - 2015/8 Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
Highly Qualified Personnel PhD Scholarship
Total Funding - 21,000 (Canadian dollar)
Portion of Funding Received - 10,500
Funding Competitive?: Yes

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

Principal Investigator : Sarah K. Wootton

2013/9 - 2015/8

Principal Investigator

The Role of Type I Interferon Receptor-Mediated Signaling in the Regulation of Cytokines Produced by Dendritic Cells (student stipend support), Scholarship

Funding Sources:

2013/9 - 2015/8 University of Guelph
Ontario Veterinary College MSc Fellowship
Total Funding - 30,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes

Funding by Year:

2013/9 - 2015/8 Total Funding - 30,000
Portion of Funding Received - 30,000
Time Commitment: 0

Principal Applicant : Alexandra Rasiuk (MSc student)

2015/5 - 2015/8

Principal Applicant

Transient Lymphopenia as a Mechanism to Allow an Oncolytic Virus to Replicate Inside a Tumour Despite Vaccination Against a Virus-Encoded Antigen (student salary support), Scholarship

Funding Sources:

2015/5 - 2015/8 Natural Sciences and Engineering Research Council of Canada (NSERC)
Undergraduate Student Research Assistantship
Total Funding - 4,400 (Canadian dollar)
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Co-applicant : Wing Ka "Amanda" Au Yeung (summer student)

2014/9 - 2015/8

Principal Investigator

Using Virus-Infected Dendritic Cells as Cancer Vaccines (student stipend support), Scholarship

Funding Sources:

2014/9 - 2016/8 University of Guelph
Graduate Research Assistant Tuition Supplement
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 8,000
Funding Competitive?: No

Principal Applicant : Robert Mould (MSc student)

2015/5 - 2015/8

Principal Applicant

Assessment of the Potential to Treat Canine Cancers with an Oncolytic Vaccine (student salary support), Scholarship

Funding Sources:

2015/5 - 2015/8 Zoetis Canada
Zoetis Summer Student Research Fund
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 8,000
Funding Competitive?: Yes

Co-applicant : Julia Kim (summer student)

2014/8 - 2015/7
Principal Applicant Replacement of a Core Facility's Heavily-Used, 22-Year-Old Analytical Flow Cytometer for Which Parts and Service are no Longer Guaranteed, Grant

Funding Sources:

2014/8 - 2015/7 Natural Sciences and Engineering Research Council of Canada (NSERC)
Research Tools and Infrastructure
Total Funding - 103,249 (Canadian dollar)
Portion of Funding Received - 34,417
Funding Competitive?: Yes

Co-applicant : Brandon Plattner; Dorothee Bienzle

2013/7 - 2015/6
Principal Applicant In Vitro Efficacy Testing of Oncolytic Viruses, Grant

Funding Sources:

2013/7 - 2015/6 Private donation
Private donation
Total Funding - 15,000 (Canadian dollar)
Portion of Funding Received - 15,000
Funding Competitive?: No

2012/6 - 2015/5
Principal Investigator Assessment of the Potential to Treat Canine Lymphoma with an Oncolytic Vaccine, Grant, Operating

Clinical Research Project?: No

Project Description: We have published a strategy to synergize immunotherapy and oncolytic virotherapy, leading to durable cures in mouse models of cancer. To translate our success into a future canine lymphoma clinical trial, we must conduct preliminary studies to demonstrate safety and efficacy. This proposal has four aims: 1. prove that oncolytic immunotherapy is safe in dogs, 2. show that robust tumour-specific immune responses can be induced, 3. confirm expression of the targeted tumour antigen on canine lymphomas, and 4. show that effector mechanisms mediated by the treatment can kill lymphoma cells. This will provide the scientific rationale for a future clinical dog lymphoma trial. It will also allow us to get a permit for field testing from the Canadian Food Inspection Agency (CFIA), which is required before clinical testing of oncolytic viruses in pets.

Research Uptake: The goal of this research is to translate the findings into a clinical veterinary trial in which dogs with lymphoma will be treated. This will serve two purposes. It will provide a direct, practical benefit to pet owners and will serve as an intermediate animal model in support of a broad collaborative effort to test oncolytic vaccines in human clinical trials. Findings from these studies will also be disseminated via submission for publication in peer-reviewed journals.

Research Uptake Stakeholders: Academic Personnel

Research Settings: Canada (Urban)

Funding Sources:

2012/6 - 2015/5 Pet Trust Fund (The)
Operating Grant
Total Funding - 45,016 (Canadian dollar)
Portion of Funding Received - 100 (Canadian dollar)
Funding Renewable?: No
Funding Competitive?: Yes

Funding by Year:

2012/9 - 2013/8 Total Funding - 45,016 (Canadian dollar)
Portion of Funding Received - 100 (Canadian dollar)
Time Commitment: 6

Research Disciplines: Immunology, Virology

Areas of Research: Vaccine and Cancer, Immunotherapy

Fields of Application: Biomedical Aspects of Human Health

Co-investigator : Dr. J. Paul Woods

2014/9 - 2015/4
Principal Applicant

Testing the Efficacy of Cancer Therapeutics in Ovarian and Mammary Carcinoma Cells
(student salary support), Scholarship

Funding Sources:

2014/9 - 2015/4 University of Guelph
Work-Study
Total Funding - 2,210 (Canadian dollar)
Portion of Funding Received - 2,210
Funding Competitive?: No

Co-applicant : Wing Ka "Amanda" Au Yeung (undergraduate student)

2012/9 - 2014/8
Principal Investigator

Characterizing a Novel Immuno-evasion Strategy for Brain Cancer and How to Circumvent
It (student stipend support), Scholarship

Funding Sources:

2012/9 - 2014/8 University of Guelph
Ontario Veterinary College MSc Scholarship
Total Funding - 30,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes

Funding by Year:

2012/9 - 2014/8 Total Funding - 30,000
Portion of Funding Received - 30,000
Time Commitment: 0

Principal Applicant : Zafir Syed (MSc student)

2014/5 - 2014/8
Principal Applicant

Evaluation of an Oncolytic Vaccine in Dogs (student salary support), Scholarship

Funding Sources:

2014/5 - 2014/8 Natural Sciences and Engineering Research Council of Canada
(NSERC)
Undergraduate Student Research Assistantship
Total Funding - 4,400 (Canadian dollar)
Portion of Funding Received - 4,400
Funding Competitive?: Yes

Co-applicant : Larissa Hattin (summer student)

2012/9 - 2014/8
Principal Applicant

Combining Histone Deacetylase Inhibition and Transient, Virus-Induced Lymphopenia to
Treat Leukemia (student stipend support), Scholarship

Funding Sources:

2012/9 - 2014/8 University of Guelph
Ontario Veterinary College MSc Scholarship
Total Funding - 30,000 (Canadian dollar)
Portion of Funding Received - 30,000
Funding Competitive?: Yes

Funding by Year:

2012/9 - 2014/8 Total Funding - 30,000
Portion of Funding Received - 30,000
Time Commitment: 0

Principal Applicant : Christian Ternamian (MSc student)

2013/6 - 2014/5
Co-applicant

Upgrade to State-of-the-Art Flow Cytometric Equipment, Grant

Funding Sources:

2013/6 - 2015/5 Natural Sciences and Engineering Research Council of Canada
(NSERC)
Research Tools and Instruments Grant
Total Funding - 148,230 (Canadian dollar)
Portion of Funding Received - 49,410
Funding Competitive?: Yes

Funding by Year:

2013/6 - 2015/5 Total Funding - 148,230
Portion of Funding Received - 49,410
Time Commitment: 7

Co-applicant : Dr. Dorothee Bienzle;

Principal Applicant : Dr. Brandon Plattner

2013/5 - 2014/4
Principal Applicant

Development of an Immune Response Monitoring Facility to Support Clinical Testing of
Novel Cancer Biotherapies in Companion Animals, Grant

Funding Sources:

2013/5 - 2014/4 The Smiling Blue Skies Cancer Fund
Donation
Total Funding - 14,554 (Canadian dollar)
Portion of Funding Received - 14,554
Funding Competitive?: No

Funding by Year:

2013/5 - 2014/4 Total Funding - 14,554
Portion of Funding Received - 14,554
Time Commitment: 3

2013/9 - 2014/4
Principal Applicant

Evaluating the Role of Akt Isoforms in the Sensitivity of Lung Cancer Cells to Oncolytic
Viruses (student salary support), Scholarship

Funding Sources:

2013/9 - 2014/4 University of Guelph
Work-Study
Total Funding - 2,210 (Canadian dollar)
Portion of Funding Received - 2,210
Funding Competitive?: No

- 2012/5 - 2013/8
Principal Applicant
- Co-applicant : Wing Ka "Amanda" Au Yeung (undergraduate student)
- Using an Innate Anti-Viral Immune Response in the Presence of a Histone Deacetylase Inhibitor to Treat Leukemias (student salary support), Scholarship
- Funding Sources:**
- 2012/5 - 2012/8 Canadian Society for Immunology
Summer Internship in Immunology
Total Funding - 2,400 (Canadian dollar)
Portion of Funding Received - 2,400
Funding Competitive?: Yes
- Funding by Year:**
- 2012/5 - 2012/8 Total Funding - 2,400
Portion of Funding Received - 2,400
Time Commitment: 0
- 2013/5 - 2013/8
Principal Applicant
- Co-applicant : Evan Lusty (summer student)
- Development of Flow Cytometry-Based Immunological Assays to Support Pre-Clinical and Clinical Companion Animal Cancer Trials (student salary support), Scholarship
- Funding Sources:**
- 2013/5 - 2013/8 University of Guelph
Undergraduate Research Assistant
Total Funding - 4,400 (Canadian dollar)
Portion of Funding Received - 4,400
Funding Competitive?: Yes
- Funding by Year:**
- 2013/5 - 2013/8 Total Funding - 6,600
Portion of Funding Received - 6,600
Time Commitment: 0
- 2012/9 - 2013/4
Principal Applicant
- Co-applicant : Wing Ka "Amanda" Au Yeung (summer student)
- Testing the Efficacy of Cancer Therapeutics in Prostate Cancer Cell Lines (student salary support), Scholarship
- Funding Sources:**
- 2012/9 - 2013/4 University of Guelph
Work-Study
Total Funding - 2,210 (Canadian dollar)
Portion of Funding Received - 2,210
Funding Competitive?: No
- 2012/5 - 2012/8
Principal Applicant
- Co-applicant : Jason Morgenstern (undergraduate student)
- Establishment of Leukemia/Lymphoma Cell Lines from Clinical Specimens and Evaluation of Their Susceptibility to Oncolytic Viruses (student salary support), Scholarship
- Funding Sources:**
- 2012/5 - 2012/8 University of Guelph
Undergraduate Research Assistantship
Total Funding - 6,000 (Canadian dollar)
Portion of Funding Received - 6,000
Funding Competitive?: Yes

Funding by Year:

2012/5 - 2012/8 Total Funding - 6,000
 Portion of Funding Received - 6,000
 Time Commitment: 0

Co-applicant : Jason Morgenstern (summer student)

Declined [n=6]

2017/9 - 2021/8 Enhancing Immunogenic Cancer Cell Death Through the Novel Combination of Oncolytic
Principal Investigator Viruses and Photodynamic Therapy (student stipend support), Scholarship

Funding Sources:

2017/9 - 2020/8 Ontario Government
 Ontario Graduate Scholarship
 Total Funding - 60,000 (Canadian dollar)
 Portion of Funding Received - 0
 Funding Competitive?: Yes

Principal Applicant : Ashley Ross;

Principal Investigator : Sarah Wootton

2017/9 - 2020/8 Enhancing Immunogenic Cancer Cell Death Through the Novel Combination of Oncolytic
Co-applicant Viruses and Photodynamic Therapy (student stipend support), Scholarship

Funding Sources:

2017/9 - 2020/8 Ontario Veterinary College (OVC)
 Doctoral Scholarship
 Total Funding - 60,000 (Canadian dollar)
 Portion of Funding Received - 0
 Funding Competitive?: Yes

Principal Applicant : Ashley Ross;

Principal Investigator : Sarah Wootton

2016/9 - 2018/12 The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic
Co-applicant Virotherapy (student stipend support; declined due to receipt of external scholarships),
 Scholarship

Funding Sources:

Ontario Veterinary College (OVC)
Graduate Scholarship
Total Funding - 17,000
Portion of Funding Received - 17,000
Funding Competitive?: Yes

Co-applicant : Sarah K. Wootton;

Principal Applicant : Jacob van Vloten

2016/9 - 2017/8 Augmentation of a Canine Melanoma Vaccine with Immunomodulatory Antibodies
Co-applicant (student stipend support), Scholarship

Funding Sources:

2016/9 - 2017/8 Pet Trust Foundation
OVC Pet Trust Scholar Program
Total Funding - 17,500 (Canadian dollar)
Portion of Funding Received - 17,500
Funding Competitive?: Yes

Principal Applicant : Wing Ka "Amanda" AuYeung (MSc student)

2015/9 - 2016/8 The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic
Principal Investigator Virotherapy (student stipend support), Scholarship

Funding Sources:

2015/9 - 2016/8 Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA)
Highly Qualified Personnel PhD Scholarship
Total Funding - 21,000 (Canadian dollar)
Portion of Funding Received - 0
Funding Competitive?: Yes

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

Principal Investigator : Sarah K. Wootton

2015/9 - 2016/8 Using Virus-Infected Dendritic Cells as Cancer Vaccines (student stipend support),
Principal Investigator Scholarship

Funding Sources:

2015/9 - 2016/8 University of Guelph
Graduate Research Assistant Tuition Supplement
Total Funding - 8,000 (Canadian dollar)
Portion of Funding Received - 0
Funding Competitive?: No

Principal Applicant : Robert Mould (MSc student; transferred to PhD)

Under Review [n=5]

2021/6 - 2026/5 Calming the Storm: Interventions to Abrogate Toxic Cytokine Responses to Viruses, Grant
Principal Applicant

Funding Sources:

2021/6 - 2026/5 Canadian Institutes of Health Research (CIHR)
Total Funding - 920,000 (Canadian dollar)
Funding Competitive?: Yes

Co-applicant : Khalil Karimi; Leonardo Susta; Sarah K. Wootton

2021/6 - 2026/5 AAV-vectored immunoprophylaxis for the prevention and treatment of infectious diseases,
Co-applicant Grant

Funding Sources:

2021/6 - 2026/5 Canadian Institutes of Health Research (CIHR)
Total Funding - 880,000 (Canadian dollar)

Co-applicant : Darwyn Kobasa; Kevin Stinson; Leonardo Susta; Rob Kozak;

Principal Applicant : Sarah K. Wootton

2021/9 - 2023/8 Mechanism of Oncolytic ORFV-Activated Innate and Adaptive Anti-Tumor Immunity in a
Co-investigator Preclinical Model of Late-Stage Ovarian Cancer, Grant

Funding Sources:

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

Principal Investigator : Sarah K. Wootton

2021/9 - 2023/8
Principal Applicant

Heat- and Cold-Adaptation of Oncolytic Rhabdoviruses to Improve Their Clinical Utility,
Grant

Funding Sources:

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

2020/11 - 2021/10
Principal Applicant

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

Funding Sources:

National Research Council Canada (NRC) (Ottawa, ON)
Collaborative R&D Initiative Pandemic Response Challenge
Program Grant Application
Total Funding - 553,685
Portion of Funding Received - 553,685
Funding Competitive?: Yes

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

Collaborator : Dr. Andrew Winterborn; Dr. Anh Tran

Student/Postdoctoral Supervision

Bachelor's [n=1]

2020/9 - 2021/4

Principal Supervisor

Julia Kakish, University of Guelph
Thesis/Project Title: Cold-Adaptation of Viruses for Use as Vaccine Vectors
(undergraduate research project student)
Present Position: Currently a member of my research team

Bachelor's Equivalent [n=10]

2020/5 - 2020/8

Principal Supervisor

Lily Chan, University of Guelph
Thesis/Project Title: Calming the Storm: Dissecting the Roles of Innate Lymphoid Cells
in Cytokine-Mediated Pulmonary Inflammation Induced by Oncolytic Vesicular Stomatitis
Virus (undergraduate summer research assistant)
Present Position: Currently a MSc student in my laboratory, University of Guelph

2020/5 - 2020/8

Principal Supervisor

Kiersten Hanada (In Progress) , University of Guelph
Thesis/Project Title: Calming the Cytokine Storm: Developing a Model to Study Toxic
Cytokine Responses to Viruses (undergraduate summer research assistant)
Present Position: Completing the DVM program, University of Guelph

- 2018/5 - 2018/8
Principal Supervisor Samantha Holtz (Completed) , University of Guelph
Student Degree Start Date: 2018/5
Student Degree Received Date: 2018/8
Thesis/Project Title: Combining Oncolytic Virotherapy with Epigenetic Modifiers to Treat Lymphomas (undergraduate summer research assistant)
Present Position: Completed a post-graduate diploma program., Queen's University
- 2017/5 - 2017/8
Principal Supervisor Julia Saturno (Completed) , University of Guelph
Student Degree Start Date: 2017/5
Student Degree Received Date: 2017/8
Thesis/Project Title: Pyrexia Can Impair Oncolytic Virotherapy (summer research assistantship)
Project Description: This student conducted research in my laboratory for the summer of 2017, while enrolled in the doctor of veterinary medicine program, University of Guelph.
Project title: Temperature as a confounding variable in oncolytic virotherapy for canine melanomas.
Present Position: veterinary practice
- 2016/5 - 2016/8
Principal Supervisor Manali Desai (Completed) , University of Guelph
Student Degree Start Date: 2016/5
Student Degree Received Date: 2016/8
Thesis/Project Title: Evaluating the Impact of Temperature on the Oncolytic Potential of Viruses in Canine and Murine Osteosarcoma Cells (summer research assistantship)
Project Description: Studied the efficacy of oncolytic viruses in a panel of canine and murine osteosarcoma cell lines.
Present Position: veterinary practice
- 2016/5 - 2016/8
Principal Supervisor Julia De Carvalho Nakamura (Completed) , University of Sao Paulo, Brazil
Student Degree Start Date: 2016/5
Student Degree Received Date: 2016/8
Thesis/Project Title: The Impact of Temperature on the Oncolytic Activity of Viruses (summer research assistantship)
Project Description: Participated in Students Without Borders Program, May-September 2016; conducted research in my laboratory studying the effect of high and low temperatures on oncolytic viruses.
Present Position: Veterinary practice, Sao Paulo, Brazil
- 2016/5 - 2016/8
Principal Supervisor Julia Saturno (Completed) , University of Guelph
Student Degree Start Date: 2016/5
Student Degree Received Date: 2016/8
Thesis/Project Title: Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas (summer research assistantship)
Project Description: Studied the efficacy of oncolytic viruses in a panel of canine melanoma cell lines.
Present Position: veterinary practice
- 2015/5 - 2015/8
Principal Supervisor Haley Spangler-Forgione (Completed) , University of Guelph
Student Degree Start Date: 2015/5
Student Degree Received Date: 2015/8
Thesis/Project Title: Par6 Influences the Susceptibility of Mammary Carcinoma Cells to Oncolytic Viruses (summer research assistantship)
Project Description: Title of project: Par6 influences the susceptibility of mammary carcinoma cells to oncolytic viruses
Present Position: Veterinary practice

- 2015/5 - 2015/8
Principal Supervisor Julia Kim (Completed) , University of Guelph
Student Degree Start Date: 2015/5
Student Degree Received Date: 2015/8
Thesis/Project Title: Assessment of the Potential to Treat Canine Cancers with an Oncolytic Vaccine (summer research assistantship)
Project Description: Undergraduate summer research assistant, May - August 2014.
Project: Used western blotting to assess canine osteosarcoma, melanoma and lymphoma specimens for the expression of various tumour-associated antigens. The results will guide the development of novel viral vectors to be used in a future canine cancer trial.
Present Position: Graduate student, Department of Population Medicine, University of Guelph
- 2014/5 - 2014/8
Principal Supervisor Julia Kim (Completed) , University of Guelph
Student Degree Start Date: 2013/9
Student Degree Received Date: 2014/8
Thesis/Project Title: Assessment of Canine Melanoma Samples from the Ontario Veterinary College-Companion Animal Tumour Bank for Expression of Antigens that can be Targeted with an Oncolytic Cancer Vaccine (summer research assistantship)
Project Description: Undergraduate summer research assistant, May - August 2015.
Project: Assessment of the potential to treat canine cancers with an oncolytic vaccine.
Present Position: Graduate student, Department of Population Medicine, University of Guelph
- Bachelor's Honours [n=22]**
- 2020/9 - 2021/4
Principal Supervisor Sierra Vanderkamp, University of Guelph
Thesis/Project Title: Evaluating the Role of Oxidative Stress in Off-Target Infections of T Cells by Oncolytic Rhabdoviruses (undergraduate research project student)
Present Position: Currently a member of my research team
- 2018/9 - 2019/4
Principal Supervisor Jessica Minott (Completed) , University of Guelph
Thesis/Project Title: Assessing the Impact of Sex Hormones on the Efficacy of Oncolytic Viruses (4th year undergraduate research project student)
Present Position: Currently a MSc student in my laboratory, University of Guelph
- 2018/5 - 2018/8
Principal Supervisor Jessica Minott (Completed) , University of Guelph
Thesis/Project Title: Assessing the Impact of Sex Hormones on the Efficacy of Oncolytic Viruses (undergraduate summer research assistant)
Present Position: Currently a MSc student in my laboratory, University of Guelph
- 2018/5 - 2018/8
Principal Supervisor Elaine Klafuric (Completed) , University of Guelph
Thesis/Project Title: Type I Interferon-Mediated Regulation of IL-17 Production by Mast Cells (undergraduate summer research assistant)
Present Position: Currently a MSc student in my laboratory
- 2017/5 - 2017/8
Principal Supervisor Mankerat Singh (Completed) , University of Guelph
Student Degree Start Date: 2017/5
Student Degree Received Date: 2017/8
Thesis/Project Title: Optimizing the Antigen Presentation Potential of Cultured Dendritic Cells Through the Use of Interleukin-4 (summer research assistantship)
Project Description: Mankerat complete his Honour's BSc program in April 2017 and then conducted a research project under my supervision for the summer 2017. Project title: Enhancing dendritic cell-based anti-cancer vaccines through adaptation to a hypoxic microenvironment.
Present Position: unknown

- 2016/9 - 2017/4
Principal Supervisor Mankerat Singh (Completed) , University of Guelph
Student Degree Start Date: 2016/9
Student Degree Received Date: 2017/4
Thesis/Project Title: Optimizing a Dendritic Cell-Based Vaccine for Induction of Immunological Memory (4th year undergraduate research project)
Project Description: Mankerat conducted research in my laboratory for two semesters as an undergraduate student enrolled in the course HK*4371/2 (Research in Human Biology and Nutritional Sciences). His project was entitled: Differentiating dendritic cells in the presence of interleukin-4 to enhance their potential as vaccines. He subsequently presented this work at the Summit for Cancer Immunotherapy, Gatineau, QC, in June 2017, where he received the only undergraduate award for best poster.
Present Position: unknown
- 2016/5 - 2016/9
Principal Supervisor Katrina Allison (Completed) , University of Guelph
Student Degree Start Date: 2012/9
Student Degree Received Date: 2016/8
Thesis/Project Title: Sex Disparity in Innate Immune Responses to Viral Infection: the Role of Type I Interferon
Project Description: Undergraduate summer research assistant in my laboratory; May-August 2016. Studied gender bias in the role of type I interferon signalling on the cytokine response to viral infection.
Present Position: Naturopathic Medicine College Training Program (Toronto, Ontario)
- 2015/5 - 2015/8
Principal Supervisor Wing Ka "Amanda" AuYeung (Completed) , University of Guelph
Student Degree Start Date: 2011/9
Student Degree Received Date: 2015/8
Thesis/Project Title: Transient Lymphopenia as a Mechanism to Allow an Oncolytic Virus to Replicate Inside a Tumour Despite Vaccination Against a Virus-Encoded Antigen (NSERC Undergraduate Student Research Assistantship)
Project Description: Undergraduate summer research assistant, May-August 2015.
Project: Transient lymphopenia as a mechanism to allow an oncolytic virus to replicate inside a tumour despite vaccination against a virus-encoded antigen
Present Position: Flow Cytometry Technician, The Hospital for Sick Children, Toronto, Ontario, Canada
- 2014/5 - 2014/9
Principal Supervisor Larissa Hattin (Completed) , University of Guelph
Student Degree Start Date: 2010/9
Student Degree Received Date: 2014/8
Thesis/Project Title: Evaluation of an Oncolytic Vaccine in Dogs (NSERC Undergraduate Student Research Assistantship)
Project Description: Assessed the oncolytic potential of a recombinant Newcastle disease virus in human prostate cancer cell lines.
Present Position: Emergency medicine residency program, University of British Columbia
- 2014/5 - 2014/8
Principal Supervisor Robert Mould (Completed) , University of Guelph
Student Degree Start Date: 2010/9
Student Degree Received Date: 2014/4
Thesis/Project Title: Combining Antigen-Presenting Cell-Based Vaccination with Oncolytic Viruses for the Treatment of Prostate Cancers (summer research assistantship)
Project Description: Undergraduate summer research assistant, May-August 2014.
Project: The potential to use Orf virus and Newcastle disease virus-infected dendritic cells and/or macrophages as cancer vaccines.
Present Position: Postdoctoral fellow in my laboratory, University of Guelph

- 2013/9 - 2014/4
Principal Supervisor Larissa Hattin (Completed) , University of Guelph
Student Degree Start Date: 2013/9
Student Degree Received Date: 2014/8
Thesis/Project Title: Testing the Oncolytic Potential of Two Recombinant Newcastle Disease Viruses in Human Prostate Cancer Cell Lines (summer research assistantship)
Project Description: Sept. 2013-April 2014: Larissa conducted her 4th-year undergraduate research project (Course codes: BIOM*4521 [Fall semester] and BIOM*4522 [Spring semester]) in my laboratory. Project title: Testing the oncolytic potential of a novel recombinant Newcastle Disease Virus in human prostate cancer cell lines. She continued this project as a summer undergraduate research assistant, May-August 2014
Present Position: Emergency medicine residency program, University of British Columbia
- 2013/9 - 2014/4
Principal Supervisor Wing Ka "Amanda" AuYeung (Completed) , University of Guelph
Student Degree Start Date: 2011/9
Student Degree Received Date: 2015/4
Thesis/Project Title: Evaluating the Role of Akt Isoforms in the Sensitivity of Lung Cancer Cells to Oncolytic Viruses (Work-Study Program; part-time research while pursuing full-time undergraduate studies)
Project Description: Undergraduate summer research assistant, May-August 2013.
Project: Development of flow cytometry-based immunological assays to support pre-clinical and clinical companion animal cancer trials.
Present Position: Flow Cytometry Technician, The Hospital for Sick Children, Toronto, Ontario, Canada
- 2013/9 - 2014/4
Principal Supervisor Sofia Oke (Completed) , University of Guelph
Student Degree Start Date: 2010/9
Student Degree Received Date: 2014/4
Thesis/Project Title: Determining Whether TLR3 and/or TLR7 Ligation Causes Dysregulation of Cytokine Signaling in Macrophages Lacking the Type I Interferon Receptor (summer research assistantship)
Project Description: Sofia conducted her 4th-year undergraduate research project (Course codes: BIOM*4521 [Fall semester] and BIOM*4522 [Spring semester]) in my laboratory, September 2013-April 2014. Project: Determining whether TLR3 and/or TLR7 ligation causes dysregulation of cytokine signaling in dendritic cells lacking the type I interferon receptor.
Present Position: Research technician (Dr. Sachdev Sidhu's lab, University of Toronto)
- 2013/9 - 2015/8
Principal Supervisor Alexandra Rasiuk (Completed) , University of Guelph
Student Degree Start Date: 2009/9
Student Degree Received Date: 2013/8
Thesis/Project Title: The Role of Type I Interferon Signalling in the Regulation of Cytokines Produced by Antigen-Presenting Cells (4th year undergraduate research project)
Project Description: Undergraduate research project course (BIOM*4521 and BIOM*4522), Sept. 2012 - August 2013. Project: Studying the role of type I interferon receptor-mediated signaling in the regulation of cytokines produced by dendritic cells.
Present Position: Research associate in industry

- 2013/5 - 2013/8
Principal Supervisor Wing Ka "Amanda" AuYeung (Completed) , University of Guelph
Student Degree Start Date: 2013/9
Student Degree Received Date: 2014/4
Thesis/Project Title: Development of Flow Cytometry-Based Immunological Assays to Support Pre-Clinical and Clinical Companion Animal Cancer Trials (NSERC Undergraduate Student Research Assistantship)
Project Description: Part-time undergraduate research assistant (work-study program, September 2013 - April 2014. Project: The role of Akt isoforms in the rate of proliferation of cancer cell lines and their susceptibility to oncolytic viruses.
Present Position: Flow Cytometry Technician, The Hospital for Sick Children, Toronto, Ontario, Canada
- 2013/5 - 2013/7
Principal Supervisor Jason Morgenstern (Completed) , University of Guelph
Student Degree Start Date: 2009/9
Student Degree Received Date: 2013/4
Thesis/Project Title: Testing the Efficacy of Oncolytic Viruses, Histone Deacetylase Inhibitors and Toll-Like Receptor Ligands in Cancer Cell Lines (summer research assistantship)
Project Description: Undergraduate summer research assistant, May -August 2012.
Project: Establishment of leukemia/lymphoma cell lines from clinical specimens and evaluation of their susceptibility to oncolytic viruses.
Present Position: Medical residency program in public health + Master's of Public Health program, McMaster University
- 2012/9 - 2013/4
Principal Supervisor Evan Lusty (Completed) , University of Guelph
Student Degree Start Date: 2009/9
Student Degree Received Date: 2013/4
Thesis/Project Title: Characterizing Oncolytic Viruses and Toll Like Receptor Ligands in the In Vitro Treatment of Human Prostate Cancer (4th year undergraduate research project)
Project Description: Evan conducted his 4th-year undergraduate research project (Course codes: BIOM*4521 [Fall semester] and BIOM*4522 [Spring semester]) in my laboratory.
Project: Testing oncolytic viruses in human prostate cancer cell lines.
Present Position: MD program, Queen's University (Kingston, Ontario)
- 2012/9 - 2013/4
Principal Supervisor Jason Morgenstern (Completed) , University of Guelph
Student Degree Start Date: 2009/9
Student Degree Received Date: 2013/4
Thesis/Project Title: Investigating the Potential to use Recombinant Newcastle Disease Viruses as Oncolytic Virotherapies for Prostate and Cervical Cancers (Work-Study Program; part-time research while pursuing full-time undergraduate studies)
Project Description: Undergraduate summer research assistant, May - July 2013. Project: Characterizing the oncolytic potential of a novel fowl reovirus in established cancer cell lines.
Present Position: Medical residency program in public health + Master's of Public Health program, McMaster University

- 2012/9 - 2013/4
Principal Supervisor Alexandra Rasiuk (Completed) , University of Guelph
Student Degree Start Date: 2009/9
Student Degree Received Date: 2013/4
Thesis/Project Title: Optimization of a Protocol for Harvesting and Differentiating Murine Bone Marrow-Derived Dendritic Cells for use as a Cancer Vaccine (4th year undergraduate research project)
Project Description: Alexandra conducted her 4th-year undergraduate research project (Course codes: BIOM*4521 [Fall semester] and BIOM*4522 [Spring semester]) in my laboratory. Research project: Optimization of a protocol for harvesting and differentiating murine bone marrow-derived dendritic cells for use as a cancer vaccine.
Present Position: Post-graduate diploma program in clinical research at Seneca College, Toronto
- 2012/5 - 2012/8
Principal Supervisor Jason Morgenstern (Completed) , University of Guelph
Student Degree Start Date: 2009/9
Student Degree Received Date: 2013/4
Thesis/Project Title: Evaluation of the Susceptibility of Cancer Cell Lines to Oncolytic Viruses (summer research assistantship)
Project Description: Part-time undergraduate research assistant (work-study program), September 2012-April 2013. Project: Testing oncolytic viruses in human prostate and cervical cancer cell lines.
Present Position: Medical residency program in public health + Master's of Public Health program, McMaster University
- 2012/5 - 2013/7
Principal Supervisor Evan Lusty (Completed) , University of Guelph
Student Degree Start Date: 2009/9
Student Degree Received Date: 2013/4
Thesis/Project Title: Testing Various Oncolytic Viruses, Histone Deacetylase Inhibitors and Toll-Like Receptor Ligands as Monotherapies in Human Prostate and Cervical Cancer Cells (summer research assistantship)
Project Description: Undergraduate summer research assistant, May - August 2012. Was awarded a Canadian Society for Immunology - Summer Internship in Immunology for this work. Project: Using an innate anti-viral immune response in the presence of a histone deacetylase inhibitor to treat leukemias.
Present Position: MD program, Queen's University (Kingston, Ontario)
- 2012/5 - 2012/8
Principal Supervisor Evan Lusty (Completed) , University of Guelph
Student Degree Start Date: 2009/9
Student Degree Received Date: 2013/4
Thesis/Project Title: Using an Innate Anti-Viral Immune Response in the Presence of a Histone Deacetylase Inhibitor to Treat Leukemias (summer research assistantship)
Project Description: Undergraduate summer research assistant May - June 2013. Project: Testing oncolytic viruses in human prostate cancer cell lines.
Present Position: MD program, Queen's University (Kingston, Ontario)
- Master's Equivalent [n=1]**
- 2020/2
Principal Supervisor Yeganeh Mehrani (In Progress) , Ferdowsi University of Mashhad, Iran
Student Degree Start Date: 2020/2
Student Degree Expected Date: 2022/10
Thesis/Project Title: Development of Flow Cytometric Methods to Evaluate Canine Innate Lymphocyte Subsets
Present Position: Visiting scientist in my laboratory

Master's Thesis [n=12]

2021/9 Academic Advisor	Sierra Vanderkamp (In Progress) , University of Guelph Student Degree Start Date: 2021/9 Student Degree Expected Date: 2023/8 Thesis/Project Title: Mechanisms Governing Off-Target Infection and Killing of T Cells by Oncolytic Viruses
2021/9 Academic Advisor	Julia Kakish (In Progress) , University of Guelph Student Degree Start Date: 2021/9 Student Degree Expected Date: 2023/8 Thesis/Project Title: Sensitization of Decitabine-Treated Leukemias to Oncolytic Virotherapy
2021/4 - 2022/8 Academic Advisor	Fatemeh Darya Fazel (In Progress) , University of Guelph Student Degree Start Date: 2020/9 Student Degree Expected Date: 2022/8 Thesis/Project Title: mRNA-Based Vaccines for Preventing the Infection of Poultry with Influenza Viruses
2020/9 Principal Supervisor	Lily Chan (In Progress) , University of Guelph Student Degree Start Date: 2020/9 Student Degree Expected Date: 2022/8 Thesis/Project Title: The Roles of Innate Leukocytes in Dendritic Cell-Based Vaccinations Present Position: Currently a member of my research team
2018/9 Principal Supervisor	Elaine Klafuric (In Progress) , University of Guelph Student Degree Start Date: 2018/9 Student Degree Expected Date: 2021/12 Thesis/Project Title: Combining Oncolytic Viruses with Epigenetic Modifiers to Treat Acute Myeloid Leukemias Present Position: Currently a member of my research team, University of Guelph
2017/9 - 2019/12 Academic Advisor	Adriana Bianco (Completed) , University of Guelph Student Degree Start Date: 2017/9 Student Degree Received Date: 2019/12 Thesis/Project Title: Anti-Cancer Effects of Beta Glucans Present Position: unknown
2016/9 - 2016/12 Principal Supervisor	Katrina Allison (Withdrawn) , University of Guelph Student Degree Start Date: 2016/9 Thesis/Project Title: Sex Disparity in Innate Immune Responses to Viral Infection: the Role of Type I Interferon Project Description: Studying gender bias in the role of type I interferon signalling on the cytokine response to viral infection. Present Position: Naturopathic Medicine College Training Program (Toronto, Ontario)
2015/9 - 2017/8 Principal Supervisor	Wing Ka "Amanda" AuYeung (Completed) , University of Guelph Student Degree Start Date: 2015/9 Student Degree Received Date: 2017/8 Thesis/Project Title: Developing Novel Biotherapies for the Treatment of Melanomas Project Description: Amanda is studying the mechanisms underlying biotherapies for melanomas. Present Position: Research Associate, Notch Therapeutics, Toronto, Ontario, Canada, The Hospital for Sick Children, Toronto, Ontario, Canada

- 2015/1 - 2016/8
Academic Advisor
Nahla El Skhawy (Completed) , University of Guelph
Student Degree Start Date: 2014/9
Student Degree Received Date: 2016/8
Thesis/Project Title: The Role of the Immune System in Johne's Disease in Cattle
Project Description: Immunological aspects of Johne's disease in cattle.
Present Position: unknown
- 2013/9 - 2015/8
Principal Supervisor
Alexandra Rasiuk (Completed) , University of Guelph
Student Degree Start Date: 2013/9
Student Degree Received Date: 2015/8
Thesis/Project Title: Role of Type I Interferon Signalling in Regulating Survival, Proliferation, and Cytokine Production in Antigen-Presenting Cells
Project Description: Thesis title: Role of Type I Interferon Signalling in Regulating Survival, Proliferation, and Cytokine Production in Antigen-Presenting Cells
Present Position: Research associate in industry
- 2012/9 - 2014/8
Principal Supervisor
Christian Ternamian (Completed) , University of Guelph
Student Degree Start Date: 2012/9
Student Degree Received Date: 2014/8
Thesis/Project Title: Targeting Acute Lymphoblastic Leukemia with Oncolytic Virotherapy and Immunotherapy
Project Description: Combining histone deacetylase inhibition and transient, virus-induced lymphopenia to treat leukemia.
Present Position: Completed Medical Doctorate program at Queen's University
- 2012/9 - 2014/8
Principal Supervisor
Zafir Syed (Completed) , University of Guelph
Student Degree Start Date: 2012/9
Student Degree Received Date: 2014/8
Thesis/Project Title: Oncolytic Immunotherapy for the Treatment of High-Grade Gliomas
Project Description: Synergizing immuno- and oncolytic viro-therapies for the treatment of primary brain cancer.
Present Position: Radiology residency program, University of Western Ontario
- Doctorate [n=19]**
- 2021/3
Academic Advisor
Ben Muselius (In Progress) , University of Guelph
Degree Name: PhD
Student Degree Start Date: 2021/1
Student Degree Expected Date: 2024/5
Thesis/Project Title: Proteomics Analysis of Infections with the Fungal Pathogen *Cryptococcus neoformans*
Present Position: graduate student
- 2020/11
Academic Advisor
Brenna Stevens (In Progress) , University of Guelph
Student Degree Start Date: 2020/9
Student Degree Expected Date: 2024/8
Thesis/Project Title: Gene Therapy for Cystic Fibrosis
Project Description: Transferred from MSc program.
Present Position: graduate student
- 2019/9
Academic Advisor
Sylvia Thomas (In Progress) , University of Guelph
Student Degree Start Date: 2019/9
Student Degree Expected Date: 2023/8
Thesis/Project Title: Adeno-Associated Virus-Vectored Gene Editing Platform for the Correction of Monogenic Lung Diseases
Project Description: Transferred from the MSc program.
Present Position: Graduate student in Wootton lab

- 2019/9 - 2023/8
Principal Supervisor Jason Knapp (In Progress) , University of Guelph
Student Degree Start Date: 2019/9
Student Degree Expected Date: 2023/8
Thesis/Project Title: Heat-Adaptation of Oncolytic Rhabdoviruses to Improve Their Clinical Utility
Present Position: Graduate student in my laboratory
- 2019/9 - 2024/8
Principal Supervisor Jessica Minott (In Progress) , University of Guelph
Student Degree Start Date: 2019/9
Student Degree Expected Date: 2022/8
Thesis/Project Title: Development of an Oncolytic Orf Virus-Infected Cell Vaccine for the Treatment of Spontaneous Mammary Carcinoma Metastases (transferred from MSc program)
Present Position: Graduate student in my laboratory
- 2018/9 - 2022/8
Academic Advisor Amira Rghei (In Progress) , University of Guelph
Student Degree Start Date: 2018/9
Thesis/Project Title: Adeno-Associated Virus-Vectored Immunoprophylaxis for Filovirus Infections
Present Position: Graduate student in Wootton lab
- 2017/9 - 2021/8
Principal Supervisor Ashley Stegelmeier (Completed) , University of Guelph
Student Degree Start Date: 2017/9
Student Degree Received Date: 2021/8
Student Canadian Residency Status: Canadian Citizen
Thesis/Project Title: Vectorizing Immunomodulatory Antibodies for the Treatment of Canine Melanomas
Project Description: The objective of this research is to enable tumour-bearing dogs to synthesize anti-canine PDL-1 in vivo using AAV with an inducible Tet-on promoter, which will allow fine control of expression of the antibody. This novel administration of an immunomodulatory canine antibody with an inducible promoter has the potential to improve efficacy of immunotherapies in melanoma-bearing dogs while minimizing risk of off-target autoimmunity.
Present Position: Research Manager, Kitchener, Ontario, Canada
- 2017/1 - 2020/1
Principal Supervisor Maedeh "Mahi Azizi" Darzaniazizi (Completed) , University of Guelph
Student Degree Start Date: 2017/1
Student Degree Received Date: 2020/1
Thesis/Project Title: Elucidating the Roles of Sex, Neutrophils and Mast Cells in Type I Interferon-Regulated Cytokine Responses to Viruses
Present Position: Working in industry
- 2017/1 - 2020/12
Academic Advisor Nadiyah Alqazlan (Completed) , University of Guelph
Student Degree Start Date: 2016/9
Student Degree Received Date: 2020/12
Thesis/Project Title: Low Pathogenic Avian Influenza Virus H9N2 in Chickens: Transmission Routes, Effects of Environmental Factors on Transmission and Means to Disrupt Transmission
Project Description: Low Pathogenic Avian Influenza Virus H9N2 in Chickens: Transmission Routes, Effects of Environmental Factors on Transmission and Means to Disrupt Transmission
Present Position: PhD student (Sharif Lab, University of Guelph)

- 2016/9 - 2020/8
Academic Advisor
Thomas McAusland (Completed) , University of Guelph
Student Degree Start Date: 2016/9
Student Degree Received Date: 2020/8
Thesis/Project Title: Development of Newcastle Disease Virus-Based Oncolytic Virotherapies
Project Description: Development of oncolytic Newcastle disease virus vectors for cancer therapy.
Present Position: Enrolled in police college
- 2015/9 - 2021/12
Academic Advisor
Kathy Matuszewska (In Progress) , University of Guelph
Student Degree Start Date: 2015/9
Student Degree Expected Date: 2021/12
Thesis/Project Title: Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer
Project Description: Using a derivative of thrombospondin-1 to normalize tumour vasculature for enhanced delivery of oncolytic viruses.
Present Position: PhD student (Petrik lab), University of Guelph
- 2015/9 - 2018/12
Academic Advisor
Laura van Lieshout (Completed) , University of Guelph
Student Degree Start Date: 2015/9
Student Degree Received Date: 2018/12
Thesis/Project Title: Using Adeno-Associated Viruses for Antibody-Mediated Vectored Immunophrophylaxis
Present Position: Postdoctoral fellow in the Wootton lab, University of Guelph
- 2015/6 - 2022/4
Academic Advisor
Peyman Asadian (In Progress) , University of Guelph
Student Degree Start Date: 2015/9
Student Degree Expected Date: 2022/4
Thesis/Project Title: The Role of SAMHD1 in Feline Immunodeficiency Virus Infections
Project Description: Thesis title: Expression profile and role of restriction of Sterile alpha motif domain- and HD domain-containing protein 1 in restriction of Feline Immunodeficiency Virus
Present Position: Leave of absence (PhD student in Bienzle lab, University of Guelph)
- 2014/9 - 2019/12
Academic Advisor
Joelle Ingrao (Withdrawn) , University of Guelph
Student Degree Start Date: 2014/9
Thesis/Project Title: Development of a Vaccine to Protect Against *Toxoplasma gondii* Infection in Sheep
Project Description: Development of a recombinant parapoxvirus vaccine to protect against *Toxoplasma gondii* infection in sheep
Present Position: Director, Catalent, Baltimore, Maryland, USA
- 2014/9 - 2020/4
Principal Supervisor
Robert Mould (Completed) , University of Guelph
Student Degree Start Date: 2014/9
Student Degree Received Date: 2020/4
Thesis/Project Title: Development of Novel Cancer Biotherapies
Project Description: Was in the MSc program Sept. 2014-Aug. 2015; transferred into the PhD program, effective Sept. 2015. Project: Development of novel biotherapies for the treatment of osteosarcomas.
Present Position: Scientist at Ensoma, USA

2014/9 - 2020/4
Co-Supervisor
Jacob van Vloten (Completed) , University of Guelph
Student Degree Start Date: 2014/9
Student Degree Received Date: 2020/4
Thesis/Project Title: The Development of Recombinant Parapoxvirus ovis (OrfV) for Use in Oncolytic Virotherapy
Project Description: Direct entry from the BSc program into the PhD program. Project: Development of a novel Orf virus natural isolate into a cancer biotherapy.
Present Position: Postdoctoral fellow in the lab of Dr. Richard Vile, Mayo Clinic, Rochester, Minnesota

2014/9 - 2017/8
Principal Supervisor
Megan Strachan-Whaley (Completed) , University of Guelph
Student Degree Start Date: 2014/9
Student Degree Received Date: 2017/8
Thesis/Project Title: Combination of Epigenetic Modifier Drugs with Oncolytic Viral Therapy as a Novel Treatment for Leukemias
Project Description: Using oncolytic viruses to potentiate histone deacetylase inhibitor-mediated killing of acute lymphoblastic leukemia B cells.
Present Position: Postdoctoral fellow in industry

2014/2 - 2016/8
Academic Advisor
Marianne Wilcox (Completed) , University of Guelph
Student Degree Start Date: 2013/9
Student Degree Received Date: 2016/8
Thesis/Project Title: Mathematical Modeling of Cytokine Storms in Rhabdovirus-Infected Mice Lacking Type I Interferon Signaling in Hematopoietic Cells
Project Description: Mathematical modeling of cytokine storms in rhabdovirus-infected mice lacking type I interferon signaling in hematopoietic cells.
Present Position: unknown

2013/8 - 2018/9
Academic Advisor
Lisa Santry (Completed) , University of Guelph
Student Degree Start Date: 2011/9
Student Degree Received Date: 2018/9
Thesis/Project Title: Functional Role of AKT Isoforms in Jaagsiekte Sheep Retrovirus Envelope Protein-Induced Lung Tumourigenesis and the Susceptibility of the Resulting Tumours to Viral Oncolysis
Project Description: Project #1: Functional role of AKT isoforms in Jaagsiekte Sheep Retrovirus envelope protein-induced lung tumorigenesis and the susceptibility of the resulting tumours to viral oncolysis. Project #2: Using a derivative of thrombospondin-1 to normalize tumour vasculature for enhanced delivery of oncolytic viruses. Project #3: Development of a Newcastle disease virus vector expressing an immunomodulatory antibody.
Present Position: Research associate in industry

Doctorate Equivalent [n=1]

2018/1 - 2022/4
Academic Advisor
Karen Carlton (In Progress) , University of Guelph
Student Degree Start Date: 2018/1
Student Degree Expected Date: 2022/4
Thesis/Project Title: Crimean-Congo Hemorrhagic Fever DNA Vaccine trial: Pilot Safety and Toxicity Study in Cattle and Goats
Present Position: DVSc student in the Arroyo and Lillie labs, University of Guelph

Post-doctorate [n=6]

- 2020/5 - 2021/4
Principal Supervisor Robert Mould (Completed) , University of Guelph
Student Degree Start Date: 2020/5
Student Degree Received Date: 2021/4
Thesis/Project Title: Development of Vaccines for COVID-19
Present Position: Still part of my research team
- 2020/3 - 2020/7
Co-Supervisor Jacob van Vloten (Completed) , University of Guelph
Student Degree Start Date: 2020/3
Student Degree Received Date: 2020/7
Thesis/Project Title: Development of Vaccines for COVID-19
Present Position: Postdoctoral fellow in the lab of Dr. Richard Vile, Rochester, MN, USA, Mayo Clinic, Rochester, Minnesota
- 2018/9 - 2019/8
Principal Supervisor Megan Strachan-Whaley (Completed) , University of Guelph
Student Degree Start Date: 2018/9
Student Degree Received Date: 2019/8
Thesis/Project Title: Combining Oncolytic Viruses and Epigenetic Modifiers to Treat Acute Leukemias
Present Position: Enrolled in medical school (Dalhousie University)
- 2015/5 - 2017/12
Co-Supervisor Dr. Li Deng (Completed) , University of Guelph
Student Degree Start Date: 2015/4
Student Degree Received Date: 2017/12
Thesis/Project Title: Engineering Virus-Vectored Cancer Vaccines for Clinical Canine Cancer Trials
Project Description: Development of novel virus vectors for use in oncolytic and immunotherapies.
Present Position: Postdoctoral fellow (Wan lab, McMaster University)
- 2013/9 - 2014/4
Principal Supervisor Dr. Scott Walsh (Completed) , University of Guelph
Student Degree Start Date: 2013/9
Student Degree Received Date: 2014/8
Thesis/Project Title: Type I Interferon Receptor Signalling as a Master Switch for the Negative Regulation of Cytokine Networks
Project Description: Type I interferon receptor signalling as a master switch for the negative regulation of cytokine networks.
Present Position: Postdoctoral fellow in the laboratory of Dr. Yonghong Wan, McMaster University, Hamilton, ON, Canada
- 2013/2 - 2013/8
Principal Supervisor Dr. Jondavid de Jong (Completed) , University of Guelph
Student Degree Start Date: 2013/2
Student Degree Received Date: 2013/8
Thesis/Project Title: Construction of Human Adenovirus Serotype 48 and Maraba Virus Vectors
Project Description: Construction of recombinant Maraba virus and human adenovirus serotype 48 vectors for use in cancer immune- and oncolytic viro-therapy.
Present Position: Research Associate, Mirexus (Guelph, Ontario; biotechnology company)

Diploma [n=4]

- 2015/10 - 2016/3
Principal Supervisor Katrina Geronimo (Completed) , St. Joan of Arc Catholic Secondary School, Mississauga, Ontario
Student Degree Start Date: 2012/9
Student Degree Received Date: 2016/6
Thesis/Project Title: Hypoxia Variably Affects Oncolytic Virus Efficacy While Potentiating the Growth of Human Cervical Cancer Cells
Project Description: September 2015 - May 2016: Participated in the Sanofi BioGENEius Challenge Canada. This is a national research competition for secondary school students (<http://biogenius.ca/>). Over a 6-month period she averaged 2-3 bus trips to the University of Guelph per week to work approximately half-days in my laboratory. Her project title was "Hypoxia variably affects oncolytic virus efficacy while potentiating the growth of human cervical cancer cells".
Present Position: BSc program, University of Guelph, University of Guelph
- 2015/10 - 2016/3
Principal Supervisor Arthane Kodeeswaran (Completed) , St. Joan of Arc Catholic Secondary School, Mississauga, Ontario
Student Degree Start Date: 2012/9
Student Degree Received Date: 2016/6
Thesis/Project Title: The Effect of Temperature on the Efficacy of Oncolytic Viruses in Human Cervical Cancer Cells
Project Description: September 2015 - May 2016: Participated in the Sanofi BioGENEius Challenge Canada. This is a national research competition for secondary school students (<http://biogenius.ca/>). Over a 6-month period she averaged 2-3 bus trips to the University of Guelph per week to work approximately half-days in my laboratory. Her project title was "The effect of temperature on the efficacy of oncolytic viruses in human cervical cancer cells". Notably, Arthane was one of the award winners for the Greater Toronto Area regional competition.
Present Position: BSc program, University of Guelph, University of Guelph
- 2013/12 - 2014/4
Principal Supervisor Micaella Talan (Completed) , St. Joan of Arc Catholic Secondary School, Mississauga, Ontario
Student Degree Start Date: 2010/9
Student Degree Received Date: 2014/6
Thesis/Project Title: High School Research Project: The Effects of Quercetin and Kaempferol on the Cytotoxicity of Carboplatin and Entinostat on Cancer Cell Lines
Project Description: I am serving as a mentor for this secondary school student as she competes in the Sanofi BioGENEius challenge (see: <http://sanofibiogeneiuschallenge.ca/>).
Project title: Using plant flavonoids quercetin and kaempferol in combination with the chemotherapeutic agent, carboplatin, to treat cancer cell lines.
Present Position: BSc program, McMaster University
- 2013/12 - 2014/4
Principal Supervisor Brittney Tin (Completed) , St. Joan of Arc Catholic Secondary School, Mississauga, Ontario
Student Degree Start Date: 2010/9
Student Degree Received Date: 2014/6
Thesis/Project Title: High School Research Project: The Effects of Quercetin and Kaempferol on the Cytotoxicity of Carboplatin and Entinostat on Cancer Cell Lines
Project Description: I am serving as a mentor for this secondary school student as she competes in the Sanofi BioGENEius challenge (see: <http://sanofibiogeneiuschallenge.ca/>).
Project title: Using plant flavonoids quercetin and kaempferol in combination with the chemotherapeutic agent, carboplatin, to treat cancer cell lines.
Present Position: BSc program, McMaster University

Research Associate [n=2]

- 2021/10 - 2022/4 David Speicher (In Progress) , University of Guelph
Principal Supervisor Student Degree Start Date: 2021/10
Thesis/Project Title: Virus Vectors for the Prevention of Infectious Diseases and Treatment of Cancers
- 2016/5 - 2023/4 Dr. Khalil Karimi (In Progress) , University of Guelph
Principal Supervisor Student Degree Start Date: 2016/5
Thesis/Project Title: Role of Type I Interferon Signalling on the Responses of Innate Lymphoid Cell Subsets to Viral Infection
Project Description: Assists with co-management of my research program, with an emphasis on studying the role of innate lymphoid cell subsets in response to viral infection.
Present Position: Research Associate/Associated Faculty Member in my laboratory, University of Guelph

Technician [n=1]

- 2019/12 - 2024/12 David Marom (In Progress) , University of Guelph
Co-Supervisor Student Degree Start Date: 2019/9
Thesis/Project Title: General research support.
Present Position: A part-time member of my research team

Staff Supervision**Event Administration**

- 2019/9 - 2020/1 Local Organizing Committee Member, Canadian Society for Virology 2020 Annual Scientific Meeting (Note: this meeting was cancelled due to COVID-19), Conference, 2020/6 - 2020/6

Editorial Activities

- 2020/7 - 2025/12 Reviewer, Viral Immunology, Journal
- 2019/11 - 2025/12 Reviewer, Clinical Cancer Research, Journal
- 2018/6 - 2025/12 Reviewer, Canadian Journal of Veterinary Medicine, Journal
- 2018/5 - 2025/12 Reviewer, Reviews in Medical Virology, Journal
- 2017/9 - 2025/12 Reviewer, Science Translational Medicine, Journal
- 2017/5 - 2025/12 Reviewer, Veterinary Immunology and Immunopathology, Journal
- 2015/5 - 2025/12 Reviewer, Canadian Journal of Veterinary Research, Journal
- 2015/5 - 2025/12 Reviewer, Viruses, Journal
- 2014/5 - 2025/12 Reviewer, Journal of Visualized Experimentation, Journal
- 2013/12 - 2025/12 Reviewer, PLOS ONE, Journal
- 2020/9 - 2025/8 Guest Editor, Viruses, Journal
- 2018/5 - 2018/5 Reviewer, Reviews in Medical Virology (reviewed the second of a linked pair of manuscripts), Journal
- 2017/12 - 2018/1 Reviewer, PLOS ONE (reviewed a manuscript), Journal

2016/11 - 2016/12	Reviewer, Canadian Journal of Veterinary Research (reviewed a manuscript), Journal
2015/10 - 2015/10	Reviewer, Viruses (reviewed a manuscript), Journal
2015/5 - 2015/5	Reviewer, Viruses (reviewed a manuscript), Journal
2014/1 - 2014/2	Reviewer, PLOS ONE (reviewed a manuscript), Journal
2013/10 - 2013/10	Reviewer, Canadian Journal of Veterinary Research (reviewed a manuscript), Journal
2013/9 - 2013/10	Reviewer, PLOS ONE (reviewed a manuscript), Journal
2013/7 - 2013/8	Reviewer, Molecular Therapy (reviewed a manuscript), Journal
2013/4 - 2013/4	Reviewer, PLOS ONE (reviewed a manuscript), Journal
2013/1 - 2013/3	Reviewer, Journal of Vaccines and Immunization (reviewed a manuscript), Journal
2012/8 - 2012/8	Reviewer, Canadian Veterinary Journal (reviewed a manuscript), Journal
2011/10 - 2011/11	Reviewer, Clinical Medicine Insights Oncology (reviewed a manuscript), Journal

Mentoring Activities

2021/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 Mentorees: Jason Knapp April 30, 2021; Jason Knapp's PhD qualifying examination
2021/4	Chair of MSc final examination committee, University of Guelph Number of Mentorees: 1 Mentorees: Christine Yanta April 27, 2021; Christine Yanta's MSc thesis defence.
2020/12	Chair of PhD final examination committee, University of Guelph Number of Mentorees: 1 December 21, 2020; Ryan Snyder's PhD thesis defence
2020/7	Chair of PhD Qualifying Examination Committee, University of Guelph Number of Mentorees: 1 July 28, 2020; Melanie Iverson's PhD qualifying examination
2020/6	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 June 12, 2020; Ran Xu's PhD qualifying examination
2020/5	PhD final examination committee member, University of Guelph Number of Mentorees: 1 May 27, 2020; Robert Mould's PhD thesis defence
2020/5	MSc final examination committee member, University of Guelph Number of Mentorees: 1 May 15, 2020; Elana Raaphorst's MSc thesis defence
2020/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 April 16, 2020; Heng Kang's PhD qualifying examination
2020/4	PhD qualifying examination committee member, University of Guelph Number of Mentorees: 1 April 20, 2020; Sugandha Raj's PhD qualifying examination

- 2020/1 PhD final examination committee member, University of Guelph
Number of Mentorees: 1
January 3, 2020; Maedeh Darzianiazizi's PhD thesis defence
- 2019/12 Chair of PhD Qualifying Examination Committee, University of Guelph
Number of Mentorees: 1
December 6, 2019; Ayumi Matsuyama's PhD qualifying examination
- 2019/5 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
May 3, 2019; Seyed Hossein's PhD qualifying examination
- 2019/4 Chair of MSc final examination committee, University of Guelph
Number of Mentorees: 1
April 15, 2019; Megan Neely's MSc thesis defence
- 2019/4 MSc final examination committee member, University of Guelph
Number of Mentorees: 1
April 26, 2019; Kristen Lamers's MSc thesis defence
- 2019/4 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
April 18, 2019; Gary Lee's PhD qualifying examination
- 2019/2 DMin final examination committee member, Tyndale University
Number of Mentorees: 1
February 3, 2019; Jeffrey Roy's DMin thesis defence
- 2019/1 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
January 29, 2019; Karen Carlton's PhD qualifying examination
- 2018/12 PhD final examination committee member, University of Western Ontario
Number of Mentorees: 1
December 6, 2018; Corby Fink's PhD thesis defence
- 2018/12 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
December 17, 2018; Thomas McAusland's PhD qualifying examination
- 2018/11 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
November 26, 2018; Ashley Stegelmeier's PhD qualifying examination
- 2018/9 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
September 4, 2018; Maedeh Darzianiazizi's PhD qualifying examination
- 2018/6 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
June 22, 2018; Laura van Lieshout's PhD qualifying examination
- 2018/4 PhD final examination committee member, University of Guelph
Number of Mentorees: 1
April 27, 2018; Jegarubee Bavananthasivam's PhD thesis defence
- 2018/1 PhD final examination committee member, University of Guelph
Number of Mentorees: 1
January 15, 2018; Lisa Santry's PhD thesis defence

- 2018/1 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
January 19, 2018; Nadiyah Alqazlan's PhD qualifying examination
- 2018/1 PhD final examination committee member, University of Guelph
Number of Mentorees: 1
January 9, 2018; Megan Strachan-Whaley's PhD thesis defence
- 2017/12 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
December 1, 2017; Benoit Cuq's PhD Qualifying Examination
- 2017/9 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
September 25, 2017: Carina Cooper's PhD qualifying examination
- 2017/8 MSc final examination committee member, University of Guelph
Number of Mentorees: 1
August 21, 2017; Amanda AuYeung's MSc thesis defence
- 2017/3 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
March 27, 2017: Jacob van Vloten's PhD qualifying examination
- 2017/1 PhD final examination committee member, University of Guelph
Number of Mentorees: 1
January 25, 2017; Neda Barjesteh's PhD thesis defence
- 2017/1 MSc final examination committee member, University of Toronto
Number of Mentorees: 1
January 16, 2017; Tiffany Ho's MSc thesis defence
- 2016/9 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
December 19, 2016: Peyman Asadian's PhD qualifying examination
- 2016/8 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
August 24, 2016: Kathy Matuszewska's PhD qualifying examination
- 2016/6 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
June 14, 2016: Megan Strachan-whaley's PhD qualifying examination
- 2016/6 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
June 6, 2016: Seyedmehdi Emam's PhD qualifying examination
- 2016/5 PhD final examination committee member, University of Guelph
Number of Mentorees: 1
May 3, 2016: Served on the examination committee for Shirene Singh's PhD defence
- 2016/4 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
April 27, 2016: Alexander Bekele-Yitbarek's PhD qualifying examination
- 2015/9 MSc examination committee member, University of Guelph
Number of Mentorees: 1
September 2, 2015: Alexandra Rasiuk's MSc thesis defense

- 2015/8 Chair of MSc examination committee, University of Guelph
Number of Mentorees: 1
August 18, 2015: Chaired James Ackford's MSc thesis defense
- 2015/4 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
April 27, 2015: Jegarubee Bavananthasivam's PhD qualifying examination
- 2015/2 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
February 18, 2015: Marianne Wilcox's PhD qualifying examination
- 2014/8 MSc examination committee member, University of Guelph
Number of Mentorees: 1
August 13, 2014: Served on the examination committee for Zafir Syed's MSc thesis defence
- 2014/8 MSc examination committee member, University of Guelph
Number of Mentorees: 1
August 12, 2014: Served on the examination committee for Christian Ternamian's MSc thesis defence
- 2014/6 Chair of MSc examination committee, University of Guelph
Number of Mentorees: 1
June 10, 2014: Chaired Kelly Fleming's MSc thesis defence
- 2014/1 PhD final examination committee member, University of Guelph
Number of Mentorees: 1
January 3, 2014: Scott Walsh's PhD defense
- 2013/12 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
December 16, 2013: Lisa Santry's PhD qualifying examination
- 2013/12 PhD qualifying examination committee member, University of Guelph
Number of Mentorees: 1
December 11, 2013: Shirene Singh's PhD qualifying examination
- 2013/11 Chair of MSc examination committee, University of Guelph
Number of Mentorees: 1
November 19, 2013: Chaired Shaun Kernaghan's MSc thesis defense
- 2013/6 MSc examination committee member, University of Guelph
Number of Mentorees: 1
June 14, 2013: Ian Villanueva's MSc thesis defense
- 2012/9 MSc examination committee member, University of Guelph
Number of Mentorees: 1
September 5, 2012: Sonja Zours' MSc thesis defense
- 2012/7 Chair of MSc examination committee, University of Guelph
Number of Mentorees: 1
July 20, 2012: Chaired Inas Elawadli's MSc thesis defense
- 2012/5 PhD qualification examination committee member, University of Guelph
Number of Mentorees: 1
May 7, 2012: Li Deng's PhD qualification examination
- 2012/4 Chair of MSc examination committee, University of Guelph
Number of Mentorees: 1
April 19, 2012: Chaired Iman Mehdizadeh Gohari's MSc thesis defense

Organizational Review Activities

2020/8	Reviewer, Canadian Institutes of Health Research Served on the Cancer Biology and Therapeutics grant review panel
2020/5	Reviewer, Cancer Research Society Served on grant review panel C2 - Tumour suppressor genes, oncogenes and DNA repair
2019/10	Reviewer, Canadian Foundation for Innovation Served on an expert committee to review an application to the John R. Evans Leaders Fund
2018/10	Reviewer, Canadian Institutes of Health Research Started a three-year term serving on the Virology and Viral Pathogenesis grant review panel
2014/6	Reviewer, Canadian Cancer Society Research Institute Served on grant review panel I3 - Immunology Signalling and Stem Cells
2020/6 - 2020/7	Reviewer, Swiss National Science Foundation Spark Grant
2019/12 - 2020/1	Reviewer, Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant
2019/12 - 2019/12	Reviewer, New Foundations in Research Fund Reviewed an Exploration Grant
2019/9 - 2019/10	Reviewer, Prostate Cancer UK Reviewed a grant application.
2018/8 - 2018/9	Reviewer, Mitacs Accelerate Reviewed one grant application.
2017/12 - 2018/1	Reviewer, Student Scinapse Competition Reviewed 7 applications.
2017/9 - 2017/10	Reviewer, Breast Cancer Now_UK Reviewed a grant application.
2017/3 - 2017/4	Reviewer, Graduate Women in Science Fellowship Reviewed one application.
2016/12 - 2017/1	Reviewer, Student Scinapse Competition Reviewed 10 applications.
2016/11 - 2016/12	Reviewer, Mitacs Accelerate Reviewed one grant application.
2015/11 - 2015/11	Reviewer, Natural Sciences and Engineering Research Council of Canada (NSERC) Collaborative Health Research Program
2014/12 - 2015/1	Reviewer, Natural Sciences and Engineering Research Council of Canada (NSERC) Served as an external reviewer for a NSERC Discovery Grant application
2014/4 - 2014/5	Reviewer, Croatian Science Foundation Reviewed a grant application.

Community and Volunteer Activities

- 2015/1 Member of the Animal Isolation Unit Advisory Committee, University of Guelph
To provide advice from the perspective of a researcher to Campus Animal Facilities in an effort to balance the needs of technicians, the administration and those conducting animal research at biosafety level 2.
- 2014/12 Volunteer Fundraiser, University of Guelph
Assisting fundraising efforts for the Global Vets program by auctioning an immunology review session (2014) and a faculty-student hockey game (2015).
- 2014/5 Volunteer Interviewer, University of Guelph
Conducting annual entrance interviews for the Doctor of Veterinary Medicine program.
- 2014/2 Member of the Dept. of Pathobiology Research Committee, University of Guelph
Deliberate on departmental research-related issues and provide recommendations to the department. Keep track of departmental equipment. Coordinate equipment grant applications.
- 2013/2 Member of the Dept. of Pathobiology Seminar Committee, University of Guelph
Organize and run the Dept. of Pathobiology's annual seminar series, which runs from September to April. Host visiting speakers. Also organize and run an annual 3-minute thesis competition for trainees. I chaired this committee Sept. 2015-Aug. 2016
- 2013/2 Member of the Dept. of Pathobiology Awards Committee, University of Guelph
Review and rank all award applications submitted in the Department of Pathobiology.
- 2013/1 Scientific Reviewer of Animal Utilization Protocols, University of Guelph
Review the scientific content of applications for animal utilization protocols for the Animal Care Committee.
- 2012/11 Volunteer Judge, University of Guelph
Annual poster judging for the Graduate Student Research Symposium (showcases graduate student research projects).
- 2012/8 volunteer judge, University of Guelph
Annual poster judging for the Career Opportunities and Research Experience Program (formerly called "Summer Leadership and Research Program"; showcases summer student research projects).
- 2012/2 Co-Manager of the University of Guelph Core Flow Cytometry Facility, University of Guelph
Manage the core flow cytometry facility at the University of Guelph in conjunction with one other faculty member.
- 2011/10 Scientific Reviewer, Various scientific journals
Review manuscripts submitted to the following journals: Molecular Therapy PLOS ONE Journal of Vaccines and Immunization Canadian Veterinary Journal Clinical Medicine Insights Oncology Canadian Journal of Veterinary Research Journal of Visualized Experimentation Reviews in Medical Virology Viruses
- 1997/1 Member, Canadian Society for Immunology
A registered member of the Canadian Society for Immunology
- 2016/3 - 2016/3 volunteer judge, University of Guelph
Judged student-run exhibits that are open to the public at the Ontario Veterinary College.
- 2014/4 - 2016/1 Grant Review Panel Member, Prostate Cancer Canada
I served on Panel C "Experimental Therapeutics"

- 2015/2 - 2015/3 Scientific Reviewer, Oxford University Press
Reviewed Chapter 12: Tumor Immunology and Immunotherapy from the textbook "Molecular Biology of Cancer, fourth edition" by Pecorino.
- 2015/1 - 2015/2 Scientific Reviewer, Natural Sciences and Engineering Research Council of Canada (NSERC)
Discovery Grant review
- 2014/5 - 2014/6 Scientific Reviewer, Croatian Science Foundation
Grant review
- 2010/9 - 2014/5 Assistant Coach, Stanley Stick Hockey Association, Guelph, Ontario
Serve as a volunteer for this not-for-profit hockey association. Assist with coaching a boys hockey team. Learn to skate program: 2010-11 Novice division: 2011-2014
- 2003/9 - 2012/4 Organizer, Men's recreational hockey group, Guelph, Ontario
Managed a men's recreational hockey group.

Knowledge and Technology Translation

- 2014/1 Co-Investigator, Technology Transfer and Commercialization Group/Organization/Business Serviced: University of Guelph
Target Stakeholder: General Public
Outcome / Deliverable: Submitted an invention disclosure form: Avian orthoreovirus (ARV) strain PB1: a potential oncolytic, vaccine and adjuvant
Activity Description: Invention disclosure to the University of Guelph Catalyst Centre: "Avian orthoreovirus (ARV) strain PB1: a potential oncolytic, vaccine and adjuvant"
- 2011/3 Co-investigator, Technology Transfer and Commercialization Group/Organization/Business Serviced: McMaster University, Hamilton, Ontario
Target Stakeholder: General Public
Outcome / Deliverable: Patent
Evidence of Uptake/Impact: Used as part of the intellectual property to establish a new biotechnology company called "Turnstone Biologics"
References / Citations / Web Sites: <http://www.turnstonebio.com/> <http://www.google.com/patents/WO2012122629A1?cl=en>
Activity Description: Bridle BW, Bell JC, Diallo JS, Lemay C, Lichty BD, Wan Y "Vaccination and HDAC inhibition" Provisional Patent 61/451,794 filed March 11, 2011, PCT Patent Application No. PCT/CA2012/000212 national phase filings in Europe, North America, China, and Japan underway
- 2011/2 Co-Investigator, Technology Transfer and Commercialization Group/Organization/Business Serviced: McMaster University, Hamilton, Ontario
Target Stakeholder: General Public
Outcome / Deliverable: Patent
Evidence of Uptake/Impact: Used as part of the intellectual property to establish a new biotechnology company called "Turnstone Biologics"
References / Citations / Web Sites: <http://www.turnstonebio.com/>
Activity Description: Bridle BQ, Lichty BD, Wan Y "Vaccination method utilizing follicular B cells" Provisional patent 61/446,248 (filed February 24, 2011)

- 2009/3 Co-Investigator, Technology Transfer and Commercialization
 Group/Organization/Business Served: McMaster University, Hamilton, Ontario
 Target Stakeholder: General Public
 Outcome / Deliverable: Patent
 Evidence of Uptake/Impact: Used as part of the intellectual property to establish a new biotechnology company called "Turnstone Biologics"
 References / Citations / Web Sites: <http://www.turnstonebio.com/> <http://www.google.com/patents/WO2010105347A1?cl=en>
 Activity Description: Bridle BW, Bramson J, Lichty BD, Wan Y "Vaccination Methods" PCT Patent application No. PCT/CA2010/000379 (PCT filed March 16, 2010) national phase filings in Europe, North America, and China underway
- 2019/9 - 2030/7 Co-Founder, Involvement in/Creation of Start-up
 Group/Organization/Business Served: IHN Pharma, Inc.
 Target Stakeholder: Patients
 Outcome / Deliverable: Novel biotherapies for the treatment of cancers.
 Evidence of Uptake/Impact: This company is in the start-up phase.
 Activity Description: Along with six collaborators, we are establishing a start-up biotechnology company called "INH Pharma, Inc." to leverage intellectual properties related to proprietary oncolytic viruses.

Committee Memberships

- 2019/8 Committee Member, Chair search committee, University of Guelph
 To recruit and hire a new Chair for the Department of Pathobiology
- 2019/6 Committee Member, Faculty Search Committee, University of Guelph
 To hire a new virologist for a tenure-track faculty position in the Department of Pathobiology
- 2018/9 Committee Member, Virology and Viral Pathogenesis Grant Review Panel, Canadian Institutes of Health Research
 Review and rank grant proposals.
- 2017/12 Chair, Department of Pathobiology Awards Committee, University of Guelph
 Review and rank applications for academic awards.
- 2017/12 Committee Member, Ontario Veterinary College Graduate Awards Committee, University of Guelph
 Review and rank award applications from graduate students at the college level.
- 2017/12 Committee Member, Scientific Review Committee for the Pet Trust Foundation, University of Guelph
 Review and rank applications to the Pet Trust Foundation's bi-annual operating grant competitions.
- 2017/12 Committee Member, Ontario Veterinary College Undergraduate Awards Committee, University of Guelph
 Review and rank award applications from students in the Doctor of Veterinary Medicine and other undergraduate programs within the Ontario Veterinary College.
- 2016/7 Committee Member, Department of Pathobiology Seminar Series Committee, University of Guelph
 Help schedule a weekly seminar series that spans the Fall and Winter semesters. Host external speakers.

- 2014/12 Co-chair, Ad hoc committee to manage the University of Guelph's flow cytometry facility., University of Guelph
Co-management of institutional core flow cytometry facility (two high-throughput analytical flow cytometers, plus one flow sorter). Other co-managers: Dorothee Bienzle and Brandon Plattner.
- 2014/9 Ex-Officio, Scientific Reviewer for Animal Care Committee, University of Guelph
Provide expert scientific reviews of animal utilization protocols that have been submitted to the institutional animal care committee.
- 2014/1 Committee Member, Department of Pathobiology Research Committee, University of Guelph
Identify, review and make recommendations related to departmental research issues.
- 2020/7 - 2020/8 Committee Member, Cancer Biology and Therapeutics Grant Review Panel, Canadian Institutes of Health Research
Review and rank grant applications.
- 2020/6 - 2020/7 Chair, PhD Qualifying Examination Committee, University of Guelph
Examinee: Melanie Iverson
- 2020/5 - 2020/6 Committee Member, PhD Qualifying Examination Committee, University of Guelph
Examinee: Ran Xu
- 2020/4 - 2020/5 Committee Member, PhD Thesis Examination Committee, University of Guelph
Examinee: Robert Mould
- 2020/4 - 2020/5 Committee Member, MSc Thesis Examination Committee, University of Guelph
Examinee: Elana Raaphorst
- 2020/3 - 2020/5 Committee Member, PhD Qualifying Examination Committee, University of Guelph
Examinee: Sugandha Raj
- 2019/12 - 2020/1 Committee Member, PhD Thesis Examination Committee, University of Guelph
Examinee: Maedeh Darzianiazizi
- 2019/11 - 2019/12 Chair, PhD Qualifying Examination Committee, University of Guelph
Examinee: Ayumi Matsuyama
- 2019/7 - 2019/8 Committee Member, Expert Review Committee, Canadian Foundation for Innovation
To review a grant application for funding from the John R. Evans Leaders Fund
- 2019/6 - 2019/7 Committee Member, Technician search committee., University of Guelph
To recruit and hire a new technician for the Department of Pathobiology
- 2019/3 - 2019/5 Committee Member, PhD Qualifying Examination Committee, University of Guelph
Examinee: Seyed Hossein Karimi
- 2019/3 - 2019/4 Committee Member, Thesis Examination Committee, University of Guelph
Examinee: Kristen Lamers (MSc)
- 2019/3 - 2019/4 Chair, Thesis Examination Committee, University of Guelph
Examinee: Megan Neely (MSc)
- 2019/3 - 2019/4 Committee Member, MSc Thesis Examination Committee, University of Guelph
Examinee: Kristen Lamers
- 2019/2 - 2019/4 Chair, PhD Qualifying Examination Committee, University of Guelph
Examinee: Gary Lee
- 2019/1 - 2019/2 Committee Member, Thesis Examination, Tyndale College and Theological Seminary
Examinee: Jeffrey Roy (DMin)

2018/11 - 2019/1	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Karen Carlton
2018/11 - 2018/12	Committee Member, Thesis Examination Committee, University of Western Ontario Examinee: Corby Fink (PhD)
2018/10 - 2018/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Thomas McAusland
2018/9 - 2018/11	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Ashley Ross
2018/7 - 2018/9	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Maedeh Darzianiazizi
2018/4 - 2018/6	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Laura van Lieshout
2018/3 - 2018/4	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Jegarubee Bavananthasivam (PhD)
2017/12 - 2018/1	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Megan Strachan-Whaley (PhD)
2017/12 - 2018/1	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Lisa Santry (PhD)
2017/11 - 2018/1	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Nadiyah Alqazlan
2017/10 - 2017/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Benoit Cuq
2012/5 - 2017/11	Committee Member, Department of Pathobiology Awards Committee, University of Guelph Review and rank applications for academic awards.
2017/7 - 2017/9	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Carina Cooper
2017/6 - 2017/8	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Amanda AuYeung (MSc)
2016/4 - 2017/4	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Megan Stachan-Whaley (written and oral portions of exam were separated due to a maternity leave).
2017/1 - 2017/3	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Jacob van Vloten
2016/12 - 2017/1	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Neda Barjesteh (PhD)
2016/12 - 2017/1	Committee Member, Thesis Examination Committee, University of Toronto Examinee: Tiffany Ho (MSc)
2016/10 - 2016/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Peyman Asadian
2014/1 - 2016/12	Committee Member, Prostate Cancer Canada - Panel C - Experimental Therapeutics Grant Review Panel, Prostate Cancer Canada Review grants submitted to the "Experimental Therapeutics" panel and make recommendations for funding.
2016/6 - 2016/8	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Kathy Matuszewska

2016/4 - 2016/6	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Seyedmehdi Emam
2015/8 - 2016/6	Chair, Department of Pathobiology Seminar Series Committee, University of Guelph Help schedule a weekly seminar series that spans the Fall and Winter semesters. Host external speakers.
2016/4 - 2016/5	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Shirene Singh (PhD)
2016/2 - 2016/4	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Alexander Bekele-Yitbarek
2015/8 - 2015/9	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Alexandra Rasiuk (MSc)
2015/6 - 2015/8	Chair, Thesis Examination Committee, University of Guelph Examinee: James Ackford (MSc)
2013/6 - 2015/8	Committee Member, Department of Pathobiology Seminar Series Committee, University of Guelph Help schedule a weekly seminar series that spans the Fall and Winter semesters. Host external speakers.
2015/5 - 2015/5	Committee Member, Doctor of Veterinary Medicine Admissions Interview Committee, University of Guelph Interviewed and ranked applicants to the Doctor of Veterinary Medicine program.
2015/2 - 2015/4	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Jegarubee Bavananthasivam
2014/12 - 2015/2	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Marianne Wilcox
2014/7 - 2014/8	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Christian Ternamian (MSc)
2014/7 - 2014/8	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Zafir Syed (MSc)
2014/5 - 2014/6	Chair, Thesis Examination Committee, University of Guelph Examinee: Kelly Fleming (MSc)
2013/12 - 2014/1	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Scott Walsh (PhD)
2013/12 - 2013/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Shirene Singh
2013/10 - 2013/12	Committee Member, PhD Qualifying Examination Committee, University of Guelph Examinee: Lisa Santry
2013/10 - 2013/11	Chair, Thesis Examination Committee, University of Guelph Examinee: Shaun Kernaghan (MSc)
2013/5 - 2013/6	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Ian Villanueva (MSc)
2012/8 - 2012/9	Committee Member, Thesis Examination Committee, University of Guelph Examinee: Sonja Zours (MSc)
2012/6 - 2012/7	Chair, Thesis Examination Committee, University of Guelph Examinee: Inas Elawadli (MSc)

- 2012/3 - 2012/5 Committee Member, PhD Qualifying Examination Committee, University of Guelph
Examinee: Li Deng
- 2012/3 - 2012/4 Chair, Thesis Examination Committee, University of Guelph
Examinee: Iman Mehdizadeh Gohari (MSc)

Other Memberships

- 2020/6 Member, One Health Institute University of Guelph
Within One Health, University of Guelph researchers work across disciplines and sectors to interrogate the biological and social factors that impinge on the health of organisms, from the level of molecules to that of ecosystems, with unique strengths in comparative medicine. This research also explores how these factors are shaped by environmental parameters, such as climate change, ultimately informing public health and environmental health practice and policy.
- 2017/6 Member Scientist, Dog Osteosarcoma Group: Biomarkers Of Neoplasia (DOG BONE)
This groups consists of eight faculty members from the Ontario Veterinary College, University of Guelph, who share a vision for collaborative research to advance our understanding of canine osteosarcomas, how to predict clinical outcomes and to develop novel therapies. The group includes two veterinary oncologists, two veterinary surgical oncologists, a statistician, a veterinary pathologist, an immunologist and a cancer biologist.
- 2016/9 Member, European Academy for Tumor Immunology
I was invited to be a member of this international organization that is based in Europe. The purpose is to promote international collaborations and unify research in the area of immunotherapies for cancers.
- 2015/4 Member Scientist, Canadian Oncolytic Virus Consortium (COVCo)
COVCo is a pan-Canadian network of fifteen clinical and basic scientists dedicated to developing and advancing the oncolytic virus platform as a targeted and revolutionary approach to cancer therapeutics. Our common vision is that an iterative cycle of discovery and clinical testing is the fastest and most effective way to develop new biological therapeutics. We are funded by the Terry Fox Research Institute (Program Project Grant).
- 2014/12 Member scientist, National Centre of Excellence in Biotherapeutics for Cancer Treatment (BioCanRx)
Total funding: \$60 million (\$25 million from the federal government + \$35 million from partners) over 5 years. Total # of researchers across Canada: 42 (representing 17 academic institutions). Also supported by: 8 private sector and 19 community partners. Scientific Director: Dr. John Bell, Ottawa Hospital Research Institute. I am one of the 42 founding members.
- 2012/1 Member, Institute for Comparative Cancer Investigation, University of Guelph
The Institute for Comparative Cancer Investigation at the University of Guelph facilitates translational oncology research in companion animals at the OVC Mona Campbell Centre for Animal Cancer by managing clinical trials and the Companion Animal Tumour Sample Bank. Our goals: to advance the understanding of cancer and improve treatment options to benefit both companion animal and human cancer patients.
- 2001/3 Member, Canadian Society for Immunology
The mandate of the Canadian Society for Immunology is to foster and support Immunology research and education throughout Canada

Most Significant Contributions

Using epigenetic modification to enhance oncolytic booster vaccine while abrogating autoimmune pathology

I discovered that an immunosuppressive histone deacetylase inhibitor (entinostat) could enhance oncolytic booster vaccines (Bridle BW et al. Molecular Therapy 2013 Apr;21(4):887-94). Regulatory T cells could be transiently suppressed with simultaneous up-regulation of major histocompatibility complex expression on tumour cells (making them more visible targets) and concomitant prolongation of viral oncolysis, resulting in more efficacious tumour-specific T cell responses. Importantly, the vitiligo normally associated with melanoma immunotherapy was abrogated. This was a novel strategy for separating anti-tumour autoimmunity from autoimmune pathology and was the first time anyone demonstrated the ability to dramatically improve anti-melanoma efficacy while simultaneously suppressing vitiligo; something the literature suggested could not be done. This garnered a patent and receipt of substantial research funding. This research is now being applied to leukemias.

Knowledge translation during the COVID-19 pandemic: Providing fact-based answers to the lay public, policy makers and courts of law

Beginning in May 2019 I began disseminating information about immunological concepts relevant to COVID-19. I have authored nine lay articles, served on two discussion panels, was a keynote speaker at five events (two were international conferences), I gave seven television interviews (three were for national news, including W5 and Global National News), I was interviewed for 35 newspaper/magazine articles (including National Geographic, The Globe and Mail, Toronto Star and Toronto Sun), I conducted 55 radio interviews spanning almost every province and one territory and included international interviews in New Zealand and Scotland, and I was asked to serve as an expert witness for two lawsuits related to COVID-19 (one in Calgary and one in the Ontario Superior Court of Justice).

From bench to bedside in five years: Synergizing oncolytic virotherapy with cancer immunotherapy

In 2010 I led a team that described a unique approach to synergize cancer immunotherapy with oncolytic virotherapy (Bridle BW, et al. Molecular Therapy 2010 Aug; 18(8):1430-9). This was accomplished using an oncolytic virus to boost pre-existing tumour-specific immune responses. The prevailing wisdom in the field was that immunotherapy and oncolytic virotherapy could not be effectively combined. However, I was able to prove this wrong and an optimized version of this therapy entered a phase I/II human clinical trial in January 2015, followed by three more clinical trials. This rapid progression from bench to bedside was facilitated by extensive collaborations, including the Terry Fox Foundation-funded Canadian Oncolytic Virus Consortium, of which I am a member. This also resulted in a patent application (I have 40% inventorship) that formed foundational intellectual property used to establish a biotechnology company (Turnstone Biologics).

Presentations

1. SIERRA VANDERKAMP, ASHLEY A. STEGELMEIER, Byram W. Bridle (Dr. Bridle's trainees capitalized). (2021). In Vitro Analysis of Oxidative Stress on Off-Target Infection of Activated T Cells by Oncolytic Vesicular Stomatitis Virus. Annual Meeting of the Canadian Society for Immunology (virtual) (poster), Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No

2. LILY CHAN, Sarah K. Wootton, Byram W. Bridle* and KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's HQP capitalized). (2021). Following Administration of Dendritic Cell-Based Vaccines There is an Increase in Type 2 Innate Lymphoid Cells in the Local Draining Lymph Node and Spleen. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
3. J Yates, R MOULD, L CHAN, J KNAPP, Y MEHRANI, Y Pei, P Pham, A Leacy, L Santry, BA McBey, P Major, Byram W. Bridle*, L Susta*, S Wootton* (*equal senior authors) (Dr. Bridle's HQP capitalized). (2021). Recombinant avian orthoavulavirus-1 engineered to express variants of the SARS-CoV-2 Spike Protein induces mucosal and systemic immune responses. American Society for Gene and Cell Therapy Annual Meeting 2021 (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
4. JASON P. KNAPP, JACOB P. VAN VLOTEN, Lisa A. Santry, Jacob Yates, JESSICA A. MINOTT, Sarah K. Wootton, and Byram W. Bridle (Dr. Bridle's trainees capitalized). (2021). Differential Susceptibility of Viral-Vectored Vaccines to Temperatures Over 37oC. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
5. JULIA E. KAKISH, JASON P. KNAPP, ARTHANE KODEESWARAN, KATRINA GERONIMO, MARY ELLEN CLARK, and Byram W. Bridle (Dr. Bridle's trainees capitalized). (2021). Investigating the Effect of Low Anatomical Temperatures on Rhabdoviruses. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
6. YEGANEH MEHRANI, LILY CHAN, ASHLEY A. STEGELMEIER, Byram W. Bridle*, KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's HQP capitalized). (2021). Antiviral Cytokine Responses in Murine Bone-Marrow-Derived Mast Cells: Disruption of Type I Interferon Signaling and Elevation of Inflammatory Cytokines. American Society for Virology Annual Scientific Meeting (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
7. ASHLEY A. STEGELMEIER, Kevin Stinson, Sarah K. Wootton, Byram W. Bridle (Dr. Bridle's trainee capitalized). (2021). Characterizing Cytokine, Chemokine, and Acute-Phase Protein Profiles of Plasma Samples Derived from Patients that Tested Positive for COVID-19. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
8. Kathy Matuszewska, Simone Ten Kortenaar, Madison Pereira, Duncan Petrik, Leslie Ogilvie, Pierre P. Major, Jack Lawler, Sarah K. Wootton, Byram W. Bridle, Jeremy Simpson, Jim Petrik. (2021). Fc3TSR Normalizes the Tumor Microenvironment and Improves Treatment Delivery in an Orthotopic, Syngeneic Mouse Model of Epithelial Ovarian Cancer. Canadian Conference on Ovarian Cancer Research (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
9. (2021). Answers to Outstanding Questions About COVID-19 Vaccines Will Dictate the Success or Failure of the Rollout. Second International COVID-19 Symposium, New Zealand
Main Audience: General Public
Invited?: Yes, Keynote?: Yes

10. ASHLEY STEGELMEIER, KIERSTEN HANADA, KHALIL KARIMI, Sarah Wootton, Byram Bridle (Dr. Bridle's HQP capitalized). (2021). Developing a Murine Cytokine Storm Model with IFNAR-Knockout Mice to Rapidly Test SARS-CoV-2 Immunotherapies. American Society for Virology Annual Scientific Meeting (virtual) (oral presentation),
Invited?: Yes, Keynote?: No, Competitive?: Yes
11. Amira Rghei, Laura van Lieshout, Benjamin McLeod, Yanlong Pei, Hugues Faust, Gary Kobinger, Brad Thompson, KHALIL KARIMI, Byram W. Bridle, Leonardo Susta, Sarah Wootton (Dr. Bridle's HQP capitalized). (2021). Vectorized Expression of SARS-CoV-2-Specific Human Antibodies in Mice and Sheep is Feasible and Well-Tolerated. American Society for Gene and Cell Therapy Annual Meeting 2021 (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
12. YEGANEH MEHRANI, LILY CHAN, ASHLEY A. STEGELMEIER, Byram W. Bridle*, KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's trainees capitalized). (2021). Excessive Antiviral Cytokine Responses in Adoptively Transferred Mast Cells: Disruption of Type I Interferon Signaling Elevates Inflammatory Cytokines. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
13. JESSICA A. MINOTT, JACOB P. VAN VLOTEN, LILY CHAN, YEGANEH MEHRANI, Sarah K. Wootton*, Byram W. Bridle* and KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's trainees capitalized). (2021). Investigating the Role of Neutrophils in Oncolytic Orf Virus-Activated Anti-Tumour Immunity in a Pre-Clinical Murine Model of Melanoma. Annual Meeting of the Canadian Society for Immunology (virtual) (poster),
Invited?: No, Keynote?: No, Competitive?: No
14. LILY CHAN, ASHLEY STEGELMEIER, Sarah K. Wootton, Byram W. Bridle* and KHALIL KARIMI* (*equal senior authors) (Dr. Bridle's HQP capitalized). (2021). The Tolerogenic Potential of Dendritic Cells Infected with an Adeno-Associated Virus Gene Therapy Vector. American Society for Virology Annual Scientific Meeting (virtual) (poster),
Main Audience: Researcher
Invited?: No, Keynote?: No, Competitive?: No
15. (2021). Answers to Outstanding Questions About COVID-19 Vaccines Will Dictate the Success or Failure of the Rollout. COVID-19 Panel Discussion: A Vaccine Recovery Hosted by the Infectious Disease Working Group, University of Toronto, Canada
Main Audience: General Public
Invited?: Yes, Keynote?: Yes
16. (2020). Tumour Microenvironmental Barriers to Successful Oncolytic Virotherapy. McMaster Immunology Research Centre Seminar Series, McMaster University, Hamilton, Ontario, January 15, 2020, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: Yes
17. (2020). COVID-19: Realistic Timelines for Vaccine Development. Kitchener Public Library: Science Literacy Week (Webinar), Canada
Main Audience: General Public
Invited?: Yes, Keynote?: Yes
18. (2020). Kitchener Public Library: Science Literacy Week. Biology and Control of SARS-CoV-2 (Webinar), Canada
Main Audience: General Public
Invited?: Yes, Keynote?: No

19. Cristine J. Reitz, Faisal J. Alibhai, Tarak N. Khatua, Mina Rasouli, Byram W. Bridle, Thomas P. Burris, Tami A. Martino. (2020). Circadian Medicine to Treat Myocardial Infarction (Heart Attack): Targeting the Cardiac NLRP3 Inflammasome (poster). Society for Research on Biological Rhythms (SRBR) 2020 Virtual Conference, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No
20. (2020). COVID-19 Vaccines: Facts to Inform Policies. New Zealand COVID-19 Science and Policy Symposium Webinar, New Zealand
Main Audience: Decision Maker
Invited?: Yes, Keynote?: Yes
21. Kiersten Hanada, Ashley Stegelmeier, Lily Chan, Yeganeh Mehrani & Byram Bridle. (2020). Calming the COVID-19 Storm: Developing a Model to Study Toxic Cytokine Responses to Viruses (poster; won 1st place). Ontario Veterinary College Summer Career Opportunities and Research Exploration Program, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
22. Ashley Stegelmeier, Kiersten Hanada, Khalil Karimi, Sarah Wootton, Byram Bridle. (2020). Developing a Murine Cytokine Storm Model with IFNAR-Knockout Mice to Rapidly Test SARS-CoV-2 Immunotherapies (oral presentation; won 1st place out of 40 presentations). University of Guelph Graduate Association On-Line Research Conference, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
23. Ashley A. Stegelmeier, Amanda W.K. AuYeung, Robert Mould, Thomas McAusland, Lisa Santry, Jacob van Vloten, Megan Strachan-Whaley, Elaine Klafuric, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). Off-Target Infection of Stimulated T Cells by Vesicular Stomatitis Virus has Implications for Single-Versus Multi-Dosing Oncolytic Virotherapy Protocols (poster and 'speed-talk' oral presentation). Annual Scientific Meeting of the Canadian Cancer Immunotherapy Consortium, Toronto, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
24. (2019). Graduate Studies in the Department of Pathobiology (oral presentation as part of a panel discussion). Career Opportunities and Research Experience Summer Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No
25. Lily Chan, Robert Mould, Sarah K. Wootton, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2019). Dendritic Cell Vaccines Provoke an Increase in the Number of Interleukin-22-Producing Type 3 Innate Lymphoid Cells in the Local Draining Lymph Nodes and in The Spleen (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
26. Jacob van Vloten, Sarah K. Wootton* and Byram W. Bridle* (*co-equal senior authors). (2019). Quantifying T-Cell and Antibody Responses Induced by Antigen-Agnostic Immunotherapies (oral presentation). Ontario Veterinary College Graduate Student Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
27. (2019). Developing Novel Cancer Biotherapies (oral presentation). Canadian Cancer Society Relay for Life, Guelph, Canada
Main Audience: General Public
Invited?: Yes, Keynote?: Yes

28. Ashley A. Ross, Amanda W.K. AuYeung, Robert Mould, Thomas McAusland, Lisa Santry, Jacob van Vloten, Megan Whaley, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). Off-Target Infection of Stimulated T Cells by Vesicular Stomatitis Virus Has Implications for Single- Versus Multi-Dosing Oncolytic Virotherapy Protocols (oral presentation). Ontario Veterinary College Graduate Student Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
29. Jacob P. van Vloten, Joelle C. Ingraio, Robert C. Mould, Lisa A. Santry, Khalil Karimi, D. Grant McFadden, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). An OrfV-Infected Cell Vaccine Induces Innate and Adaptive Immune Responses Against Osteosarcoma Metastases Resulting in Long-Term Survival. Annual Scientific Meeting of the Canadian Cancer Immunotherapy Consortium (poster and 'speed talk' oral presentation), Toronto, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
30. E Klafuric, M Strachan-Whaley, L Santry, A AuYeung, J van Vloten, R Mould, T McAusland, ME Clark, J Minott, S Holtz, J Saturno, K Karimi, A Mutsaers, S Wootton and Byram W. Bridle. (2019). Combining Decitabine with Oncolytic Virotherapy Preferentially Kills Acute Leukemia Cells Via Lethal Oxidative Stress (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
31. Maedeh Darzianiazizi (Mahi Azizi), Jacob Van Vloten, Shayan Sharif, Ravi Kulkarni, Byram W. Bridle*, Khalil Karimi* (*co-equal senior authors). (2019). Differential Sex-Mediated Hepatotoxicity Caused by a Viral Infection with a Concomitant Defect in Type I Interferon Signaling (oral presentation). Ontario Veterinary College Graduate Student Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
32. Robert Mould, Jacob van Vloten, Ashley Ross, Mankerat Singh, Anthony Mutsaers, James Petrik, Leonardo Susta, Geoffrey Wood, Sarah Wootton, Byram W. Bridle*, Khalil Karimi* (*co-equal senior authors). (2019). The Functional Utility Of A Unique Subset Of Bone Marrow-Derived Dendritic Cells For Cancer Vaccines (poster presentation). Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
33. Robert Mould, J. van Vloten, C. Fink, A. Ross, M. Singh, L. Susta, A. Mutsaers, J. Petrik, G. Wood, S. Wootton, G. Dekaban, Byram W. Bridle*, Khalil Karimi* (*co-equal senior authors). (2019). IL-12-secreting Dendritic Cells That Do Not Produce TNF- α Are A Minor Component Of 'Dendritic Cell Cultures' But The Dominant Antigen Presenters (poster presentation). Ontario Veterinary College Graduate Student Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
34. Elaine Klafuric, Megan Strachan-Whaley, Lisa Santry, Amanda AuYeung, Jacob van Vloten, Robert Mould, Thomas McAusland, Khalil Karimi, Anthony Mutsaers, Sarah Wootton and Byram W. Bridle. (2019). Combining Decitabine with Oncolytic Virotherapy Preferentially Kills Acute Myeloid Leukemia Cells Via Lethal Oxidative Stress (oral presentation). Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

35. Jacob P. van Vloten, Joelle C. Ingraio, Robert C. Mould, Lisa A. Santry, Khalil Karimi, D. Grant McFadden, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). An ORF Virus-Infected Cell Vaccine Induces Innate and Adaptive Immune Responses Against Osteosarcoma Metastases Resulting in Long-Term Survival (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
36. Rghei, AD, Lieshout, LV, Shihua, H, Soule, G, Bridle, BW, Qui, X, and Wootton, SK. (2019). AAV-Mediated Expression of Monoclonal Antibodies for the Prevention of Marburg Virus Infection (poster). Annual Meeting of the American Society of Gene and Cell Therapy, Washington DC, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No
37. Robert Mould, J van Vloten, C Fink, L Chan, A Stegelmeier, M Singh, L Susta, A Mutsaers, J Petrik, G Wood, S Wootton, G Dekaban, Byram W. Bridle* and Khalil Karimi* (*co-equal senior authors). (2019). IL-12-secreting Dendritic Cells That Do Not Produce TNF- α Are A Minor Component Of 'Dendritic Cell Cultures' But The Dominant Antigen Presenters. Annual Scientific Meeting of the Canadian Cancer Immunotherapy Consortium (poster and 'speed talk' oral presentation), Toronto, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
38. Jason P. Knapp, Megan R. Strachan-Whaley, Elaine M. Klafuric and Byram W. Bridle. (2019). Combining Epigenetic Modifiers and Oncolytic Viruses to Treat Acute Leukemias throughout the Central Nervous System (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
39. Cristine J. Reitz, Faisal J. Alibhai, Tarak N. Khatua, Mina Rasouli, Byram W. Bridle, Thomas P. Burriss and Tami A. Martino. (2019). Circadian Medicine: Targeting the Cardiac Inflammasome to Prevent Heart Failure. 2nd Southern Ontario Cardiovascular Research Association Annual Conference, York University, October 18, 2019, Toronto, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
40. Ashley A. Stegelmeier and Byram W. Bridle. (2019). Off-Target Infection of Stimulated T Cells by Vesicular Stomatitis Virus has Implications for Single- Versus Multi-Dosing Oncolytic Virotherapy Protocols. Annual Inter-Lab Retreat for the Canadian Oncolytic Virus Consortium, Elgin, Ontario, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
41. Thomas McAusland, Jacob van Vloten, Lisa Santry, Joelle Ingraio, Matthew Guilleman, Rozanne Arulanandam, Pierre Major, Jean-Simon Diallo, Leonardo Susta, Khalil Karimi, Byram W. Bridle, Sarah Wootton. (2019). Viral Sensitizer-Mediated Enhancement of Oncolytic NDV Leads to Rapid Clearance of Primary Tumours in a Mouse Model of Melanoma (poster and oral presentations). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
42. Alicia Vilorio-Petit, Geoffrey Wood, Anthony Mutsaers, Michelle Oblak, Brigitte Brisson, Byram Bridle, Paul Woods and David Pearl. (2019). DOGBONE: A Canine Research Platform for the Discovery of Reliable Biomarkers of Osteosarcoma Progression. Canadian Society for Molecular Biosciences, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

43. J Vloten, K Matuszewska, A Stegelmeier, L Santry, J Minott, T McAusland, E Klafuric, R Mould, K Karimi, G McFadden, J. Petrik, Byram W. Bridle*, and Sarah K. Wootton* *equal senior authors. (2019). ORF Virus as an Immunotherapy for Advanced-Stage Ovarian Cancers (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
44. Ashley A. Stegelmeier, Amanda W.K. AuYeung, Robert Mould, Thomas McAusland, Lisa Santry, Jacob van Vloten, Megan Whaley, Elaine Klafuric, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). Off-Target Infection of Stimulated T Cells by Vesicular Stomatitis Virus has Implications for Single-Versus Multi-Dosing Oncolytic Virotherapy Protocols (poster and oral presentations). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
45. R Mould, J van Vloten, C Fink, L Chan, A Ross, M Singh, L Susta, A Mutsaers, J Petrik, G Wood, S Wootton, G Dekaban, Byram W. Bridle* and Khalil Karimi* *equal senior authors. (2019). IL-12-Secreting Dendritic Cells that do not Produce TNF- α are a Minor Component of 'Dendritic Cell Cultures' but the Dominant Antigen Presenters (poster). Summit for Cancer Immunotherapy, October 20-23, 2019, Victoria, BC, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
46. Jacob P. van Vloten, Lisa A. Santry, Elaine M. Klafuric, Thomas M. McAusland, Khalil Karimi, Grant McFadden, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2019). Quantifying T-Cell and Antibody Responses Induced by Antigen-Agnostic Immunotherapies (poster presentation). Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
47. Ashley A. Ross, Wing Ka Amanda AuYeung, Jim J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2018). Elucidating Infection of Stimulated Leukocytes by Oncolytic Viruses (poster presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
48. Elaine Klafuric, M. Strachan-Whaley, L. Santry, A. AuYeung, J. van Vloten, R. Mould, T. McAusland, M.E. Clark, J. Minott, S. Holtz, J. Saturno, K. Karimi, A. Mutsaers, S. Wootton and Byram W. Bridle. (2018). Combining Decitabine with Oncolytic Virotherapy Preferentially Kills Acute Leukemia Cells Via Lethal Oxidative Stress (oral and poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
49. Robert Mould, Jacob P. Van Vloten, Anthony Mustsaers, James J. Petrik, Leonardo Susta, Geoffrey Wood, Sarah K. Wootton, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2018). A Systematic Analysis of the Functional Utility of Bone Marrow-Derived Dendritic Cells as a Vaccine: Comparing Several Common Culturing Protocols (poster presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

50. Robert Mould, Jacob P. Van Vloten, Anthony Mustsaers, James J. Petrik, Leonardo Susta, Geoffrey Wood, Sarah K. Wootton, Byram W. Bridle* and Khalil Karimi* (*co-senior authors). (2018). A Systematic Analysis of the Functional Utility of Bone Marrow-Derived Dendritic Cells as a Vaccine: Comparing Several Common Culturing Protocols (poster presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
51. Maedeh Darzianiazizi (aka Mahi Azizi), Robert C. Mould, Jacob P. van Vloten, Ashley A. Ross, Shayan Sharif, Ravi Kulkarni, Byram W. Bridle* and Khalil Karimi* (*co-senior authors). (2018). Upregulation of Programmed Death Ligand-1 (PDL-1) on Neutrophils in Response to Recombinant Vesicular Stomatitis Virus (rVSV?m51) Infection (oral and poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
52. Jacob P van Vloten, Robert C Mould, Joelle C Ingraio, James J Petrik, Grant McFadden, Sarah K Wootton and Byram W Bridle. (2018). An Orf Virus-Infected Cell Vaccine Elicits Long-Term Survival in an Osteosarcoma Lung Metastasis Model Through NK Cell Activity (poster and oral presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
53. Jacob P. van Vloten, Robert Mould, Mary Ellen Clark, Arthane Kodeeswaran, Katrina Geronimo, Julia De Carvalho Nakamura, Julia Saturno, Grant McFadden, James Petrik, Sarah Wootton and Byram W. Bridle. (2018). Pyrexia Impedes Oncolytic Rhabdovirus-Mediated Therapy (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
54. Samantha Holtz, Megan Strachan-Whaley, Mary-Ellen Clark, Robert Mould, Lisa Santry, Thomas McAusland, Sarah K. Wootton, Khalil Karimi and Byram W. Bridle. (2018). Combining Oncolytic Virotherapy with Epigenetic Modifiers to Treat Lymphomas (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
55. Megan R. Strachan-Whaley, Julia Saturno, Wing Ka Amanda AuYeung, Jacob P. vanVloten, Anthony Mutsaers, Sarah K. Wootton and Byram W. Bridle. (2018). Combining Decitabine with Oncolytic Viruses to Kill Acute Leukemias by Oxidative Stress (poster and oral presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
56. Maedeh Darzianiazizi (aka Mahi Azizi), Robert C. Mould, Jacob Van Vloten, Ashley Ross, Shayan Sharif, Ravi Kulkarni, Byram W. Bridle and Khalil Karimi. (2018). Innate Immune Responses to Recombinant Vesicular Stomatitis Virus: the Role of Type I Interferon Signaling and Neutrophils (poster presentation). Canadian Society for Immunology Annual Scientific Meeting, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

57. Maedeh Darzianiazizi (Aka Mahi Azizi), Robert C. Mould, Jacob Van Volten, Ashley Ross, Shayan Sharif, Ravi Kulkarni, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2018). Innate Immune Responses to Recombinant Vesicular Stomatitis Virus: Immunosuppressive Neutrophils (poster presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
58. Robert Mould, Mankerat Singh, Jacob van Vloten, Ashley Ross, Leonardo Susta, Anthony Mutsaers, James Petrik, Geoffrey Wood, Sarah Wootton, Byram W. Bridle* and Khalil Karimi* (*co-senior authors). (2018). Analyzing The Functional Utility Of Bone Marrow-Derived Dendritic Cells As A Cancer Vaccine: Investigation Of A Unique IL-12-Producing DC Subset (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
59. Jacob P. van Vloten, Robert Mould, Mary Ellen Clark, Arthane Kodeeswaran, Katrina Geronimo, Julia De Carvalho Nakamura, Julia Saturno, Grant McFadden, James Petrik, Sarah Wootton and Byram W. Bridle. (2018). Pyrexia Impedes Oncolytic Rhabdovirus-Mediated Therapy (oral presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
60. J. Paul Woods, Byram Bridle, Michelle Oblak, Robert Foster, Geoffrey Wood, Victoria Sabine, Jeff Hummel and Brian Lichty. (2018). Novel Oncolytic Maraba virus for the Adjuvant Treatment of Feline Mammary Carcinoma (poster presentation). Veterinary Cancer Society: Immunotherapy Workshop, Anchorage, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No
61. Jacob P van Vloten, Robert C Mould, Joelle C Ingrao, James J Petrik, Grant McFadden, Sarah K Wootton and Byram W Bridle. (2018). An Orf Virus-Infected Cell Vaccine Elicits Long-Term Survival in an Osteosarcoma Lung Metastasis Model Through NK Cell Activity (oral presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
62. Ashley A. Ross, Amanda W.K. AuYeung, Robert Mould, Thomas McAusland, Lisa Santry, Jacob van Vloten, Megan Strachan-Whaley, James J. Petrik, Sarah K. Wootton and Byram W. Bridle. (2018). Infection of Stimulated Leukocytes by Oncolytic Viruses: Implications for Single- Versus Multi-Dosing Protocols (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
63. Lisa A. Santry, Jacob P. van Vloten, Robert C. Mould, Amanda W.K. AuYeung, Thomas M. McAusland, Byram W. Bridle* and Sarah K. Wootton* (*co-senior authors). (2018). Recombinant Newcastle Disease Viruses Expressing Checkpoint Inhibitors Induce a Proinflammatory State and Enhance Tumor-Specific Immune Responses in Two Syngeneic Mouse Models of Cancer (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

64. Ashley Ross, Amanda AuYeung, Robert Mould, Thomas McAusland, Jim Petrik, Sarah Wootton and Byram Bridle. (2018). Infection of Stimulated Leukocytes by Oncolytic Viruses: Implications for Single- Versus Multi-Dosing Protocols (oral presentation). Graduate Student Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
65. Thomas M. McAusland, Jacob P. van Vloten, Lisa A. Santry, Joelle C. Ingraio, Matthew Guilleman, Rozanne Arulanandam, Jean-Simon Diallo, Leo Susta, Khalil Karimi, Byram W. Bridle and Sarah K. Wootton. (2018). Enhancement of NDV-Mediated Oncolysis and Tumor Regression Through the Addition of Small Molecule Viral Sensitizers (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
66. Jessica Minott, Robert Mould, Mary Ellen Clark, Khalil Karimi and Byram W. Bridle. (2018). Assessing the Impact of Estrogen Receptor Signaling on the Efficacy of Oncolytic Viruses (poster presentation). Summit for Cancer Immunotherapy, Oct. 27-30, Banff, Alberta, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
67. Megan R. Strachan-Whaley, Amanda W.K. AuYeung, Jacob P. vanVloten, Julia Saturno, Lisa A. Santry, Thomas M. McAusland, Robert C. Mould, Anthony J. Mutsaers, Sarah K. Wootton and Byram W. Bridle. (2018). Decitabine Increases the Sensitivity of Leukemias to Oncolytic Viruses Through the Induction of Oxidative Stress (poster presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
68. Ashley A. Ross, Wing Ka Amanda AuYeung, Thomas McAusland, Lisa Santry, Jim J. Petrik, Sarah K. Wootton, Byram W. Bridle. (2018). Elucidating Infection of Stimulated Leukocytes by Oncolytic Viruses (oral presentation). The 11th annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
69. Li Deng, Robert C. Mould, Julia Kim, Wing Ka Amanda AuYeung, Byram W. Bridle. (2017). Construction and Validation of a Novel Vaccine for the Treatment of Canine Melanomas (poster presentation). Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
70. Li Deng, Robert C. Mould, Julia Kim, Wing Ka Amanda AuYeung, Byram W. Bridle. (2017). Construction and Validation of a Novel Vaccine for the Treatment of Canine Melanomas (poster presentation). 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
71. Kathy Matuszewska, Lisa Santry, Byram Bridle, Sarah K. Wootton, Jack Lawler, Jim Petrik. (2017). Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

72. Julia Saturno, Jacob van Vloten, Lisa Santry, Robert Mould, Sarah Wootton, Byram Bridle. (2017). Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
73. Megan Strachan-Whaley and Byram W. Bridle. (2017). Combining Oncolytic Viruses With Epigenetic Modifiers in Leukemia. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
74. Mankerat Singh, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2017). Differentiating Dendritic Cells in the Presence of Interleukin-4 to Enhance their Potential as Vaccines (poster presentation; won first place in the undergraduate student category). Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
75. (2017). Cancer Biotherapies: Lessons Learned from Translational Research. RGE Murray Seminar Series, Western University, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: Yes
76. Megan Rae Strachan-Whaley, Amanda AuYeung, Julia Saturno, Lisa Santry, Byram W. Bridle. (2017). Decitabine Increases the Sensitivity of Acute Leukemic Cells to Oncolytic Viruses (poster and speed-talk presentations). 2017 Annual Scientific Meeting of the Terry Fox Research Institute November 4, 2017, Vancouver, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Cancer Research Society (The) - PIN #19046; Terry Fox Research Institute (TFRI) - Project #1041
77. Megan Rae Strachan-Whaley, Amanda AuYeung, Julia Saturno, Lisa Santry, Byram W. Bridle. (2017). Decitabine Increases the Sensitivity of Acute Leukemic Cells to Oncolytic Viruses (poster presentation). Canadian Cancer Research Conference November 5-7, 2017, Vancouver, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Cancer Research Society (The) - PIN #19046; Terry Fox Research Institute (TFRI) - Project #1041
78. Amanda WK AuYeung, Robert C. Mould, Jacob van Vloten, Mahi Azizi, Lisa Santry, Sarah K. Wootton, J. Paul Woods, Geoffrey Wood, James Petrik, Khalil Karimi and Byram W. Bridle. (2017). Virus-Induced Leukopenia: Challenging the Cell Trafficking Paradigm During Oncolytic Virotherapy. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
79. Anthony Mutsaers, Byram W. Bridle, Brigitte Brisson, Michelle Oblak, Alicia Vilorio-Petit, Geoffrey Wood and Paul Woods. (2017). Naturally-Occurring Bone Cancers in Pet Dogs as a Model of Human Osteosarcomas (poster presentation). Cancer Bone Society Annual Scientific Meeting, Indianapolis, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No

80. Jacob van Vloten, Mary Ellen Clark, Arthane Kodeeswaran, Katrina Geronimo, Julia De Carvalho, Julia Saturno, Rob Mould, Grant McFadden, James Petrik, Sarah Wootton and Byram W. Bridle. (2017). Simulated Pyrexia Attenuates Rhabdovirus-Mediated Oncolysis of Cancer Cells. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
81. Maedeh Darzianiazizi, Katrina Allison, Byram Bridle* and Khalil Karimi* *co-senior authors. (2017). Sex Disparity in Innate Immune Responses to Recombinant Vesicular Stomatitis Virus: the Role of Type I Interferon Signaling and Neutrophils. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
82. Mankerat Singh, Byram W. Bridle* and Khalil Karimi* *co-senior authors. (2017). Differentiating Dendritic Cells in the Presence of Interleukin-4 to Enhance Their Potential as Vaccines. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
83. Megan Strachan-Whaley, Amanda AuYeung, Lisa Santry, Tony Mutsaers, Sarah Wootton, Byram Bridle. (2017). A Combination of Oncolytic Viruses and Epigenetic Modifiers as a Novel Therapy for Acute Leukemias. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
84. R. Mould, A. AuYeung, J. van Vloten, D. Yu, L. Zhang, A. Pelin, J. Bell, Y. Wan, K. Karimi, L. Susta, J. Petrik, A. Mutsaers, G. Wood, S. Wootton and Byram W. Bridle. (2017). Clodronate-Mediated Depletion of Marginal Zone Macrophages Potentiates Rapid Induction of Tumour-Specific T Cell Responses by Oncolytic Virus Booster Vaccines. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
85. Lisa A. Santry, Amanda AuYeung, Thomas M. McAusland, Jacob P. van Vloten, Rob C. Mould, Kathy Matuszewska, Byram W. Bridle, James J. Petrik, Sarah K. Wootton. (2017). Evaluating the Therapeutic Potential of Oncolytic Newcastle Disease Virus in Mouse Models of Melanoma and Colon Carcinoma. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
86. Amanda WK AuYeung, Robert C. Mould, Jacob van Vloten, Mahi Azizi, Lisa Santry, Sarah K. Wootton, J. Paul Woods, Geoffrey Wood, James Petrik, Khalil Karimi and Byram W. Bridle. (2017). Virus-Induced Leukopenia: Challenging the Cell Trafficking Paradigm During Oncolytic Virotherapy. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
87. Kathy Matuszewska, Lisa Santry, Byram Bridle, Sarah K. Wootton, Jack Lawler, Jim Petrik. (2017). Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer. Summit for Cancer Immunotherapy, Gatineau, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
88. Maedeh Darzianiazizi, Katrina Allison, Khalil Karimi, Byram Bridle. (2017). Sex Disparity in Innate Immune Responses to Recombinant Vesicular Stomatitis Virus: The Role of Type I Interferon Signaling and Neutrophils. 10th Annual Institute for Comparative Cancer Investigation Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

89. Presented by: Allison K Co-authors: Karimi K, Bridle BW. (2016). Gender Disparity in Innate Immune Responses to Viral Infection: The Role of Type I Interferon. Ontario Veterinary College - Career Opportunities and Research Experience Program (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
Funding Sources: Natural Sciences and Engineering Research Council of Canada (NSERC) - 436264-2013
90. Presenter: Strachan-Whaley M Co-authors: AuYeung WA, Santry L, Mutsaers A, Wootton SK, Bridle BW. (2016). Sensitization of Leukemic Cells to Oncolytic Viruses Using Epigenetic Modifiers. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Cancer Research Society (The) - 19046
91. Presenter: AuYeung WA Co-authors: Mould R, Woods JPI, Wood G, Petrik J, Bridle BW. (2016). Mechanisms That Allow Oncolytic Viral Replication Inside a Tumour Despite Pre-Existing Immunity Against a Virus-Encoded Antigen. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3
92. Presenter: Matuszewska K Co-authors: Santry L, Bridle BW, Wootton S, Petrik JJ. (2016). Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer. Summit for Cancer Immunotherapy (podium and poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
93. Presenter: de Carvalho J Co-authors: van Vloten J, Bridle BW. (2016). The Impact of Temperature on the Oncolytic Activity of Viruses. Ontario Veterinary College - Career Opportunities and Research Experience Program (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
Funding Sources: Cancer Research Society (The) - 19046
94. Presenter: Deng L Co-authors: Kim J, Mould RC, van Vloten J, AuYeung WA, Desai M, Bridle BW. (2016). From Mice to Humans Via Dogs: Development of a Novel Biotherapy for Osteosarcomas. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Terry Fox Research Institute (TFRI) - 1041
95. Katrina Geronimo, Mary Ellen Clark, Arthane Kodeeswaran, Glen Kim and Byram Bridle. (2016). Hypoxia Variably Affects Oncolytic Virus Efficacy While Potentiating the Growth of Human Cervical Cancer Cells. Sanofi Biogenius Canada, Ontario - Greater Toronto Poster Competition, Toronto, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

96. (2016). Career Night (small group meetings with academic trainees to discuss aspects of a career as a faculty member). A career night hosted by the Faculty of Health Sciences PDF Association at McMaster University, Hamilton, ON. This was open to all trainees at McMaster University and other regional universities (there were attendees from U. of Waterloo and Guelph), Hamilton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
97. Presenter: AuYeung WA Co-authors: Mould R, Woods JP, Wood G, James P, Bridle BW. (2016). Mechanisms that Allow Oncolytic Viral Replication Inside a Tumour Despite Pre-Existing Immunity Against a Virus-Encoded Antigen (podium and poster presentation). Summit for Cancer Immunotherapy, Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3
98. Presenter: Desai M Co-authors: van Vloten J, Santry L, Bridle BW. (2016). Evaluating the Impact of Temperature on the Oncolytic Potential of Viruses In Canine and Murine Osteosarcoma Cells. Ontario Veterinary College - Career Opportunities and Research Experience Program (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

Funding Sources: Terry Fox Research Institute (TFRI) - 1041
99. Presenter: Woods JP Co-authors: Bridle BW, Oblak M, Foster R, Sabine V, Skowronski K, Hummel J, Lichty B. (2016). Novel Oncolytic Maraba Virus for the Adjuvant Treatment of Feline Mammary Carcinoma. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
100. (2016). Cancer Biotherapies: Lessons Learned from Translational Research. Department of Molecular and Cellular Biology Seminar Series, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: Yes
101. Presenter: Strachan-Whaley M Co-authors: AuYeung WA, Santry L, Mutsaers A, Bienzle D, Wootton SK, Bridle BW. (2016). Sensitization of Leukemic Cells to Oncolytic Viruses Using Epigenetic Modifiers. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Cancer Research Society (The) - 19046
102. Presenter: Woods JP Co-authors: Bridle BW, Bienzle D, Delay J, Morrison A, Cieplak M, Hummel J, Lichty B. (2016). A Safety Assessment of a Novel Oncolytic Maraba Virus in Cats. American College of Veterinary Internal Medicine Forum (poster presentation), Denver, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No
103. Presenter: Mould R Co-authors: AuYeung WA, Wood G, Wootton SK, Susta L, Petrik JJ, Mutsaers A, Bridle BW. (2016). Increasing the Magnitude of Tumour-Specific T Cell Responses by Spreading a Vaccine Dose Across Multiple Injection Sites. Summit for Cancer Immunotherapy (podium and poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Terry Fox Research Institute (TFRI) - 1041

104. Presenter: Deng L Co-authors: Kim J, Mould RC, van Vloten J, AuYeung WA, Bridle BW. (2016). From Mice to Humans Via Dogs: Development of a Novel Biotherapy for Osteosarcomas. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Terry Fox Research Institute (TFRI) - 1041
105. Presenter: Santry L Co-authors: van Vloten JP, Matuszewska K, Bridle BW, Petrik JJ, Wootton SK. (2016). Recombinant Newcastle Disease Virus as an Oncolytic Therapy for Ovarian and Prostate Cancers. American Society of Gene and Cell Therapy Annual Meeting (poster presentation), Washington, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No
106. Presenter: Ingraio J Co-authors: Shapiro K, de Jong J, van Vloten J, Barta JR, Menzies PI, Bridle BW, Wootton SK. (2016). Development of a Vaccine Against Parasitic Abortion in Sheep. OMAFRA/Rural Policy Learning Commons 2016 Product Development Research Day, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
107. Arthane Kodeeswaran, Mary Ellen Clark, Katrina Geronimo, Glen Kim and Byram W. Bridle. (2016). The Effect of Temperature on the Efficacy of Oncolytic Viruses in Human Cervical Cancer Cells (awarded 3rd place). Sanofi Biogenius Canada, Ontario - Greater Toronto Poster Competition, Toronto, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
108. Presenter: van Vloten J Co-authors: Clark M, Geronimo K, Kodeeswaran A, Santry L, Mould RC, McFadden G, Petrik JJ, Wootton SK, Bridle BW. (2016). Fever-Grade Temperatures Attenuate Rhabdovirus-Mediated Oncolysis of Cancer Cells. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Cancer Research Society (The) - 19046
109. Presenter: Saturno J Co-authors: van Vloten J, Santry L, Bridle BW. (2016). Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas. Ontario Veterinary College - Career Opportunities and Research Experience Program (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3
110. Presenter: Mould RC Co-authors: AuYeung WA, Wood G, Wootton SK, Susta L, Petrik JJ, Mustaers A, Bridle BW. (2016). Increasing the Magnitude of Tumour-Specific T Cell Responses by Spreading a Vaccine Dose Across Multiple Injection Sites. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Terry Fox Research Institute (TFRI) - 1041

111. Presenter: Saturno J Co-authors: van Vloten J, Santry L, Bridle BW. (2016). Temperature as a Confounding Variable in Oncolytic Virotherapy for Canine Melanomas. 2016 Meriel NIH National Veterinary Scholars Symposium (poster presentation), Columbus, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3
112. Presenter: AuYeung WA Co-authors: Spangler-Forgione H, Woods JP, Petrik JJ, Wood G, Bridle BW. (2016). Suppression of Oxygen Reactive Species Decreases Melanogenesis Resulting in Melanomas with Reduced Immunogenicity. Summit for Cancer Immunotherapy (poster presentation), Halifax, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3
113. Presenter: van Vloten J Co-author: Bridle BW. (2016). Fever-Grade Temperatures Attenuate Rhabdovirus-Mediated Oncolysis of Cancer Cells. Institute for Comparative Cancer Investigation 9th Annual Cancer Research Symposium (podium presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Cancer Research Society (The) - 19046
114. Poster presented by: AuYeung WKA Co-authors: Mould RC, Kim J, Spangler H, Bridle BW. (2015). Mechanisms that Allow Oncolytic Viral Replication Inside a Tumour Despite Pre-Existing Immunity Against a Virus-Encoded Antigen. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
115. Presenter: Matuszewska K Co-authors: Santry L, Petrik J, Bridle BW, Wootton SK. (2015). Combined Vessel Normalization and Oncolytic Virus Therapy in the Treatment of Advanced Stage Ovarian Cancer. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
116. Presenter: AuYeung WA Co-authors: Mould RC, Spangler H, Kim J, Bridle BW. (2015). Mechanisms that Allow Oncolytic Viral Replication Inside a Tumor Despite Pre-Existing Immunity Against a Virus-Encoded Antigen. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: National Centre of Excellence in Biotherapies for Cancer Treatment (BioCanRx) - FY16 / ES3
117. Talk given by: Santry LA Co-authors: van Lieshout L, Au Yeung WKA, Bridle BW, Wootton SK. (2015). Manipulation of Akt Isoform Expression Levels and Their Effect on Transformation by the Jaagsiekte Sheep Retrovirus Envelope Protein. Workshop #22: Retroviruses II, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

118. Poster presented by: Spangler H* Co-authors: van Vloten J*, Wootton SK, Vilorio-Petit A, Bridle BW. (2015). Par6 Influences the Susceptibility of Mammary Carcinoma Cells to Oncolytic Viruses. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
119. Poster presented by: Rasiuk A* Co-authors: Walsh S*, Bridle BW. (2015). The Necessity of the Type I Interferon Receptor in Regulating Cytokines Produced Upon Viral Infection. Poster Session #35: Viruses and Innate and Acquired Immunity, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
120. (2015). Companion Animal Cancer Biotherapies. The Hamilton Academy of Veterinary Medicine, Hamilton, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: Yes
121. Presenter: Mould R Co-authors: Kim J, Walsh S, de Jong J, Wood G, Wootton S, Susta L, Petrik J, Mutsaers A, Bridle BW. (2015). Combining Virotherapy with Immunotherapy to Treat Osteosarcoma in a Preclinical and Clinical Model. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Terry Fox Research Institute (TFRI) - 1041
122. Poster presented by: van Vloten JP* Co-authors: Ingraio J, Mould RC*, Bridle BW, Wootton SK. (2015). Assessing the Oncolytic Potential of ORFV Strains In Vitro. Poster Session #12: Oncolytic Viruses and Gene Therapy, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
123. Presenter: van Vloten J Co-authors: Wootton S, Bridle BW. (2015). Harnessing Immunogenic Cell Death to Potentiate Anti-Cancer Efficacy During ORFV-Induced Oncolysis. Ontario Veterinary College Graduate Student Research Symposium (podium presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
Funding Sources: Cancer Research Society (The) - 19046
124. Poster presented by: Strachan-Whaley MR* Co-authors: AuYeung A*, Kim J*, Bienzle D, Wootton SK, Bridle BW. (2015). Using Viruses to Potentiate Epigenetic Modifier-Mediated Killing of Leukemic Cells. Poster Session #12: Oncolytic Viruses and Gene Therapy, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
125. Presenter: Ingraio J Co-authors: van Vloten J, Shapiro K, Barta J, Menzies P, Bridle BW, Wootton S. (2015). Development of Orf Virus (Parapoxvirus ovis) as a Multivalent Viral Vector Platform Against *Toxoplasma gondii*. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

126. Talk given by: Kozak RA Co-authors: Hattin L*, Biondi MJ, Walsh S*, Morgenstern J*, Lusty E*, Chereponov V, McBey B-A, Leishman DP, Feld JJ, Bridle BW, Nagy É. (2015). In Vitro Oncolytic Activity of a Novel Orthoreovirus Against Hepatocellular Carcinoma. Workshop #43: Oncolytic Viruses, 34th Annual Meeting of the American Society for Virology, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
127. Poster presented by: Kim J Co-authors: AuYeung A, Deng L, Mould RC, Bridle BW. (2015). Assessment of the Potential to Treat Canine Cancers with an Oncolytic Vaccine. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
128. Presenter: Strachan-Whaley M Co-authors: AuYeung WA, Kim J, Bienzle D, Mutsaers A, Wootton S, Bridle BW. (2015). Combining Oncolytic Viruses with Epigenetic Modifiers as a Novel Therapy for Leukemia. Ontario Veterinary College Graduate Student Research Symposium (poster presentation), Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

Funding Sources: Cancer Research Society (The) - 19046
129. (2015). Canine Osteosarcoma Biotherapy: Revolutionizing How Bone Cancers are Treated in Humans. Valérie's Flutter Foundation Gala Dinner, Ottawa, Canada
Main Audience: General Public
Invited?: Yes, Keynote?: Yes
130. Hattin, L.* , Kozak, R., & Bridle, B. W. (2014). Investigation of Recombinant NDV as an Oncolytic Therapy for Prostate Tumors. Poster presented by summer student Larissa Hattin. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
131. Mould, R.* , Walsh, S.* , van Vloten, J.* , Wootton, S., & Bridle, B. W. (2014). Combining Antigen Presenting Cell-Based Vaccination with Oncolytic Viruses for the Treatment of Prostate Cancer Poster presented by summer student Robert Mould (awarded 3rd place). Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
132. Kim, J.* , Walsh, S.* , & Bridle, B. W. (2014). Screening Canine Melanoma and Osteosarcoma Specimens for Putative Tumour-Associated Antigen Expression. Poster presented by summer student Julia Kim. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
133. van Vloten, J.* , de Jong, J.* , Rasiuk, A.* , Bridle, B. W., & Wootton, S. (2014). The Generation of Immune-Modulatory Gene-Knockout Orf Virus Recombinants for Use in Oncolytic Virotherapy Poster presented by Jacob Van Vloten. International Union of Microbiological Societies, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
134. Kozak, R., Hattin, L.* , Yeung, W. A., Lusty, E.* , Leishman, D., J. Feld, B. W. Bridle, E. Nagy. (2014). A Novel Orthoreovirus as a Potential Therapeutic for Hepatocellular Carcinoma Talk given by Robert Kozak. International Union of Microbiological Societies, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No

135. Talan, M.*, Tin, B.*, Ternamian, C.*, Syed, Z.*, & Bridle, B. W. (2014). The Effects of Quercetin and Kaempferol on the Cytotoxicity of Carboplatin and Entinostat on Various Cancer Cell Lines Poster presented by Micaella Talan and Brittney Tin. Sanofi BioGENEius Challenge Canada, Toronto, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
136. Ternamian, C.* & Bridle, B. W. (2014). Oncolytic Rhabdoviruses in Combination with Histone Deacetylase Inhibition Synergistically Kill Murine B Lymphoblastic Leukemia Cells Talk given by Christian Ternamian. Institute for Comparative Cancer Investigation 7th Annual Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
137. Santry, L., Yeung, W. A.*, Bridle, B. W., & Wootton, S. (2014). Function of Akt Isoforms in Transformation by the Jaagsiekte Sheep Retrovirus Envelope Protein Talk given by Lisa Santry. International Union of Microbiological Societies, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
138. Kozak, R., Hattin, L.*, Feld, J., Ackford, J., Nagy, E., B. W. Bridle. (2014). Oncolytic Viruses as Therapy for Hepatocellular Carcinoma Poster presented by Robert Kozak. National CIHR Research Training Program in Hepatitis C, 3rd Canadian Symposium on HepC Virus, Toronto, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
139. Syed, Z.*, Walsh, S.*, & Bridle, B. W. (2014). Treating High-Grade Glioma with Oncolytic Virotherapy and Histone Deacetylase Inhibitors Poster presented by Zafir Syed. Institute for Comparative Cancer Investigation 7th Annual Cancer Research Symposium, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
140. Walsh, S.*, Rasiuk, A.*, & Bridle, B. W. (2014). Negative Regulation of Cytokine Expression by Type One Interferon Signaling in VSV Infection Poster presented by Scott Walsh. International Union of Microbiological Societies, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
141. Van Vloten, J.*, de Jong, J.*, Rasiuk, A.*, Bridle, B. W., & Wootton, S. (2014). The Development of Recombinant Parapoxvirus ovis (Orfv) for Use in Oncolytic Virotherapy. Poster presented by summer student Jacob Van Vloten. Summer Research and Leadership Program, Ontario Veterinary College, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
142. (2014). Treating Feline Mammary Carcinoma With an Oncolytic Vaccine: Companion Animal Trials as a Stepping Stone Towards Successful Translation into Human Patients. Cancer Grand Rounds at Western University, London, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
143. (2013). A Novel Barrier to Cancer Immunotherapy in the Brain. Talk in the speed-poster session of the 6th annual meeting of the Canadian Cancer Immunotherapy Consortium; plus a poster presentation., Toronto, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

144. Poster presentation by my MSc student, Zafir Syed* Co-author: B. Bridle. (2013). Oncolytic Immunotherapy for the Treatment of High-Grade Glioma. Graduate Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
145. A poster presented by my MSc student, Christian Ternamian* Co-author: B. Bridle. (2013). Synergizing Oncolytic Virotherapy and HDAC Inhibition in a Murine Model of B-Cell Lymphoblastic Leukemia. Graduate Research Symposium, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
146. This was a talk given by my fourth-year research project student, Evan Lusty* Co-author: B. Bridle. (2013). Characterizing Oncolytic Viruses, Toll-Like Receptor Ligands and Histone Deacetylase Inhibitors in the In Vitro Treatment of Human Prostate Cancer. 6th Annual Cancer Research Symposium, Institute for Comparative Cancer Investigation, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
147. (2013). Tumour Immunology. Seminar presentation in the Cancer Biology rounds, Clinical Oncology Group, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
148. A poster presented by my undergraduate research assistant, Wing Ka Au Yeung* Co-author: B. Bridle. (2013). Development of a Flow Cytometry-Based Immunological Assay to Support Pre-Clinical and Clinical Companion Animal Cancer Trials. Ontario Veterinary College's Summer Leadership and Research Program, poster presentations., Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
149. Poster presentation by my undergraduate research associate, Evan Lusty* Co-presenter: Jason Morgenstern* Co-author: B. Bridle. (2012). Establishment of Leukemia/Lymphoma Cell Lines from Clinical Specimens and Evaluation of Their Susceptibility to Oncolytic Viruses. Summer Leadership and Research Program, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
150. (2012). Replication-Deficient Adenovirus and Oncolytic Rhabdoviruses as Cancer Vaccines. Keynote speaker at symposium entitled "Viral delivery and nanoparticle vectors" organized by students in Molecular Virology (MICR*4330) course, University of Guelph., Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: Yes, Competitive?: No
151. (2012). Paradoxically, Immunotherapy Might be More Efficacious When Tumours are Inside the Brain. Plenary talk at the "Modelling Cancer In Vivo, In Vitro and In Silico" session of the Institute for Comparative Cancer Investigation 4th Annual Cancer Research Symposium, University of Guelph., Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes
152. Poster presentation by my undergraduate research assistant, Jason Morgenstern* Co-presenter: Evan Lusty* Co-author: B. Bridle. (2012). Using an Innate Anti-Viral Immune Response in the Presence of a Histone Deacetylase Inhibitor to Treat Leukemias. Summer Leadership and Research Program, Ontario Veterinary College, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No

153. (2012). Using Oncolytic Viruses to Potentiate Immunotherapy for Childhood Cancers. Talk given at the Canadian Oncolytic Virus Consortium Annual Meeting, Lake Cecebe, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No
154. Poster presentation by B. Bridle Co-authors: Chantal Lemay, Jean-Simon Diallo, Lan Chen, Jonathan Pol, Andrew Nguyen, Jonathan Bramson, John Bell, Brian Lichty and Yonghong Wan. (2011). A Histone Deacetylase Inhibitor Dramatically Improves the Therapeutic Index of an Oncolytic Vaccine by Augmenting Anti-Tumour Activity While Inhibiting Autoimmune Sequellae. CIHR New Principal Investigators Meeting, Toronto, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
155. Poster presentation by Jonathan Pol Co-authors: Byram Bridle, Liang Zhang, Stephen Hanson, Natasha Kazdhan, Jonathan Bramson, David Stojdl, Yonghong Wan, Brian Lichty. (2011). Maraba virus: a new vector for oncolytic viro-immunotherapy. 6th International Conference on Oncolytic Viruses as Cancer Therapeutics, Las Vegas, United States
Main Audience: Researcher
Invited?: No, Keynote?: No
156. Poster presentation by Jonathan Pol Co-authors: Byram Bridle, Liang Zhang, Stephen Hanson, Natasha Kazdhan, Jonathan Bramson, David Stojdl, Yonghong Wan, Brian Lichty. (2011). Maraba virus: a new vector for oncolytic viro-immunotherapy. 14th Annual Meeting of the Translational Research Cancer Centers Consortium, Seven Springs, United States
Main Audience: Researcher
Invited?: No, Keynote?: No
157. (2011). Oncolytic Vaccines: the Billion Dollar Idea. Seminar Series, Ottawa Hospital Research Institute, Ottawa, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No
158. (2011). A Histone Deacetylase Inhibitor Dramatically Improves the Therapeutic Index of an Oncolytic Vaccine by Augmenting Anti-Tumour Activity While Inhibiting Autoimmune Sequella. Talk given in the concurrent symposium "Personalized Medicine: From Discovery and Validation to Implementation", 1st Annual Canadian Cancer Research Conference., Toronto, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes
159. (2011). Rapid and Massive Boosting of Tumour-Specific T Cells by Targeting Antigen Presentation to Follicular B Cells. Concurrent session, 14th Annual Meeting of the Translational Research Cancer Centers Consortium., Seven Springs, United States
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes
160. (2011). Immunoediting and Immunotherapy of Cancers. Seminar presentation in the Cancer Biology rounds, Clinical Oncology Group, University of Guelph, Guelph, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No
161. (2010). Antigen Presentation by B Cells Maximizes Secondary T Cell Number and Quality: Implications for Booster Vaccines. 1st Annual McMaster University Faculty of Health Sciences Post-Doctoral Research Day (received award for best presentation), Hamilton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes

162. Poster presented by Liang Zhang. Co-authors: Byram Bridle, Jonathan Pol, Allison Rosen, Jonathan Bramson, Brian Lichty, Yonghong Wan. (2010). Virus infected B cells are potent antigen presenting cells. 3rd Annual Cancer Immune Therapy Symposium, Niagara Falls, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
163. Poster presented by Stephen Hanson. Co-authors: Byram Bridle and Brian Lichty. (2010). The placenta specific gene Plac1 is a potential target for therapeutic cancer vaccines. Ontario Institute for Cancer Research Annual Meeting, Alliston, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
164. Additional co-chair: Tommy Alain, McGill University. (2010). Improving the Therapeutic Index of Cancer Immunotherapy With A Histone Deacetylase Inhibitor Also, was the session co-chair, leading a discussion on the viro- vs. immune-centric approach to oncolytic virotherapy. Ontario Regional Biotherapeutics Program, 2nd Annual Scientific Retreat, Haliburton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No
165. (2010). Fine-Tuning Oncolytic Immunovirotherapy With A Histone Deacetylase Inhibitor. Meeting of the Canadian Oncolytic Virus Consortium, Montreal, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No
166. Oral presentation by Brian Lichty. Co-authors: Byram Bridle, K. Stephenson, J. Boudreau, S. Koshy, N. Kazdhan, E. Pullenayegum, J. Brunellière, J. Bramson and Y. Wan. (2010). Potentiating cancer immunotherapy using an oncolytic virus. 4th European Congress of Virology, Cernobbio, Italy
Main Audience: Researcher
Invited?: Yes, Keynote?: No
167. Poster presented by Jonathan Pol. Co-authors: Byram Bridle, Natasha Kazdhan, Jonathan Bramson, David Stojdl, Yonghong Wan, Brian Lichty. (2010). Maraba virus: a new oncolytic vaccine vector. Ontario Institute for Cancer Research Annual Meeting, Alliston, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
168. (2010). Antigen Presentation by B Cells Maximizes Secondary T Cell Number and Quality: Implications for Booster Vaccines. 1st session, 3rd Annual Meeting of the Canadian Cancer Immunotherapy Consortium, Niagara Falls, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes
169. (2010). Fine-Tuning Oncolytic Immunovirotherapy with a Histone Deacetylase Inhibitor. Concurrent session, Annual Meeting, Ontario Institute for Cancer Research, Alliston, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: Yes
170. Poster presented by Liang Zhang. Co-authors: Byram Bridle, Jonathan Pol, Allison Rosen, Jonathan Bramson, Brian Lichty, Yonghong Wan. (2010). Virus infected B cells are potent antigen presenting cells. 23rd Annual Meeting of the Canadian Society for Immunology, Niagara Falls, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
171. (2009). Treating Brain Cancer with Immunotherapy and Oncolytic Viruses. Research Seminar Series, Central Animal Facility, McMaster University, Hamilton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

172. Poster Presentation by B. Bridle Co-authors: Kyle Stephenson, Jeanette Boudreau, Sandeep Koshy, Natasha Kazdhan, Jonathan Bramson, Brian Lichty and Yonghong Wan. (2009). Potentiating cancer immunotherapy using an oncolytic virus. McMaster Industry Liaison Office Innovation Showcase, Hamilton, Canada
Main Audience: Knowledge User
Invited?: Yes, Keynote?: No
173. Jean-Simon Diallo, Ottawa Hospital Research Institute. (2009). Session Co-Chair; Led a discussion on: Combination Cancer Treatment Strategies. Ontario Regional Biotherapeutics Program, 1st Annual Scientific Retreat, Haliburton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No
174. Poster presentation. Co-presenters: Kyle Stephenson, Jeanette Boudreau, Sandeep Koshy, Natasha Kazdhan, Jerome Brunellière, Jonathan Bramson, Brian Lichty B and Yonghong Wan. (2009). Embracing anti-viral immunity to make an oncolytic vector more effective. The 5th International Meeting on Replicating Oncolytic Virus Therapeutics, Banff, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
175. Poster Presentation by B. Bridle Co-authors: Ruby Chang, Brian Lichty, Shucui Jiang, jonathan Bramson and Yonghong Wan. (2009). Immunotherapy can reject intracranial tumour cells without overt damage to the brain despite sharing the target antigen. Ontario Institute for Cancer Research Annual Meeting, Alliston, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
176. Poster presentation given by Jeanette Boudrea. Co-authors: Kyle Stephenson, Patrick Palidino, Byram Bridle, Brian Lichty, Jonathan Bramson and Yonghong Wan. (2009). Activation of natural killer cells by dendritic cell vaccines is strongly influenced by maturation protocol and plays a key role in determining cancer therapeutic efficacy. Ontario Institute for Cancer Research Annual Meeting, Alliston, Canada
Main Audience: Researcher
Invited?: No, Keynote?: No
177. Oral presentation given by Brian Lichty. Co-authors: Byram Bridle, Kyle Stephenson, Jeanette Boudreau, Sandeep Koshy, Natasha Kazdhan, Jerome Brunellière, Jonathan Bramson and Yonghong Wan. (2009). Vaccinating against an oncolytic virus can enhance therapy. Plenary Session, The 5th International Meeting on Replicating Oncolytic Virus Therapeutics, Banff, AB, 2009, Banff, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No
178. (2008). Combining Cancer Vaccination with Viral Oncolysis to Maximize Tumour Destruction. Ottawa Hospital Research Institute Seminar Series, Ottawa, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No
179. (2008). Combining Immunological and Oncolytic Virotherapy to Treat Brain Cancer. Infection and Immunity Seminar Series, McMaster University, Hamilton, Canada
Main Audience: Researcher
Invited?: Yes, Keynote?: No, Competitive?: No

Broadcast Interviews

- 2021/05/01 Since May 2021, I have engaged in ~50 media commitments related to COVID-19.
- 2021/04/07 Decisions Made by the National Advisory Committee on Immunization Re: COVID-19 Vaccines, Interviewed by host Alex Pierson for the ON Point radio show, AM640 Toronto

- 2021/04/01 Transmission of SARS-CoV-2 Via Aerosols, Interviewed by host Arlene Bynaon for the ON Point radio show, AM640 Toronto
- 2021/03/25 COVID-19 Vaccine Hesitancy, Interviewed by host Alex Pierson for the ON Point radio show, AM640 Toronto
- 2021/03/23 Risk of Damage to Children's Immune Systems Due to Prolonged COVID-19 Policy-Mandated Isolation, Interviewed by host Alex Pierson for the ON Point radio show, AM640 Toronto
- 2021/03/16 Risk of Damage to Children's Immune Systems Due to Prolonged COVID-19 Policy-Mandated Isolation, Interviewed by host Mike Stubbs for Global News Radio London (980 CFPL).
- 2021/03/12 Risk of Damage to Children's Immune Systems Due to Prolonged COVID-19 Policy-Mandated Isolation, Interviewed by host Shayne Ganam for 770CHQR Global News, Calgary.
- 2021/03/12 Risk of Damage to Children's Immune Systems Due to Prolonged COVID-19 Policy-Mandated Isolation, Interviewed by host Alex South for Sputnik Radio in Edinburgh, Scotland
- 2021/03/11 A year of COVID-19 lockdown is putting kids at risk of allergies, asthma and autoimmune diseases, 570 News Talk Radio (Kitchener, Ontario, Canada) I was interviewed by host Brian Burke.
- 2021/03/11 A year of COVID-19 lockdown is putting kids at risk of allergies, asthma and autoimmune diseases, CTV National News Interviewed by Merella Fernandez for the national news show.
- 2021/03/11 A year of COVID-19 lockdown is putting kids at risk of allergies, asthma and autoimmune diseases, CTV News Kitchener I was interviewed by host Carmen Wong for the local news show.
- 2021/03/09 5 factors that could dictate the success or failure of the COVID-19 vaccine rollout, 106.5 ELMNT FM Toronto/95.7 ELMNT FM Ottawa I was interviewed by host David Moses for a show called "Moment of Truth".
- 2021/02/22 Byram Bridle, Associate Professor of Viral Immunology at the University of Guelph talks to Peter about the COVID vaccine, Magic Talk radio program, New Zealand, <https://www.magic.co.nz/home/news/2021/02/byram-bridle--associate-professor-of-viral-immunology-at-the-uni.html>, Peter Williams
- 2021/02/18 5 factors that could dictate the success or failure of the COVID-19 vaccine rollout, Magic Talk Radio, Mediaworks, New Zealand I was interviewed live on air by host Peter Williams
- 2021/02/12 5 factors that could dictate the success or failure of the COVID-19 vaccine rollout, 570 News Talk Radio (Kitchener, Ontario, Canada) Interviewed live on radio by host Mike Farwell
- 2020/12/14 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Windsor, Ontario I was interviewed on radio.
- 2020/12/14 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Peterborough/Kingston/Barrie, Ontario I was interviewed on the "Ontario Morning" radio show.
- 2020/12/14 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, ELMNT FM Radio, 106.5 FM in Toronto and 95.7 FM in Ottawa I was interviewed on the David Moses talk show.

- 2020/12/14 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Toronto, Ontario I was interviewed on radio.
- 2020/12/14 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, London, Ontario I was interviewed on radio.
- 2020/12/14 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Sudbury, Ontario I was interviewed on radio.
- 2020/12/14 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Sudbury, Ontario I was interviewed on radio.
- 2020/12/14 Article title: The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Kitchener, Ontario I was interviewed on radio.
- 2020/11/25 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Sudbury, Ontario I was interviewed by host Jonathan Pinto on the "Up North" program.
- 2020/11/25 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Montreal, Quebec I was interviewed by host Sabrina Marandola on the "Let's Go" program.
- 2020/11/25 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Vancouver, British Columbia I was interviewed by host Gloria Macarenko on the "On the Coast" program.
- 2020/11/25 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, London/Windsor, Ontario I was interviewed by host Chris dela Torre on the "Afternoon Drive" program.
- 2020/11/25 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Whitehorse, Yukon I was interviewed by host Dave White on the "Airplay" program.
- 2020/11/25 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, UK Radio, Radio Sputnik, Edinburgh, Scotland I was interviewed by host Alex South.
- 2020/11/25 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Saskatchewan I was interviewed by host Garth Materie on the "Afternoon Edition" program.
- 2020/11/25 The mink link: How COVID-19 mutations in animals affect human health and vaccine effectiveness, CBC Radio, Winnipeg, Manitoba I was interviewed on the "Up to Speed" program.
- 2020/10/12 - 2020/10/12 "U of G Covid Vaccine Research", <https://www.facebook.com/uofguelph/videos/u-of-g-covid-vaccine-research/274022033801852/>, Facebook video
- 2020/10/10 - 2020/10/10 "Training our immune systems: Why we should insist on a high-quality COVID-19 vaccine", Interviewed live on-air (two time slots) for "Weekend Mornings on CKNW" by host Stirling Faux, CKNW Radio, Vancouver, BC
- 2020/10/08 - 2020/10/08 "Training our immune systems: Why we should insist on a high-quality COVID-19 vaccine", Interviewed live on-air by host Brian Bourke, 570 News Talk Radio (Kitchener, Ontario, Canada)
- 2020/08/16 - 2020/08/16 "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk", Interviewed by Miriam Harris for a radio show, Newshub in Auckland, New Zealand
- 2020/08/16 - 2020/08/16 "COVID-19 Vaccines:<?>Facts to Inform Policies", <https://www.youtube.com/watch?v=HndetYzK8gU>, New Zealand's COVID-19 Science and Policy Symposium

- 2020/08/05 - "Why vaccines are less effective in the elderly, and what it means for COVID-19",
2020/08/05 Interviewed live on-air on the Mike Farwell show, 570 News Talk Radio (Kitchener, Ontario, Canada)
- 2020/07/29 - "Why vaccines are less effective in the elderly, and what it means for COVID-19",
2020/07/29 Interviewed live on-air by host Scott Radley, 900 CHML (radio station in Hamilton, Ontario, Canada)
- 2020/07/27 - "Why vaccines are less effective in the elderly, and what it means for COVID-19",
2020/07/27 Interviewed live on air by host Jill Bennett, NewsTalk 980 CKNW, Vancouver (radio)
- 2020/07/13 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/07/13 Interviewed by host David Moses for a second, follow-up talk show, ELMNT FM Radio; 106.5 FM in Toronto and 95.7 FM in Ottawa
- 2020/07/07 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/07/07 Interviewed by host David Moses for a talk show, ELMNT FM Radio; 106.5 FM in Toronto and 95.7 FM in Ottawa
- 2020/07/01 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/07/01 Interviewed for television by host Neetu Garcha (<https://globalnews.ca/video/7128780/when-will-a-covid-19-vaccine-be-ready>), Global BC's Morning News
- 2020/07/01 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/07/01 Interviewed live on-air by host Mike Stubbs, Global News Radio 980 CFPL (London, Ontario, Canada)
- 2020/06/22 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/06/22 Interviewed live on-air by host Devon Peacock, Global News Radio 980 CFPL (London, Ontario, Canada)
- 2020/06/21 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/06/21 Interviewed by Mercedes Stephenson (<https://globalnews.ca/video/7088465/short-timelines-for-coronavirus-vaccine-are-giving-people-false-hope-bridle>), The West Block (Global National News)
- 2020/06/18 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/06/18 Live on-air interview with host Kristy Cameron, CFRA 580 News Talk Radio (Ottawa, Ontario, Canada)
- 2020/06/18 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/06/18 Live on-air interview with hosts Sue Deyell And Andrew Schultz, Global News Radio 770 CHQR (Calgary, Alberta, Canada)
- 2020/06/17 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/06/17 Global News Radio 900 CHML (Hamilton, Ontario, Canada), Live on-air interview with host Scott Thompson
- 2020/06/17 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/06/17 Live on-air interview with hosts Chelsea Bird and Shaye Ganam, Global News Radio 630 CHED (Edmonton, Alberta, Canada)
- 2020/06/15 - "Fast COVID-19 vaccine timelines are unrealistic and put the integrity of scientists at risk",
2020/06/15 Interviewed live on-air for the Jill Bennett Show by guest host Stirling Faux, Global News Radio 980 CKNW (Vancouver, British Columbia, Canada)
- 2020/05/28 - "Can antibody tests tell us who is immune to COVID-19?", Interviewed live on-radio by
2020/05/28 hosts Sue Deyell and Andrew Schultz., Global News Radio 770 CHQR (Calgary, Alberta, Canada)
- 2019/09/20 - "Biotherapies for the Treatment of Bone Cancers", Video made for students prior to their
2019/09/20 participation in the Terry Fox Run., Country Day School, King City, Ontario

- 2016/07/15 - "Ontario Vet College cancer treatment breakthrough spurs human clinical trials", Radio One, Live on-air 7-minute radio interview
2016/07/15
- 2016/07/14 - "Cancer breakthrough out of the OVC", CTV News (video) <http://guelph.ctvnews.ca/cancer-breakthrough-out-of-the-ovc-1.2987216>, CTV
2016/07/14
- 2016/05/10 - "Dogs with cancer could lead researchers to treatments for humans", Toronto Star (video) <https://www.thestar.com/news/2016/05/10/dogs-with-cancer-could-lead-researchers-to-treatments-for-humans.html>, Toronto Star
2016/05/10
- 2015/08/29 - "Canine osteosarcoma biotherapy trial", CTV Kitchener News (video) <http://kitchener.ctvnews.ca/video?clipId=692297>, CTV Kitchener
2015/08/29
- 2015/08/19 - "Dog Cancer Research", CHCH Hamilton News (video) <http://www.chch.com/dog-cancer-research/>, CHCH Hamilton
2015/08/19

Text Interviews

- 2021/03/30 'It is essentially akin to solitary confinement': UofG viral immunologist frustrated by child COVID-19 quarantine messaging, Jessica Lovell, Guelph Mercury
Description / Contribution Value: <https://www.guelphmercury.com/news-story/10360821--it-is-essentially-akin-to-solitary-confinement-uofg-viral-immunologist-frustrated-by-child-covid-19-quarantine-messaging/>
- 2021/03/24 U of G scientists concerned about extended interval between COVID-19 vaccine doses, Joanne Shuttleworth, The Wellington Advertiser
Description / Contribution Value: <https://www.wellingtonadvertiser.com/u-of-g-scientists-concerned-about-extended-interval-between-covid-19-vaccine-doses/>
- 2021/03/22 Viral immunologist speaks out against 'abusive' child-quarantine policies, Anthony Furey, Toronto Sun
Description / Contribution Value: <https://torontosun.com/news/provincial/viral-immunologist-speaks-out-against-abusive-child-quarantine-policies>
- 2021/03/17 COVID-19: Isolation increases risk of immunological disorders, immunologist says, Luke Schulz, Guelph Today
Description / Contribution Value: <https://www.guelphtoday.com/around-ontario/covid-19-isolation-increases-risk-of-immunological-disorders-immunologist-says-3546013>
- 2021/03/11 Lockdown measures could impact children's immune systems, Carmen Wong, CTV News Kitchener
Description / Contribution Value: <https://kitchener.ctvnews.ca/lockdown-measures-could-impact-children-s-immune-systems-1.5344205>
- 2021/03/10 A year of COVID-19 lockdown is putting kids at risk of allergies, asthma and autoimmune diseases, National Post
Description / Contribution Value: <https://nationalpost.com/pmnl/news-pmn/a-year-of-covid-19-lockdown-is-putting-kids-at-risk-of-allergies-asthma-and-autoimmune-diseases>
- 2020/12/15 Lack of reviews of COVID vaccine raises concern with U of G expert, Anam Khan, Guelph Today
Description / Contribution Value: <https://www.guelphtoday.com/coronavirus-covid-19-local-news/lack-of-reviews-of-covid-vaccine-raises-concern-with-u-of-g-expert-3184264>
- 2020/12/05 How COVID-19 mutations in animals affect human health and vaccine effectiveness, Halifax Today
Description / Contribution Value: <https://www.halifaxtoday.ca/coronavirus-covid-19-local-news/how-covid-19-mutations-in-animals-affect-human-health-and-vaccine-effectiveness-3154400>

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Conference Date: 2015/6
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Intellectual Property

Patents

1. ONCOLYTIC VIRUSES WITH REPLICATIVE ABILITY AT TEMPERATURES HIGHER THAN WILDTYPE AND USES THEREOF. United States. Provisional Application No. 62/976,616. 2020/02/21.
Patent Status: Pending
Inventors: Byram W. Bridle Jacob P. van Vloten
Describes two novel oncolytic rhabdoviruses with superior oncolytic activity at temperatures above 37°C as compared to the parental viruses. Also describes a method to generate these types of viruses. This will enhance efficacy of oncolytic rhabdoviruses in tumours that are at higher temperatures than ambient tissues and in human patients that develop fevers (a common response to this therapy) and in veterinary patients whose normal body temperatures are >37°C.
2. AVIAN ONCOLYTIC VIRUS HAVING MODIFIED SEQUENCES AND USES THEREOF. United States. 2018/12/14.
Patent Status: Pending
Inventors: KOZAK; Robert; (London, CA) ; BRIDLE; Byram; (Guelph, CA) ; NAGY; Eva; (Puslinch, CA) ; THOMPSON; Bradley; (Calgary, CA)
The present disclosure relates to one or more modified avian-virus based agents, therapies, treatments, and methods of use of the modified avian-virus based agents and/or therapies and/or treatments for cancer. The disclosure also provides for methods of generating modified avian-virus based agents. One of the five claims is particularly notable: "The oncolytic agent of claim 1, where the modified avian virus is one of an avian pox virus, an avian reovirus, a Newcastle's disease virus, a duck hepatitis virus, an infectious bursal disease virus, a chicken parvovirus and a combination thereof."
3. A METHOD OF VACCINATION COMPRISING A HISTONE DEACETYLASE INHIBITOR. Canada. International Application No.: PCT/CA2012/000212. 2012/09/03.
Patent Status: Pending
A vaccination method is provided. The method comprises administering to a mammal a histone deacetylase inhibitor in conjunction with a vaccine that expresses an antigen to which the mammal has a pre-existing immunity.

Funding Sources: Canadian Institutes of Health Research (CIHR) - MOP-67066

4. VACCINATION METHODS. Canada. PCT/CA2010/000379. 2011/09/16.

Patent Status: Pending

In one aspect, a method of treating cancer in a mammal is provided. The method comprises administering to the mammal an oncolytic vector that expresses a tumour antigen to which the mammal has a pre-existing immunity. In another aspect, a method of boosting immune response in a mammal having a pre-existing immunity to an antigen is provided comprising intra-venous administration to the mammal of a B-cell infecting vector that expresses the antigen.

Funding Sources: Canadian Institutes of Health Research (CIHR) - MOP-67066

Disclosures

1. Heat-Adapted Maraba Virus for Treating Cancers
Disclosed
Filing Date: 2019/08/09
An application was submitted to patent a novel oncolytic virus. There is one other co-inventor (my PhD student Jacob van Vloten).
2. Quantifying Antigen-Specific T-Cell Responses When Using Antigen-Agnostic Immunotherapies
Disclosed
Filing Date: 2019/07/05
A report of invention for a novel method to quantify T cell responses was submitted to the intellectual property office at the University of Guelph. There is one other co-inventor (my PhD student Jacob van Vloten).
3. Quantifying Antibody Responses Induced by Antigen-Agnostic Immunotherapies
Disclosed
Filing Date: 2019/07/05
A report of invention for a novel method to quantify antibody responses was submitted to the intellectual property office at the University of Guelph. There is one other co-inventor (my PhD student Jacob van Vloten).
4. Avian Orthoreovirus Strain PB1: A Novel Oncolytic Virus
Disclosed
Filing Date: 2019/02/05
An application was submitted to patent a novel oncolytic virus. There are two other co-inventors (research collaborators).
5. Combining Epigenetic Modifiers with Oncolytic Viruses for the Treatment of Leukemias
Disclosed
Filing Date: 2018/03/21
A report of invention was submitted to the University of Guelph's intellectual property office. There are four other co-inventors (all former students of mine; Megan Strachan-Whaley, Christian Ternamian, Jason Morgenstern and Evan Lusty).
6. Avian orthoreovirus (ARV) strain PB1: a potential oncolytic, vaccine and adjuvant
Disclosed
Filing Date: 2014/01/31

This is the attachment marked BRI-2 referred to in the Affidavit/Declaration of Byram BRIDLE sworn/affirmed/declared at Washburn, GOREHAM, NH this 05 day of JANUARY, 2022, before me:
 Signature Au Lon POSSON

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

the hood
TODAY + TOMORROW + ALWAYS

1. The Problem: COVID-19

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can cause atypical pneumonia, known as ‘coronavirus disease that was identified in 2019’ (COVID-19) in a subset of individuals. For most people, COVID-19 causes, at most, mild or moderate illness. For some, SARS-CoV-2 is not even a pathogen since it does not cause disease in them. However, two well-defined demographics are at enhanced risk of potentially severe and even lethal COVID-19. This includes individuals who are immunocompromised and the frail elderly, especially if comorbidities exist. Shortly after the COVID-19 pandemic was declared in Canada, caution was exercised through the declaration of emergency orders and implementation of what was supposed to be a short-term lockdown to allow time to: (a) assess the severity of the situation, and (b) slow the first wave of cases of COVID-19 so hospitals would not get overwhelmed. This was to be a temporary measure to ‘flatten the curve’, which referred to a stabilization in the daily reported cases of COVID-19 when plotted on a graph. Then, Canadians would learn to live with the virus, like they have with the many other respiratory pathogens to which they were exposed on a regular basis. However, more than one-and-a-half years later, Canadians have experienced cyclic emergency lockdown orders on a background of constant isolation, physical distancing, and masking measures. Canada’s response to the declared pandemic in terms of the aforementioned measures has not altered substantially despite overwhelming scientific data that show the risk of severe and lethal disease is almost entirely limited to two well-defined demographics. In early 2021 Health Canada provided authorization for interim use of several "designated C19 drugs" that were akin to vaccines, although the definition of a vaccine had to be changed to officially recategorize them as such. These ‘vaccines’, more accurately referred to as ‘inoculations’ throughout much of this report have become designated as the only viable way to exit from this declared pandemic; to the point where attempts to mandate these is become commonplace. Generally, rather than taking a balanced approach, in which economic, physical, and human resources could be focused on protecting the most vulnerable, Canada’s political and public health leaders opted for a very long-term ‘one-size-fits-all’ approach. Further, the ever-emerging science accumulating about Canada’s currently available COVID-19 inoculations has clearly demonstrated that these have dramatically underperformed relative to initial expectations and are associated with risks that were not appreciated at the time of their initial authorization. These issues have had dramatic long-term consequences for all Canadians. What follows is a discussion of some of the data that highlight where COVID-19 policies, especially those involving COVID-19 inoculations, have been flawed and/or have caused or could continue to cause harm, which, in some cases, will be irreparable.

2. Dr. Byram Bridle’s Credentials and Expertise Relevant to COVID-19

Dr. Bridle is an Associate Professor of Viral Immunology in the Department of Pathobiology at the University of Guelph. His academic appointment as an independent researcher and faculty member began in January 2012. He received a MSc and PhD in immunology and completed a post-doctoral fellowship in viral immunology. His research program focuses on the development of vaccines to prevent infectious diseases and treat cancers, as well as studying the body’s immune

responses to viruses. The overall aim of Dr. Bridle's research efforts is to develop safe and effective new therapies for people. Indeed, one of his previous cancer therapies progressed into four human clinical trials. He teaches in several courses at the undergraduate and graduate level on the topics of immunology, virology, and cancer biology. He is also involved in training Canada's next generation of multidisciplinary researchers. With respect to COVID-19, Dr. Bridle received funding from the Ontario government (COVID-19 Rapid Research Fund, Ministry of Colleges and Universities) and federal government (Pandemic Response Challenge Program, National Research Council of Canada) to develop vaccines against COVID-19. The scope of this COVID-19 'vaccine' research is limited to the pre-clinical realm and is, realistically, likely years away from being ready for testing in a clinical trial. Notably, clinical trial work would require new funding at a substantially higher dollar value. He also holds numerous grants in support of his cancer research and basic viral immunology research programs including, but not limited, to the Canadian Institutes for Health Research, Natural Sciences and Engineering Research Council of Canada, Canadian Cancer Society, and Cancer Research Society. Since the declaration of a COVID-19 pandemic he has been actively involved in disseminating fact-based, balanced scientific information to the public and policy makers to assist people with making fully informed decisions. This has included ~200 media engagements ranging from radio shows, published articles, and appearances on televised news programs, spanning the local to international scope. Dr. Bridle was also an invited keynote speaker for two international conferences that focused on COVID-19 and served as an invited member of ~10 COVID-19-focused discussion panels. Vaccinology is a sub-discipline of immunology. Dr. Bridle teaches the value of high-quality, well-validated, robustly safety-tested vaccines and promotes their use. He considers vaccines that have been developed on a foundation of sound science to be the most efficient type of medicine; they have cost-effectively saved millions of people from sickness and/or death. However, Dr. Bridle is concerned that the risk-benefit profile of SARS-CoV-2 'vaccines' currently being used in Canada and elsewhere is not appropriate for mass immunization, let alone mandating them. His scientific reasoning, which is substantiated by extensive peer-reviewed scientific literature is contained within this report.

It is important to note that Dr. Bridle was qualified as an expert within a previous judicial proceeding dealing with issues very similar to those being opined upon within this report (*Her Majesty the Queen in Right of Ontario v. Adamson Barbeque Limited & William Adamson Skelly*, Court File No. CV-20-00652216-0000). Additional qualifications can be found in Dr. Bridle's *curriculum vitae* (attached).

3. Dr. Bridle Has a Track Record for Identifying Safety Concerns with COVID-19 Vaccines

Here are two examples that illustrate Dr. Bridle's successful track record for following the accumulation of scientific data to accurately identify safety signals that were eventually heeded by federal agencies managing Canada's COVID-19 vaccine program:

Example #1: When Health Canada authorized the use of AstraZeneca's vaccine, Dr. Bridle, along with two colleagues, wrote an open letter that was sent on March 16, 2021 to many people, including Health Canada, the Public Health Agency of Canada, Prime Minister Trudeau, Canada's Chief Medical Officer, Ontario Public Health, Ontario's Medical Officer of Health, Ontario's Minister of Health, and the National Advisory Committee on Immunization, requesting that this vaccine not be used, in part on the grounds that it was being investigated for a link to potentially fatal blood clots in many European countries. Approximately two months later, Canada suspended the AstraZeneca COVID-19 vaccination program, because it was deemed to be too unsafe because of causing blood clots that cost the unnecessary loss of lives of Canadians. This also resulted in a fiasco that left many Canadians with having received only a single dose of the AstraZeneca vaccine. This led to the unusual decision to start mixing and matching doses from different manufacturers, which lacked scientific evidence of safety and efficacy.

Example #2: More recently, Dr. Bridle was heavily criticized for raising concerns in a short radio [interview](#)¹ about a potential link between mRNA-based COVID-19 vaccines and heart inflammation in young people, especially males. This is now a well-recognized problem that has been officially listed as a potential side-effect of the mRNA COVID-19 vaccines. It was also the subject of a recent Public Health Ontario Enhanced Epidemiological Summary [Report](#)² highlighting the increased risk of myocarditis and pericarditis to young males following COVID-19 mRNA vaccination. This was followed by a suspension of Moderna's COVID-19 vaccination program in [Ontario](#) for males 18-24 years of age³.

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

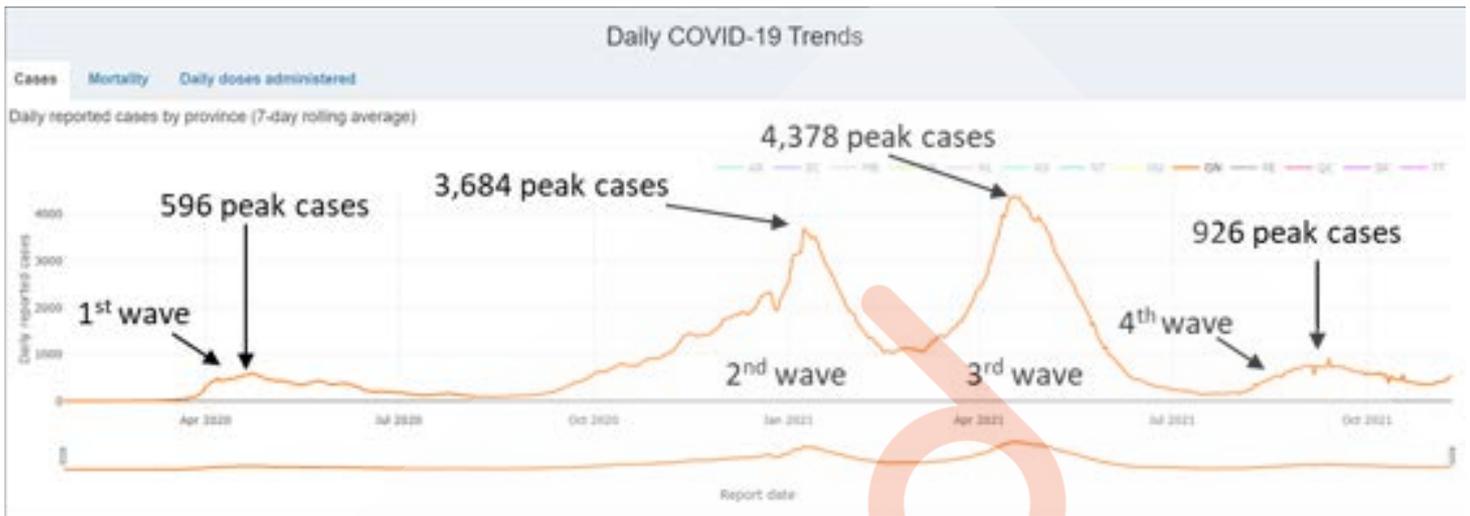
Infection fatality rate (IFR) is a way to assess how dangerous a pathogen is. It is calculated based on the number of people that die from among the total number that were infected. Early in the declared COVID-19 pandemic, it was estimated that the IFR for SARS-CoV-2 was at least 10-fold higher than for a serious outbreak of an influenza virus, or ~1%. Indeed the IFR for a bad 'flu' season can be as high as ~0.1%⁴.

It is important to note that calculating an accurate IFR requires having accurate data for the denominator in the equation, which is the total number of people that have been infected. Exacerbated by Canada's lack of testing for evidence of seroconversion (*i.e.*, when pathogen-specific antibodies are present in an individual, which indicates they were infected) against SARS-CoV-2, it has been impossible to ascertain how many Canadians have been infected. However, as data have accumulated in countries that did practice due diligence in this area, the total number of infections that have occurred keeps getting re-adjusted to higher numbers. This is due to phenomena such as the large number of people that were infected but did not realize it because they never became ill. As a result, the actual IFR for SARS-CoV-2 has been steadily declining. Remarkably, as the data regarding total infections has become more accurate, the IFR for SARS-CoV-2 has dropped to only ~0.15%⁵. It is likely that this IFR will drop even further as the extent of unnoticed infections is further elucidated. Indeed, a recent study found that ~90% of randomly tested healthy adults in British Columbia had been exposed to SARS-CoV-2. This suggests that

the denominator for determining the true IFR is likely substantially [higher](#) than previously appreciated, which would mean the IFR is less than 0.15%⁶. Further, this IFR includes the high-risk frail elderly and immunocompromised. For Canadians who are outside of these high-risk demographics, the IFR would be much less than 0.15%.

As of April 1, 2021, the [population](#) of Ontario was 14,789,778⁷. As seen in figure 1a, there have been four complete waves of reported cases of COVID-19 in this province. Note that waves three and four occurred despite the public rollout of COVID-19 vaccines. Further, there is some evidence that a fifth wave of 'cases' may be developing. This provides strong evidence that the current COVID-19 vaccines are unable to control the spread of SARS-CoV-2. Unfortunately, Ontario has refused to document the severity of 'cases', which can potentially range from asymptomatic (in which case they should not be defined as having COVID-19 because there is no apparent disease) to mild to moderate to severe but non-lethal to severe and lethal. As such, one is unable to appreciate that the cases have progressed towards lower average severity over time. Where this is evident, however, is in figure 1b, which shows ever-declining fatality associated with cases of COVID-19, despite dramatic increases in the peak number of daily cases in waves two and three relative to wave one; and more daily cases in the fourth wave compared to wave one. A reasonable and probable explanation for this is that those who were most susceptible to COVID-19 died in the first wave, which is to be expected for any potentially lethal new infectious pathogen. Remarkably, only six Ontarians under the age of 20 have had their deaths attributed to COVID-19 in a period of almost 22 months (figure 2); and this is with a complete absence of COVID-19 vaccination in those under the age of twelve. Among all Ontarians under the age of 60, only 803 (out of a total of 14,789,778 people⁸) have had their deaths attributed to COVID-19 after almost 22 months (figure 2); and this includes people who had pre-disposing medical conditions. This clearly demonstrates that SARS-CoV-2 is not a major issue for young Ontarians.

(A)



(B)



Figure 1: COVID-19 case and mortality data for Ontario.

(A) This graph shows the number of daily 'cases' of COVID-19 in Ontario. Note that the definition of a case is controversial due to issues related to how these are defined. (B) The number of daily deaths attributed to COVID-19 in Ontario. These data were downloaded on November 11, 2021, from the COVID-19 dashboard, for which data are curated by the COVID-19 Canada Open Data Working Group, Dalla Lana School of Public Health, University of Toronto (<https://art-bd.shinyapps.io/covid19canada/>).

Counts and rates of deaths among cumulative COVID-19 cases by age group in Ontario

January 15, 2020 to November 10, 2021

The bars show the total confirmed COVID-19 deaths reported since the beginning of the pandemic.

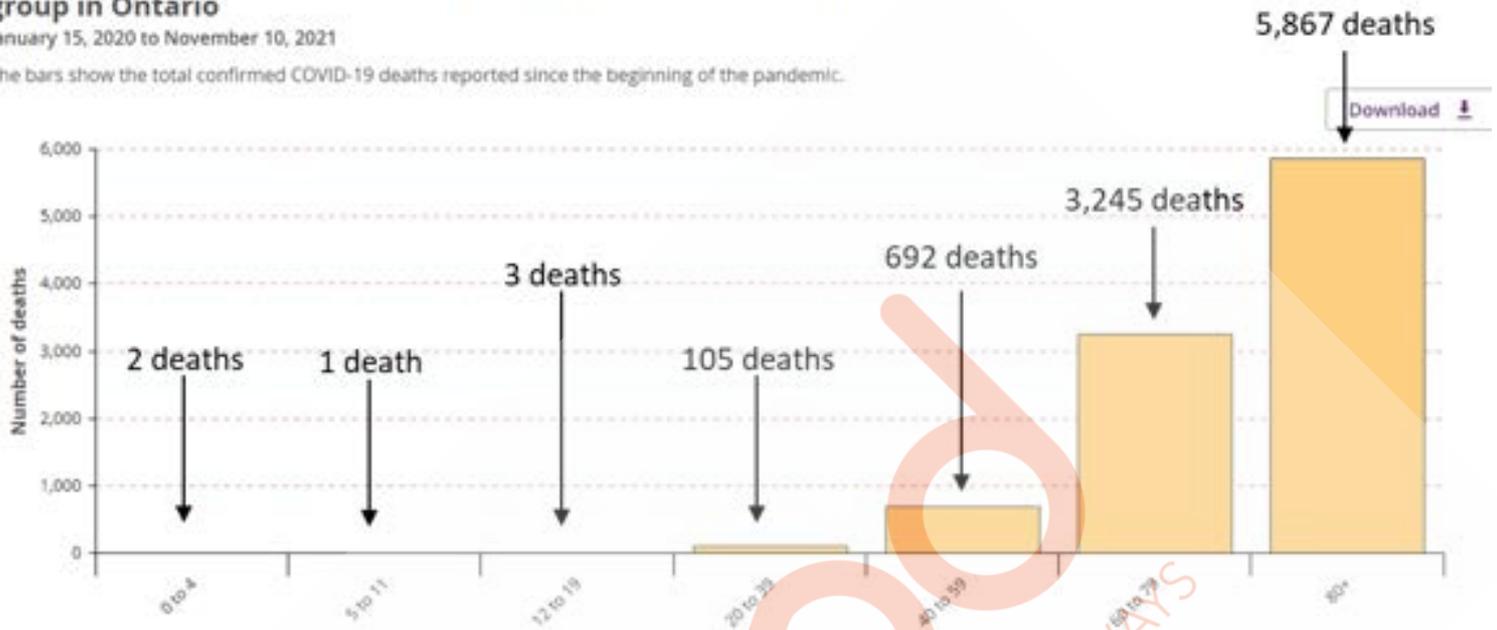


Figure 2: Cumulative deaths in Ontario that were attributed to COVID-19.

This graph shows cumulative deaths by age group between January 15, 2020, and November 10, 2021 (a span of 1 year, 9 months, and 28 days). These data were downloaded on November 11, 2021, from the website for Public Health Ontario (<https://www.publichealthontario.ca/en/data-and-analysis/infectious-disease/covid-19-data-surveillance/covid-19-data-tool?tab=ageSex>)

The dynamics of spreading of SARS-CoV-2 and its decreasing harm to the population of Ontario over time is typical of infectious diseases. SARS-CoV-2 has not demonstrated novel or unprecedented population dynamics, other than causing much less harm than expected in very young children whose immune systems are still developing. From an immunological perspective, the data in figures 1 and 2 are indicative of an infectious agent that has been running a typical course in the population. Its harm is decreasing over time. Mortality data for Ontarians under the age of 60 demands that a proper risk-benefit analysis be performed to place the high cost of pandemic-associated public health policies into a proper context. For example, in the year 2019, 543 Ontarians died due to motor vehicle accidents⁹. These deaths would also be preventable with the implementation of stay-at-home orders. Further, many chronic fatal diseases (*e.g.* cancers, heart disease, *etc.*) have been relatively neglected in favour of diverting resources to COVID-19 lockdown measures. This will result in irreparable future harm in the form of increased death rates that have yet to be determined. And this does not account for other deaths indirectly caused by COVID-19 policies, including suicides due to increased mental health issues, *etc.* Indeed, the government of Ontario needs to determine if their current policies have placed a premium on lives

lost due to COVID-19 over those lost to other causes. Revising or revoking lockdown policies could result in a net saving of lives in Ontario. Notably, vaccines that fail to confer sterilizing or near-sterilizing immunity and that have a duration of immunity of less than one year can never resolve the cyclic nature of SARS-CoV-2. This virus is now endemic and will likely follow an annual wave-like pattern (in terms of cases) similar to other respiratory pathogens that we live with. This annual cyclic pattern in Ontario is largely driven by what immunologists like to call 'low vitamin D season' (others call it the cold and flu season). This is because vitamin D is an essential vitamin that is needed in substantial quantities for the immune system to perform its myriad duties. A lack of vitamin D is to the immune system what a lack of fuel is for a car. The reason why we have not yet progressed to a seasonal cycle of SARS-CoV-2 infections is due to the lockdown measures that have been implemented. Lockdowns in conjunction with poorly performing COVID-19 vaccines can only delay 'cases'. Ontarians must not fear 'cases'. Remember, the common cold is a 'case' of a respiratory disease but attempts to avoid this should never involve anything that looks like the current lockdowns. The available public health data clearly demonstrate that the danger of SARS-CoV-2 has steadily declined over the past 22 months. Obviously, the predictions of a horrific fourth wave driven by the Delta variant failed to be realized.

Conclusion: The IFR for SARS-CoV-2 was vastly overestimated at the beginning of the declared pandemic. It is now approaching the range of a serious influenza outbreak (less severe than a serious flu for people outside the highest risk demographics). Also, severe forms of COVID-19 are limited to a more restricted demographic (*i.e.*, unlike influenza viruses, SARS-CoV-2 is not particularly dangerous to the very young). An IFR of only 0.15% is not suggestive of an infectious disease of pandemic proportions. This is further supported by case fatality data that clearly suggest that COVID-19 is not a serious issue for most Ontarians, even as multiple variants of concern have passed through the population. A more logical approach to managing the pandemic would have been and still would be to implement the standard, historically successful public health policy of isolating and protecting the relatively few high-risk individuals, not the entire population. Excessive slowing of the development of naturally acquired SARS-CoV-2-specific immunity among the majority of Canadians who are at low risk of developing anything more than moderate COVID-19 probably has and continues to allow deaths to occur among the high-risk demographics who otherwise would have been protected following the acquisition of 'herd immunity' in Canada. The public health data suggest that the current COVID-19 vaccines, unlike naturally acquired immunity, will be unable to support the goal of stopping the spread of SARS-CoV-2 via herd immunity.

5. PCR Testing Should Not Have Been the Gold Standard to Detect SARS-CoV-2

A common way to detect the presence of a virus in a clinical sample is to use what is called a nucleic acid test (NAT). These kinds of tests work by detecting the presence of the genetic material (*i.e.*, genome) of the virus. Indeed, viral genomes are composed of building blocks known

as nucleic acids. Commonly used NATs fall under the umbrella term ‘nucleic acid amplification tests’ (NAATs). These tests incorporate a step that amplifies or increases the amount of the virus-derived genetic material, thereby making it easier to detect. There are different kinds of NAATs, including but not limited to ‘reverse transcription - polymerase chain reaction’ (RT-PCR), ‘transcription-mediated amplification’ (TMA), and ‘loop-mediated isothermal amplification’ (LAMP). However, since RT-PCR is the most common method being used in laboratory-based testing during the pandemic, that will be the focus of this discussion.

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

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

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

material. The National Collaborating Centre for Infectious Diseases in Canada published the general guide for interpreting results of RT-PCR tests for SARS-CoV-2 shown in table 1¹⁰.

In addition to the potential for false signals at high Ct values, note that high values can also be indicative of detection of non-viable viral particles. It is important to note that SARS-CoV-2 particles can exist in two basic forms: 1. Replication-competent; this is the form with the potential to cause COVID-19. 2. Replication incompetent; this cannot cause COVID-19. Following clearance of SARS-CoV-2 from the body, full and/or partial genomes of SARS-CoV-2 can remain for many days. One key reason for this is that some phagocytic cells, which are a component of the innate immune system, can be long-lived. The three primary phagocytic cells in the body are neutrophils, macrophages, and dendritic cells. Neutrophils are the ‘first responders’ of the immune system. They rapidly infiltrate sites of SARS-CoV-2 infection and begin to phagocytose (*i.e.*, consume or internalize) SARS-CoV-2 particles. The neutrophils, which are short-lived, then recruit macrophages and dendritic cells to the site of infection. Note that dendritic cells also reside at strategic sites of infection where they can immediately begin to phagocytose SARS-CoV-2. The macrophages and dendritic cells are much larger than neutrophils and can phagocytose relatively large quantities of the virus and can be relatively long-lived. One of the reasons for this is because these two cell types are critical for activating T cells and B cells, which are the key effectors against viral infections. Phagocytosis of SARS-CoV-2 is a mechanism to kill and remove the virus from the body and to activate other immunological effector cells. As such, these can be a source of SARS-CoV-2 genomes that could be amplified by a RT-PCR test. However, these genomes would not have the potential to cause COVID-19. Persistence of whole or partial genomes that are not associated with infectious particles is well-documented for a variety of viruses, including measles¹¹, Middle East respiratory syndrome-coronavirus¹², and other coronaviruses¹³.

A very recent scientifically peer-reviewed article argued that a reasonable cut-off for cycle numbers for good-quality RT-PCR tests for SARS-CoV-2 is thirty-four¹⁴. However, most RT-PCR tests for SARS-CoV-2 exceed 34 cycles¹⁵. For example, Public Health Ontario runs the test at 40 cycles. Their definition of a negative result is if there was no fluorescent signal detected at the end of the full 40 cycles. Any signal detected at the end of 38 cycles is declared to be a positive case. Remarkably, if they detect the viral genome between 38 and 40 cycles, they define the result as a ‘probable case’ for public health reporting.

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

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

Jonathan Gubbay, a medical microbiologist with Public Health Ontario, has been quoted on their website as saying the following: "In Ontario, we use PCR as the gold standard of testing for COVID-19 because it is able to successfully detect tiny amounts of the virus (sensitivity) with a low chance for error (accuracy) compared to other types of lab tests."¹⁶ The problem is that PCR tests do not represent gold standard assays for determining if potentially infectious viruses are present. Instead, the gold standard assay for this is the inoculation of cultured cell lines and then looking for evidence of infection (e.g. cytopathic effect, which means killing of cells¹⁷). An in vitro biological assay like this can then be used to correlate Ct values with infectivity of SARS-CoV-2. However, this type of gold standard functional test has not actually been standardized to date in Canada. Interpreting the RT-PCR test is challenging, to say the least, without a functional test to compare it to. Of particular concern in the context of the high cycle numbers being used by labs such as those at Public Health Ontario (*i.e.*, 40 cycles, with 38 being defined as 'positive'), is the fact that several studies have been conducted to determine the highest Ct value at which SARS-CoV-2 could be successfully cultured in cells. The results were 25¹⁸, 26¹⁹, 22-27²⁰, 30²¹, and 24 for a study conducted at Canada's own National Microbiology Laboratory¹⁸. This suggests that tests with Ct values above 22-30 are almost certainly not indicative of the presence of replication-competent SARS-CoV-2. The conclusion is that it is erroneous to declare samples with high Ct values, especially those above 30, as being positive for infectious SARS-CoV-2. It was even concluded in a study by La Scola B, et al., concluded that patients testing 'positive' with Ct values above 33-34 could likely be discharged from hospitals²². This means that a very large but unknown number of positive cases reported in Ontario were likely not true positives.

RT-PCR-based testing in Ontario is not standardized. Across the province labs use different sample preparation methods, protocols, and gene targets. Variability in Ct values (up to 8 cycles). This has prompted Public Health Ontario to discourage the reporting of Ct values <35 alongside test results. Indeed, Ct values <35 are only available upon special request¹⁶.

The types of specimens and the quality of their collection can influence the results of RT-PCR tests. Public Health Ontario recommends this for sample collection for use with the RT-PCR assay: "The gold standard for sample collection method is the nasopharyngeal swab, a swab inserted deep into a person's nose. However, other sample types exist including combinations of a nose and throat swab and also saliva samples."¹⁶ This is of concern because the United States Centres for Disease Control and Prevention "does not recommend NAATs that use oral specimens (*e.g.*, saliva) for confirmatory testing and instead suggests the use of specimens that are considered optimal for detection, such as nasopharyngeal, nasal mid-turbinate, and anterior nasal swabs."²³

It is important to note that the problems associated with laboratory-based RT-PCR assays for the detection of SARS-Cov-2 are likely worse for point-of-care tests that rely on similar technology. Indeed, the United States Centres for Disease Control and Prevention acknowledge that "Sensitivity varies by test, but laboratory-based NAATs generally have higher sensitivity than point-of-care tests or tests that can be used anywhere."²³ Further, the United States Centres for Disease Control and Prevention and the United States Food and Drug Administration note the following limitations of RT-PCR tests for SRS-CoV-2: 1. The presence of viral RNA in the sample might not indicate the presence of infectious virus, 2. The presence of viral RNA does not

necessarily imply that SARS-CoV-2 is the causative agent of COVID-19, 3. The test cannot rule out diseases caused by other bacterial or viral pathogens, 4. The test is not suitable for screening blood and blood products for the presence of SARS-CoV-2, 5. If the virus mutates in the predetermined target region, the test is invalid²⁴.

Conclusion: RT-PCR tests are based on a remarkable technology. However, they never should have been used as a stand-alone gold standard test for defining cases of COVID-19. Every lab running 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 >24 failed to demonstrate the presence of potentially infectious viral particles. Further, the presence of replication-competent viral particles in a sample does not necessarily equate to a case of COVID-19. The latter can only be defined if an active infection is present in conjunction with signs and/or symptoms of illness; the latter would require assessment by a physician. Remarkably, however, places like Public Health Ontario have been categorizing samples with ct cut-offs of up to 38 cycles and, in some cases, an absence of clinical data, as representing positive cases of COVID-19. This is preposterous, especially in the absence of publicly available data proving that the ct cut-off was established using the gold standard functional virology assay. Consequently, cases of COVID-19 have likely been dramatically overestimated, but to an unknown degree. Overestimation of the problem of COVID-19 has resulted in unnecessary pressures to force COVID-19 vaccines on individuals.

6. Asymptomatic Transmission of SARS-CoV-2 is Negligible

The definition of an asymptomatic individual is a person who is known to be infected with a microorganism but fails to develop symptoms associated with a disease. Indeed, we are all 'asymptomatic carriers' in the sense that we harbor vast numbers of bacteria and viruses in and on our bodies. However, these normal microbiomes usually do not cause us any disease, unless we become immunosuppressed or 'safe' microbes get transferred to anatomical locations where they can potentiate disease (*e.g.*, fecal-to-oral transfer of some strains of *Escherichia coli*). So, in the context of SARS-CoV-2, an asymptomatic carrier would be defined as an individual that is infected with the virus but fails to develop COVID-19.

Viral culture studies suggest that pre-symptomatic individuals can potentially shed infectious SARS-CoV-2 one to two days before the onset of symptoms and continue to be infectious up to seven days thereafter²⁵. However, a study of the prevalence of SARS-CoV-2 in ~10 million people in Wuhan, China found no evidence of asymptomatic [transmission](#)²⁶. In the United Kingdom, the 'Scientific Advisory Group for Emergencies' recommended that "Prioritising rapid testing of symptomatic people is likely to have a greater impact on identifying positive cases and reducing transmission than frequent testing of asymptomatic people in an outbreak area"²⁷. Consequently,

they have asked their government to [change](#) their testing policy by moving away from asymptomatic testing.

The World Health Organization [notes](#) that “Most PCR assays are indicated as an [aid for diagnosis](#), therefore, health care providers must consider any result in combination with timing of sampling, specimen type, assay specifics, clinical observations, patient history, confirmed status of any contacts, and epidemiological information”²⁸.

On its own, a positive result on a PCR test to detect SARS-CoV-2 is insufficient to diagnose COVID-19, yet this has become routine in Ontario and the rest of Canada. In addition to the potential for false positive tests, true positive results can also be obtained from genomes of SARS-CoV-2 particles that are no longer infectious. An example of the latter would be an individual who has mounted an effective immune response and may have remnant replication-incompetent viral particles or partially degraded viral genetic material inside relatively long-lived phagocytic cells that have killed the virus. Indeed, following clearance of SARS-CoV-2 from the body, full and/or partial genomes of SARS-CoV-2 can remain for up to several weeks. One key reason for this is that some phagocytic cells, which are a component of the innate immune system, can be long-lived. Phagocytosis of SARS-CoV-2 is a mechanism to kill and remove the virus from the body and to activate other immunological effector cells. As such, these can be a source of SARS-CoV-2 genomes that could be amplified by a PCR test. However, these genomes would not have the potential to cause COVID-19. Persistence of whole or partial genomes that are not associated with infectious particles is well-documented for a variety of other viruses, including measles¹¹, Middle East respiratory syndrome-coronavirus¹², and other coronaviruses¹³.

Too often, a positive PCR test for the presence of SARS-CoV-2 is being used, on its own, to define positive cases of COVID-19. However, the presence of a portion of the viral genome in an individual, on its own, does not necessarily equate with disease (*i.e.* COVID-19). To be declared COVID-19, the infection would also have to be associated with expected signs and/or symptoms. The latter is known as a clinical diagnosis and would be based on evaluation by a physician, in conjunction with the test results. A gold-standard test for infectivity of a virus is a cell-based functional assay that determines the potential to cause cell death. However, such an assay is not in routine use in Canada. The absence of a test of the infection-potential of a virus further confounds any meaningful interpretation of positive results in asymptomatic people. Drawing conclusions based solely on the results of laboratory tests, would take the diagnosis of diseases out of the hands of physicians, and place the onus for this on technicians employed by testing laboratories. Further confounding this issue is the fact that cases of COVID-19 can be claimed in the absence of confirming infection with SARS-CoV-2 (this is known as “[ICD code U07.2](#) COVID-19, virus not identified”)²⁹. Worse, the definition of a case of COVID-19 has [changed](#) over time in Canada. Indeed, the government of Canada has stated the following on their website: “[Previous versions of the COVID-19 case definition](#) are available upon request. Please email COVID19Surveillance@canada.ca to request a copy or for more information.”²⁹.

Positive PCR tests for SARS-CoV-2 in asymptomatic people are often based on high Ct values, which, in and of themselves, raise the question of whether these individuals harbor infectious viral particles. The low prevalence of positive PCR tests in asymptomatic people often does not differ

much from the false positive rate. These issues combined with the absence of a functional cell-based assay to prove infectivity renders results of asymptomatic testing nearly impossible to interpret accurately. Indeed, the World Health Organization, agreeing with many health professionals around the world, has emphasized that spreading of SARS-CoV-2 by asymptomatic individuals is [rare](#) and an emphasis should be placed, therefore, on testing people with signs or symptoms of illness, not those who are apparently healthy³⁰. Of particular concern in the context of the high cycle numbers being used by labs in Ontario (*i.e.* up to 38 cycles being defined as ‘positive’ by Ontario Public Health¹⁶), is the fact that several studies have been conducted to determine the highest Ct value at which SARS-CoV-2 could be successfully cultured in cells. The results were 24¹⁸, 25¹⁸, 22-27²⁰, 30²¹. This suggests that tests with Ct values above 24-30 are not indicative of the presence of replication-competent SARS-CoV-2. The logical conclusion is that it is erroneous to declare samples with high Ct values, especially those above 30, as being positive for infectious SARS-CoV-2 unless the gold standard functional virology assay has been used to justify it. Indeed, figure 3 shows results of a published [study](#) that depicts the frequency at which asymptomatic people tested positive for SARS-CoV-2 relative to that observed for people with symptomatic infections³¹. Remarkably, if the cut-off for positive test results was set to Ct values of 24-30 (*i.e.* the point beyond which samples fail to yield potentially infectious virus particles), the vast majority of ‘positive test results’ would be rendered negative. It was even concluded in a study by La Scola B, *et al*, that patients testing ‘positive’ with Ct values above 33 could likely be discharged from hospitals²². This means that an unknown number of positive cases reported in Ontario were likely not true positives, especially if individuals were asymptomatic. This is further supported by evidence that asymptomatic people have detectable SARS-CoV-2-specific memory T cells after exposure to the virus, which would be inconsistent with a risk of them spreading the virus to others³².

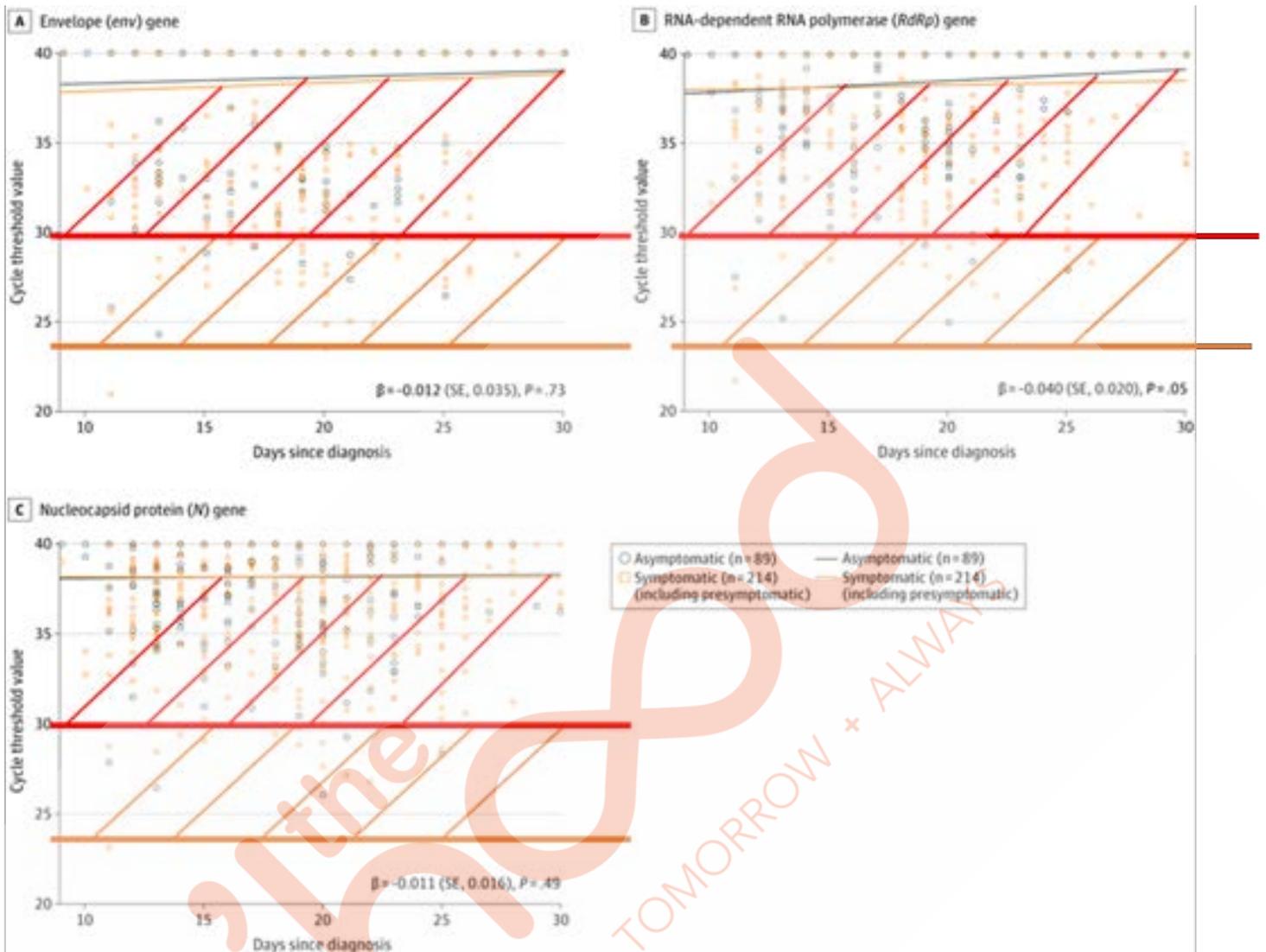


Figure 3: Most 'positive' results for the SARS-CoV-2 PCR test are negative based on the gold standard virology assay.

Shown are graphs from figure 2 of a paper published in the *Journal of the American Medical Association*. The argument being made was that the frequency at which asymptomatic people tested positive for SARS-CoV-2 was like that observed for people with symptomatic infections. However, new cut-offs for a positive test result were placed at 24 (orange line) and 30 (red line) PCR cycles. These are the limits (depending on the laboratory) at which replication-competent SARS-CoV-2 can no longer be recovered from samples according to the gold standard functional virology assay. When this is done, it is apparent that most the results would be negative (*i.e.*, these samples would fail to transmit infectious SARS-CoV-2).

Importantly, false positive test results, which have a greater risk of happening among asymptomatic people, have been shown to have numerous negative [consequences](#) in terms of physical and mental health, and causes financial losses³³.

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

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

Several published studies have shown that the immune response against SARS-CoV-2 infections is robust, effective, broadly targets multiple components of the virus and confers memory that lasts at least as long this aspect has been able to be studied within the context of a novel pandemic³⁴⁻³⁹.

Conclusions: Testing of asymptomatic people for the presence of portions of the SARS-CoV-2 genome does not make medical nor economic sense. Positive test results from asymptomatic individuals cannot be interpreted in a clinically meaningful way. Although asymptomatic transmission is possible, it is improbable that it is occurring in substantial numbers and does not represent a significant risk of causing COVID-19-related hospitalizations or deaths in others. The scientific evidence demonstrates that immune responses following infection with SARS-CoV-2 are protective and long-lasting. There is no evidence that people who previously tested positive for SARS-CoV-2 represent a substantial risk of causing COVID-19-related hospitalizations or deaths in others. In immunology anything is possible, but not everything is probable. This is the case for the concept of asymptomatic transmission of viruses. People who test positive for SARS-CoV-2 with the RT-PCR test set an appropriate cut-off such as a ct value of 24, as determined by the National Microbiology Laboratory, are asymptomatic. This mis-labeling of healthy individuals as asymptomatic spreaders of SARS-CoV-2 is almost certainly due to the misuse of the RT-PCR test. People who are ‘asymptomatic’ and then become sick with COVID-19 were technically pre-symptomatic and most of these people would have insufficient quantities of viral particles to meet the threshold needed to infect someone else.

7. It is Improbable That Individuals Who Overcame a SARS-CoV-2 Infection Can Re-Transmit the Virus

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

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

Several published studies have shown that the immune response against SARS-CoV-2 infections is robust, effective, broadly targets multiple components of the virus and confers memory that lasts at least as long this aspect has been able to be studied within the context of a novel pandemic³⁴⁻³⁹.

Conclusion: The scientific evidence demonstrates that immune responses following infection with SARS-CoV-2 are protective and long-lasting. There is no evidence that people who previously tested positive for SARS-CoV-2 represent a substantial risk of causing COVID-19-related hospitalizations or deaths in others.

8. SARS-CoV-2 Variants of Concern

Many viruses mutate over time. This includes coronaviruses. Indeed, these viruses have an error-prone mechanism of copying their genome. This provides a strategy to adapt to novel environmental pressures. Of concern for SARS-CoV-2 is the potential for randomly generated mutants to sufficiently alter the structure of their spike protein to be able to evade the narrowly conferred spike protein-specific immunity conferred by all the first-generation COVID-19 vaccines while maintaining the ability to infect cells. Since the beginning of the pandemic, large numbers of mutant viruses have been identified. However, three core lineages of the variants are of current concern⁴⁰: 1. B.1.1.7, also known as the UK variant⁴¹, 2. B.1.351, also known as the

South African variant⁴¹, 3. P.1, the Brazilian variant⁴². SARS-CoV-2 from the B.1.351 lineage can largely bypass the immunity conferred by AstraZeneca's COVID-19 vaccine. However, the Pfizer and Moderna vaccines remain effective against all three lineages for the VOCs.

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

Importantly, naturally acquired immunity against SARS-CoV-2 has been shown to be both long-lasting and protective. Notably, this type of immunity would be expected to be particularly protective against emerging VOCs because it is very broad, meaning that it targets multiple components of SARS-CoV-2, with both T cells and antibodies induced as effector mechanisms. Indeed, evidence of the breadth of naturally acquired immunity has recently been published⁶. In contrast, current vaccine-induced immunity targets a single protein, with a strong bias towards antibody-mediated responses. Notably, the B.1.1.7, B.1.351, and P.1 variants of SARS-CoV-2 are of concern because of their altered spike proteins, particularly in the 'receptor binding domain' (*i.e.*, the portion that binds to the ACE2 molecule on host cells), which is the primary target of neutralizing antibodies. So, although there is evidence of some monoclonal antibodies failing to recognize the spike protein in some VOCs and some convalescent sera (*i.e.*, sources of antibodies) being less able to neutralize the VOCs, T cells can effectively recognize conserved regions of the spike protein as well as other viral proteins.

Since SARS-CoV-2 has shown such a propensity to mutate, it is reasonable to expect this virus will become endemic. Indeed, should a variant emerge that can completely bypass the spike-specific immunity conferred by the current vaccines, additional immunizations will be required with re-designed vaccines, especially for those without naturally acquired broad-based immunity. Repeated boosting with an ineffective vaccine would simply be a waste of time, money, and resources and would increase the risks of harm associated with the current COVID-19 inoculations.

The current COVID-19 vaccines have become relatively ineffective in combating the transmission of the newer delta variant and are expected to be even less effective with the emerging 'mu' variant. A recent United Nations report states that mu "has a number of mutations that suggest it could be more resistant to vaccines."⁴³ Also, on August 19, 2021, the United States Centres for Disease Control admitted that, "those who were vaccinated early are at increased risk of severe disease as vaccine effectiveness is waning."⁴⁴ The current global situation is that fully vaccinated individuals can play a role in the production of variants, can catch, and transmit the virus, and can even die from the virus.⁴⁵⁻⁴⁸

Conclusion: The goal in Canada should not be to get everyone vaccinated *per se*. Instead, the goal should be to get as many Canadians immune to SARS-CoV-2 as possible. There are two ways to achieve this: 1. Vaccination, 2. Natural acquisition of immunity. The great news is that Canada might be closer to the natural acquisition of herd immunity than what was previously appreciated⁶, likely due, in large part, to the ongoing spread of the virus after the implementation of ineffective

masking and misguided physical distancing policies that failed to account for the physics behind aerosol-mediated transmission of SARS-CoV-2. Like many other viruses, including other coronaviruses and influenza viruses, SARS-CoV-2 will likely become endemic, meaning that we may encounter new versions of the virus on a regular and long-term basis. As such, it is imperative that we learn to live with SARS-CoV-2 rather than attempting to hide from it; just like we have done with the other respiratory pathogens that we have accepted as a trade-off for living our lives outside the confines of lockdowns. This can be supported by prophylactic strategies such as promoting vitamin D supplementation and via the use of effective, scientifically supported early treatment strategies based on drugs with extensive safety records such as ivermectin. Current data such as those shown in figures 1 and 2 demonstrate that the current VOCs are more transmissible, but less dangerous. Transmissibility in and of itself is not something to fear. Common cold-causing viruses are highly transmissible but not dangerous.

9. Low-Cost Masks Cannot Prevent Spreading of Aerosols and, Therefore, Lack Rationale for Use with Asymptomatic/Healthy People

It is now widely recognized that SARS-CoV-2 is effectively spread via aerosols coming from the respiratory system⁴⁹⁻⁵³. A pulmonary (*i.e.*, lung-derived) aerosol is a suspension of fine water droplets suspended in exhaled air. Many people who wear glasses will be familiar with these aerosols. Indeed, when a person exhales onto the lenses of their glasses to polish them with a cloth, the liquid being deposited is due to the condensation of the lung-derived aerosol. Also, these aerosols can be readily visualized when exhaling into cold air, which causes the fine droplets to condense (*i.e.*, drop out of the gaseous phase). Indeed, this condensation effect of cold air minimizes the distance that respiratory aerosols can travel since the condensed water droplets are relatively large. However, in warm air these aerosols are invisible and can potentially travel long distances depending on the rate of ambient air flow. The masks in common use among Canadians (*e.g.*, surgical and cloth masks) lack standardization, users are not required to undergo fit-testing, and even if these were done, they would still lack the ability to prevent the spread of aerosols. Low-cost masks do not seal properly around the face, with leaks commonly occurring around the nose and at the joints of the jaw. Due to simple physics in which air will follow the path of least resistance, most exhaled and inhaled air will leave and enter via these gaps in the masks. This is further exacerbated by anything that increases these gaps. An example would include a beard, which would separate the mask from the chin, thereby replacing the mask material with a coarse-haired filter with massive pore sizes relative to the size of a virus. Anyone who wears glasses, and a mask can attest to the venting issue around the nose, as it often causes the lenses to fog. It seems illogical to force a person's pulmonary exhaust to flow over their eyes, since this is a known route of infection for SARS-CoV-2 and could, therefore, potentiate spreading of the infection in an individual. It was shown that ocular tissues express entry receptors for SARS-CoV-2 and conjunctivitis is common among people diagnosed with COVID-19, sometimes even preceding the onset of signs and symptoms of respiratory distress⁵⁴. As such the eyes could potentially serve as both a portal of entry and a source of person-to-person transmission.

Air venting past the ears, which is the other common location of leakage with low-cost masks, means that aerosols are generally directed behind a person. However, public health policies usually recommend that people turn away from other individuals if they must pass within proximity. If anything, this simply increases the chance of someone being exposed to pulmonary aerosols with a higher flow rate. The principles of distributing pulmonary aerosols over the eyes and behind a person also holds true for face shields. This highlights how poorly thought-out masking policies are. Even if low-cost masks were properly sealed around the neck and face, SARS-CoV-2-laden aerosols and still readily pass through the relatively large pore sizes of the filtering material. Indeed, a study published in 2019 found that the low-cost masks had pore sizes ranging from 80 to 500 μm in diameter⁵⁵. Water droplets that come from the lungs are defined as ‘large droplets’, ‘small droplets’ or ‘droplet nuclei’ and range in size from $>60 \mu\text{m}$, $10\text{-}60 \mu\text{m}$, and $<10 \mu\text{m}$ in diameter, respectively⁵⁶. Coughs and sneezes will discharge droplets of all sizes. However, regular breathing and talking primarily discharges small droplets and droplet nuclei. Notably, SARS-CoV-2 has a diameter of only $\sim 1 \mu\text{m}$. This means that virus-laden droplets in pulmonary aerosols will have a maximum diameter of $\sim 62 \mu\text{m}$, with the vast majority being much smaller (remember that the pores in low-cost masks are $\geq 80 \mu\text{m}$). As such, low-cost masks fail to stop the spread of SARS-CoV-2. One of the biggest challenges in relaying the science is the ‘invisibility’ of the microbial world. To place this into a context that is easier to picture, this would be akin to thinking that a person is locked inside a house when the walls have huge gaping holes (*i.e.*, the leakage points were there proper seals are lacking) and the front door is open (*i.e.*, representing the pore size of a mask). The reality of this scenario is that the person is free to come and go as they wish.

Also, aerosols from the lungs can travel beyond two meters and the directionality will be dictated by air currents⁵⁷. Although the viral load that a person would be exposed to from aerosols would decrease with distance, the long-range potential of aerosols highlights the arbitrariness of two-meter physical distancing policies. Also, buildings with poor ventilation, which encompasses most buildings in Canada, facilitate the build-up of aerosols over time, which further confounds the value of two-meter distancing⁵⁸.

Demonstration of inadequate sealing of low-cost masks around the face are shown in figures 4 and 5. The relative size of SARS-CoV-2-laden water particles and pores of low-cost masks is shown in figure 6. Figure 7 shows how readily aerosols can pass through masks, even when having to pass through five three-ply surgical masks. Figure 8 shows the personal protective equipment required to safely work with containment level-3 pathogens such as SARS-CoV-2.

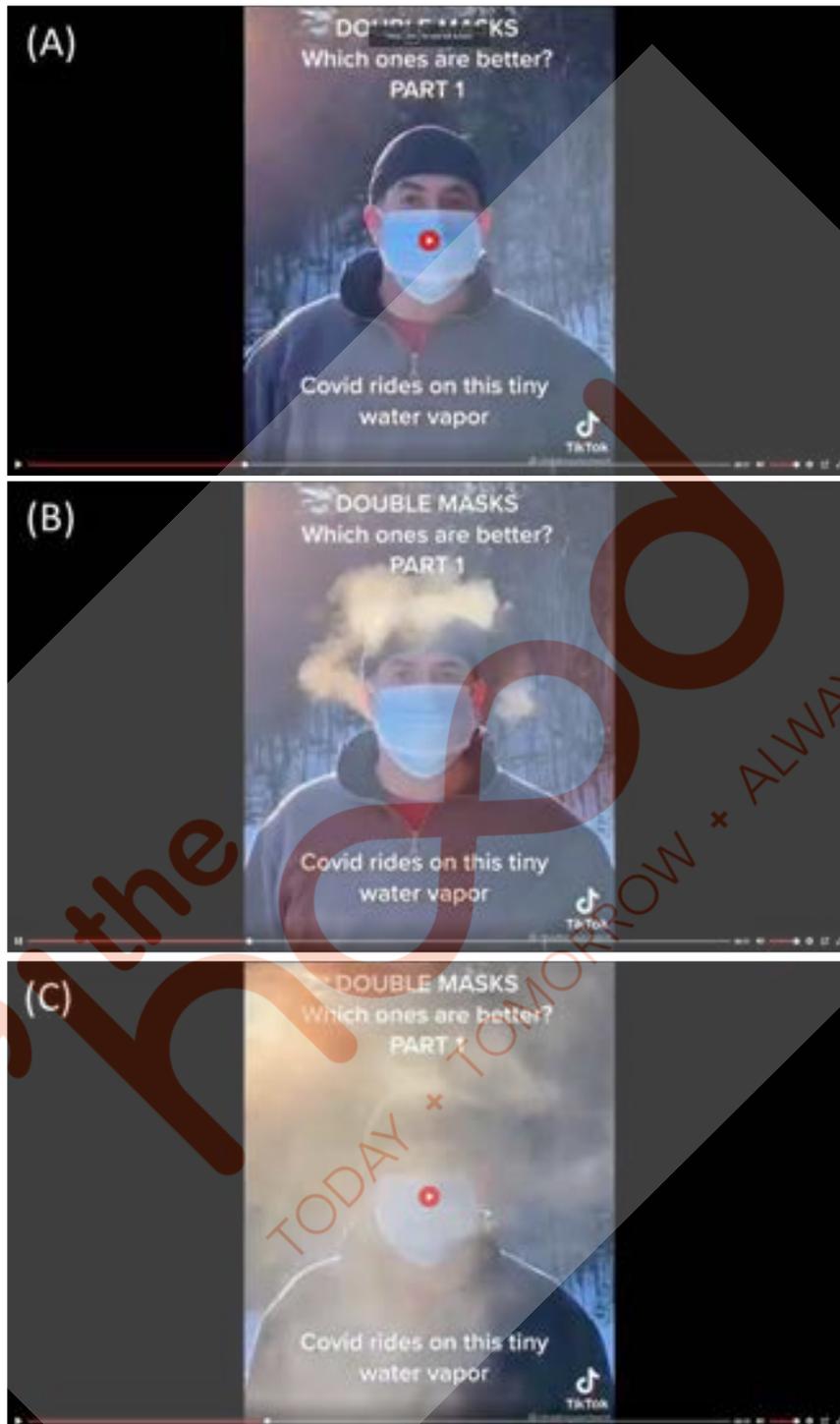


Figure 4: The leakiness of low-cost masks.

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

(A)



(B)

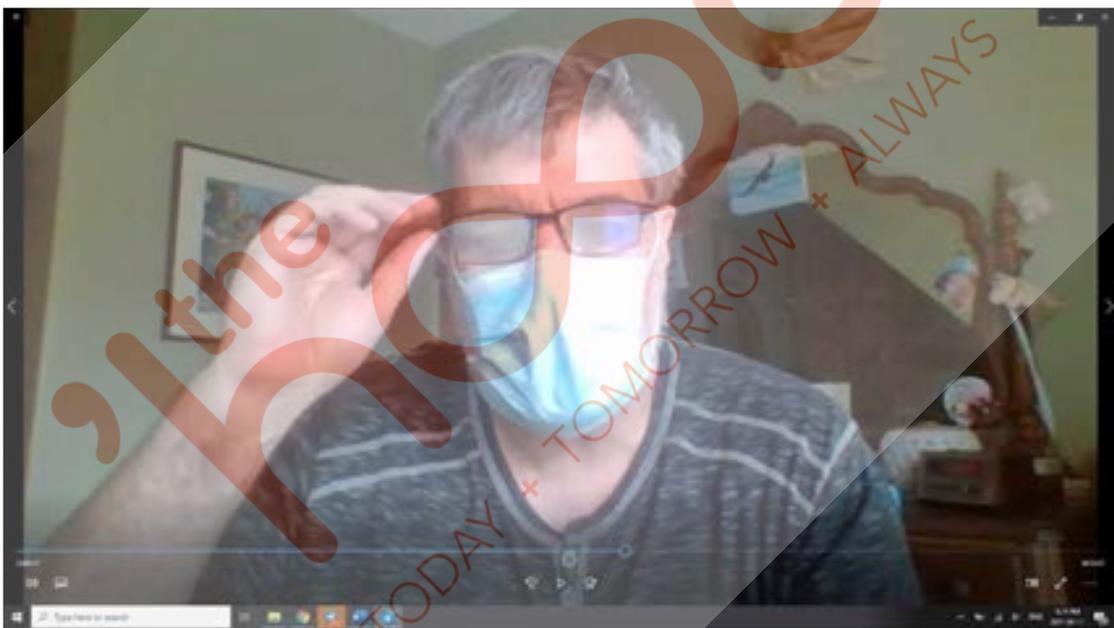


Figure 5: The leakiness of low-cost masks.

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

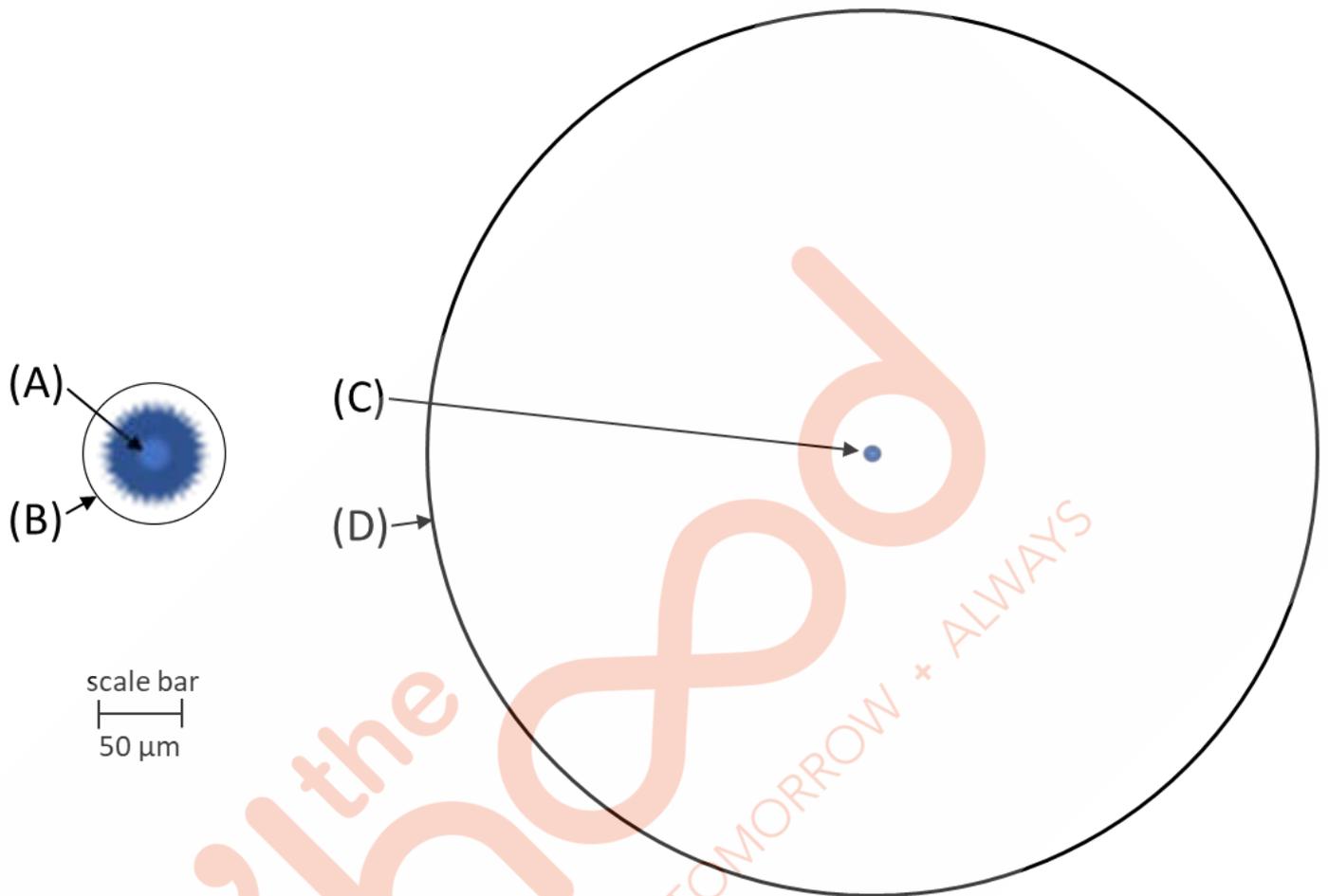


Figure 6: The relative size of SARS-CoV-2-laden water particles and pores of low-cost masks.

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

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

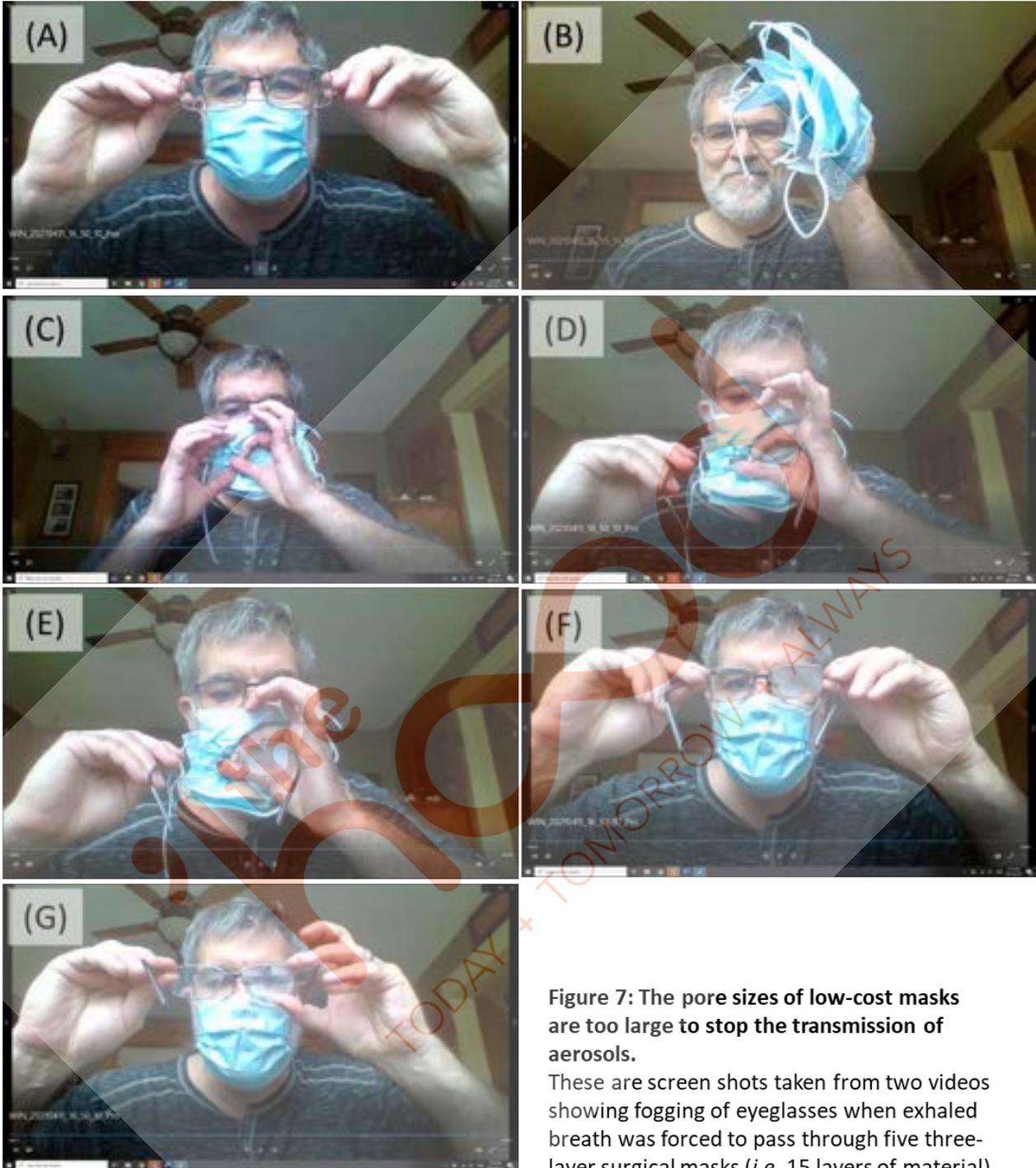


Figure 7: The pore sizes of low-cost masks are too large to stop the transmission of aerosols.

These are screen shots taken from two videos showing fogging of eyeglasses when exhaled breath was forced to pass through five three-layer surgical masks (*i.e.*, 15 layers of material).

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

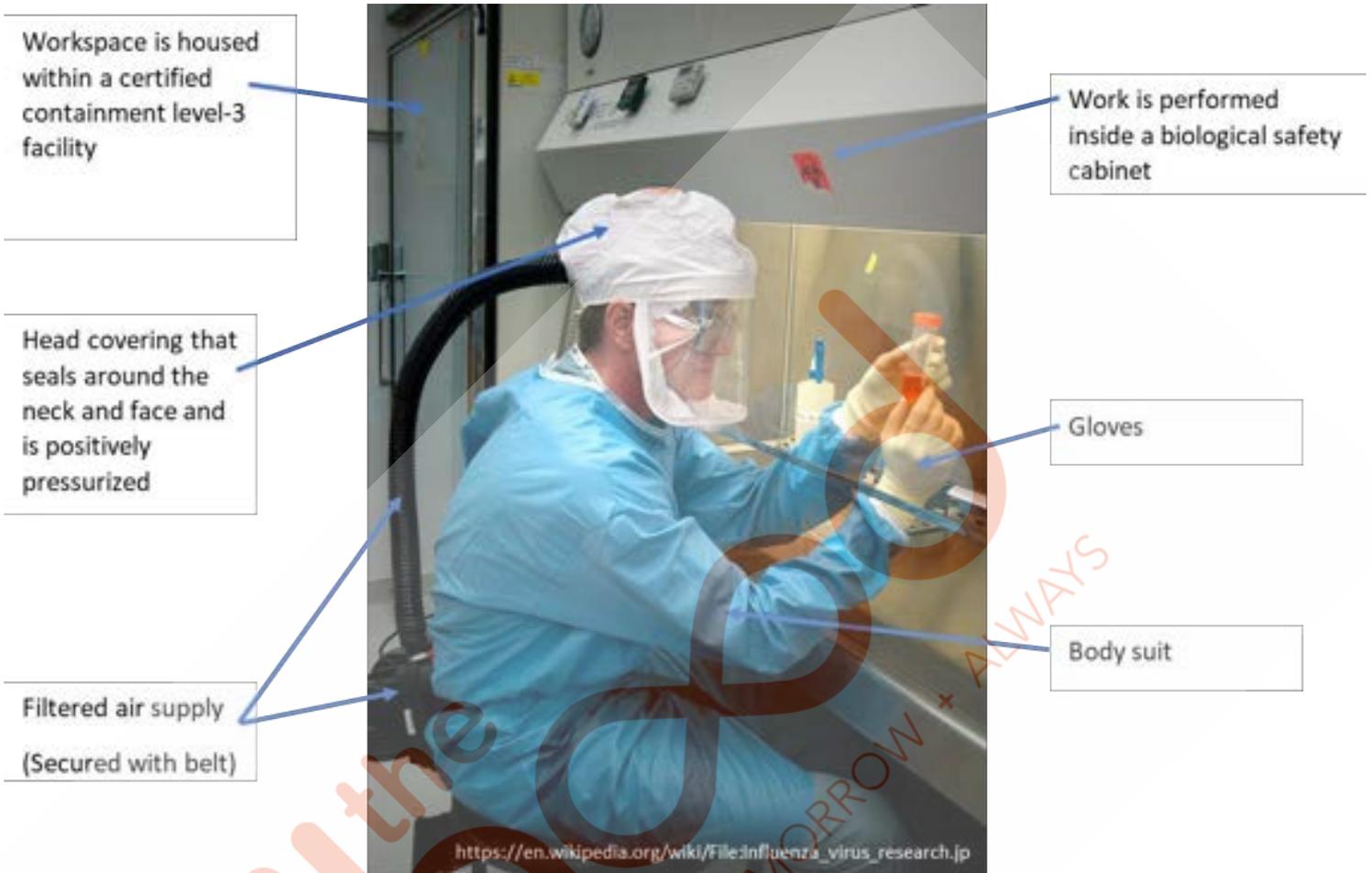


Figure 8: Personal protective equipment required to safely work with containment level-3 pathogens such as SARS-CoV-2.

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

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

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

Conclusion: Once one realizes that SARS-CoV-2 can pass through low-cost masks and travel >2 meters and sometimes much further on ‘droplet nuclei’ in pulmonary aerosols, it becomes readily apparent that the policies of mask-wearing and two-meter physical distancing are not adequately protective against the spread of SARS-CoV-2. If low-cost masking combined with only two-meter physical distancing does little to prevent the spread of SARS-CoV-2, it would be expected that a relatively high proportion of Canadians would have naturally acquired immunity to the virus over the past year. Indeed, this is precisely what was found in a recently published study that showed that the majority of apparently healthy adults in British Columbia have evidence of naturally acquired immunity⁶. Masking of asymptomatic individuals simply makes no sense. As described earlier, they are not significant sources of transmissible SARS-CoV-2. Low-cost masks are only effective at reducing transmission mediated by large droplets expelled when coughing and sneezing. These sick individuals should not be in public places anyways. Masking has simply become a proverbial carrot to dangle in front of people to coerce them in to taking one of the

current COVID-19 vaccines; if they get vaccinated, they will be able to unmask at some point in the future. However, this is not supported by the science.

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

There is an immunological concept known as the ‘hygiene hypothesis’^{59,60}. The core of the idea is that we live in a microbial world; an environment full of bacteria, parasites, viruses, and fungi. Further, our interactions with these microbes after birth are extremely important to educate our immune systems to function properly. When we are born, our immune systems are still maturing. Sally F. Bloomfield, et al., described the concept of immunological development post-birth well in their published study: “The immune system is a learning device, and at birth it resembles a computer with hardware and software but few data. Additional data must be supplied during the first years of life, through contact with microorganisms from other humans and the natural environment.”⁶¹. The immune system has many potent mechanisms for killing pathogens. It needs to be carefully regulated to ensure it can eliminate dangerous microbes from the body without causing excessive harm to our own tissues⁶². The interactions we have with our environment early in life are essential for our immune systems to learn to differentiate between safe versus dangerous disease-causing microbes. Our bodies are covered inside and out with micro-organisms that, under normal circumstances, happily co-habitate with us and promote a healthy immune system. If infants, toddlers, and young children are not sufficiently exposed to the microbial world around them, their ability to properly regulate their own immune systems can be compromised⁶³. As per the computer analogy, the data that get uploaded into the software are incomplete. This ‘lack of data’ can cause the immune system to struggle to differentiate between what is truly dangerous and should be eliminated, and what is not dangerous and should not be responded to. In plain terms, this scenario can promote allergies⁶³, asthma⁶⁴, and autoimmune diseases⁶⁵.

Scientists are moving away from using the term ‘hygiene hypothesis’ because it could be misinterpreted as meaning that hygiene is not good for a developing immune system. This is not true. Moderation and targeted hygiene would be best. Specifically, we need to practice proper hygiene in the context of trying to prevent infectious diseases, but still allow our immune systems to interact with safe and essential microbes. Many middle-income countries have seen an epidemic of allergic diseases over the past several decades⁶⁶. This is, in part, due to increased urbanization which is akin to living in ‘concrete jungles’ with reduced exposure to the natural environment⁶⁷. Societies have also adopted behaviours that limit exposure to microbes⁶⁸. Overuse of antibiotics exacerbates the problem by non-discriminately eliminating ‘good’ microbes along with the ‘bad’ ones⁶⁹.

Here are important conclusions stated in a recent article: “Evidence suggests a combination of strategies, including... increased social exposure through sport, other outdoor activities, less time spent indoors... may help... reduce risks of allergic disease. Preventive efforts must focus on early life”⁶¹. Now think about government-led reactions to the pandemic caused by SARS-CoV-2. The policies that have been enacted contradict the recommendations to ensure proper immunological

development in children. Data suggest that SARS-CoV-2 does not represent a greater danger to children than the annual flu^{70,71}. Yet social interactions of children have been severely limited, including removing them from schools. Most of their extracurricular activities have been cancelled and they have been discouraged from leaving their homes. Even the air they breathe is often filtered by masks and there is prevalent use of hand sanitizers. In short, most COVID-19 policies have maximized the potential for children to develop dysregulated immune systems. As a viral immunologist, I was not overly concerned about this in the early stages of the pandemic when ‘temporary’ measures were put in place to ‘flatten the curve’ depicting daily cases of COVID-19⁷¹. However, many governments now seem to have adopted a zero-tolerance policy for COVID-19, even though they have not declared this. Consequently, the youngest among us have had their immunological development compromised for one year and growing. An unfortunate and under-appreciated long-term legacy of Canada’s reaction to the pandemic will likely be a cluster of ‘pandemic youth’ that grow up to suffer higher-than-average rates of allergies, asthma, and autoimmune diseases. This will hold true for children in all countries that enacted isolation policies. Interestingly, it has been noted that the new messenger RNA-based COVID-19 vaccines⁷² that are packaged inside liposome nanoparticles are contraindicated for some individuals with a propensity towards severe allergic responses⁷³. Ironically, we may be setting up many of our youth to develop hypersensitivities to this vaccine technology when they are older.

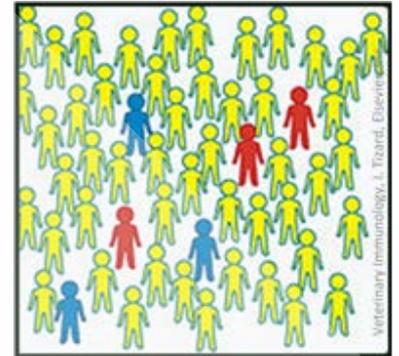
Notably, some of Ontario’s polices took the isolation of children to an extreme. This included orders to place young apparently healthy children into isolated quarantine for fourteen consecutive days if they had schoolmate test positive for SARS-CoV-2.

Conclusion: Raising children during the pandemic has largely occurred in isolated and highly sanitized environments that are unprecedented in extent and duration. These kids are at greater risk of developing hypersensitivities and autoimmune diseases than anyone before them. The immune systems of children are not designed to develop in isolation from the microbial world. To minimize further life-long damage to their immune systems, masking and isolation policies must be rescinded as soon as possible. Like the issue of masking in general, isolation of children should not be a ‘carrot’ dangled in front of adults to get them to take one of the current COVID-19 vaccines. Early in the declared pandemic children were mis-labeled as asymptomatic super-spreaders who would kill adults; therefore, adults needed to get vaccinated. Now the argument is that children cannot yet be vaccinated and are, therefore, at risk of dying from COVID-19 (which is patently false as per Ontario’s own COVID-19 death statistics for children). As such, adults should get vaccinated to protect the children. This type of contradictory and false messaging to promote vaccination is nothing short of coercion.

11. Known and Emerging Safety Concerns with the Current COVID-19 Inoculations, Especially for Young People

What is 'herd immunity'?

The concept of '[herd immunity](#)' means that a virus will stop spreading among a population once most of the people in that population acquire a protective immune response. Importantly, this does not require every person to become immune, just a large majority. There are two ways for people to acquire immunity to SARS-CoV-2 and thus avoid the debilitating effects of COVID-19:



Natural infection:

When infected with SARS-CoV-2, most people clear this virus from their body by mounting a robust, long-lasting immune response that targets multiple components of the virus⁷⁴. These people will be protected from re-infection with the same variant of SARS-CoV-2 and, due to the breadth of a natural immune response, will also likely have some degree of protection against emerging new variants of SARS-CoV-2. Indeed, most people who have naturally acquired immunity should not be at risk of developing severe disease even if variants arise that can effectively bypass the narrower immunity conferred by COVID-19 vaccines that are focused on a single component of SARS-CoV-2, such as the spike protein⁷⁵. Interestingly, a landmark [study](#) in Canada suggested that a majority of healthy adults in British Columbia have evidence of pre-existing or naturally acquired immunity to SARS-CoV-2⁷⁶.

1. Vaccination:

Vaccines that have undergone properly conducted preclinical studies and the full suite of clinical trials to ensure they are (i) effective; and (ii) have excellent short-term and long-term (*i.e.* a minimum of two years; preferably longer) safety profiles, can allow an individual to become immune to a virus without having to be naturally infected.

How do vaccines work?

A successful vaccine must provide two things:

Thing 1: The virus or a piece(s) of the virus (*i.e.*, a target for the immune system).

Thing 2: A danger signal (*i.e.*, something that tells the person's immune system that the target it is seeing is dangerous and, therefore, worth responding to).



An effective vaccine simulates just enough of a natural infection, to trigger a person's body to develop an appropriate immune response without causing disease. Then, when the person becomes infected the first time by the natural virus, their body's immune system senses it is seeing the virus for the second time. This is because an immune response triggered by successful vaccination involves the body's development of 'immunological memory'. Therefore, the person's vaccine-primed immune response to the natural viral exposure will be faster and more robust, and the virus will be cleared without the person experiencing disease. Mass vaccination can accelerate progress of a population towards herd immunity.

How do Canada's COVID-19 vaccines work?

When COVID-19 vaccine mandates were first introduced in Canada there were four COVID-19 vaccines that Health Canada had "[Authorized by Interim Order](#)". The Interim Orders enable the widespread deployment of the vaccines while the Phase 3 clinical studies (experiments in people) are being conducted. In the Phase 3 studies, all vaccine recipients must be followed for two years following the administration of the second vaccine dose. As long-term effects of the vaccine have yet to be understood, the vaccine is largely investigational. This is why the authorizations were "interim" and continued use is contingent on the collection of additional data from the Phase 3 studies, as well as other surveillance systems to assess the safety and effectiveness of the vaccines. The Pfizer-BioNTech and Moderna mRNA vaccines were re-named "Comirnaty" and "Spikevax", respectively, after their authorization by interim order expired on Sept 16th, 2021. These two vaccines are now listed as "Approved by Health Canada" under an authorization subject to the Food and Drug Regulations. Despite this symbolic approval, this does not change the fact that the phase 3 clinical trials are ongoing.



Because the COVID-19 vaccines are being administered in Canada under experimental trial conditions, people receiving these vaccines should provide informed consent prior to being immunized. Informed consent demands that people be provided with all the known pros and cons and legitimate scientific questions that remain unanswered, in an objective fashion and without undue pressure or coercion. This is a basic tenet of bioethics. Anyone administering a COVID-19 vaccine should be able to explain the benefits and risks based on the weight of the evidence provided in peer-reviewed, published scientific papers. They should also be aware of the plethora of legitimate scientific questions that have emerged since the public rollout of these vaccines began. Lay persons should be encouraged to ask public health officials to explain the rationale for any statements made regarding COVID-19 vaccines and to have the sources of this information identified. Data in printed documents that do not contain citations do not necessarily reflect the robustness of the scientific literature.

The four COVID-19 vaccines currently being used in Canada include:

1. AstraZeneca/COVISHIELD vaccine (ChAdOx1-S):

These are two different names for the same vaccine (COVISHIELD is the brand name of AstraZeneca's vaccine that is manufactured by Verity Pharmaceuticals Inc. with the Serum Institute of India). Developed by AstraZeneca and Oxford University, the backbone of this vaccine is an adenovirus that does not cause disease in people. This adenovirus virus carries genetic material that provides instructions for a cell to manufacture a piece of SARS-CoV-2 (*i.e.*, the spike protein). When this adenovirus-based vaccine gets injected into the shoulder muscle, it is intended to infect cells and use the 'machinery' in these cells to manufacture small amounts of the SARS-CoV-2 spike protein. The SARS-CoV-2 spike protein and the adenovirus backbone provide the 'thing 1' and 'thing 2', respectively, that are needed to trigger an immune response.

Unfortunately, the rollout of the AstraZeneca vaccine in Canada proved to be a frustrating and complicated series of ever-changing, safety-triggered, recommendations given to a growing number of confused and distrusting members of the public. While many other countries paused their AstraZeneca vaccination programs to investigate safety issues related to potentially fatal blood clots, Canadians were told the AstraZeneca vaccine was safe for some population segments and vaccinations with the AstraZeneca vaccine were initiated. After other countries practiced due diligence and confirmed that blood clotting was an adverse event associated with this vaccine, Canadians were then told that it was too unsafe for those under 55 years of age. Then Canadians between 40-55 years of age were told it was safe enough for them to use. Several weeks later, the message changed again, and the current messaging is that it is too unsafe to use as a first dose in much of Canada. Millions of Canadians who received a single dose of this vaccine have since been wondering what to do. This highlights why the scientific method exists and why it should not be over-ridden by zealous public health officials. Safety testing should never be cut short. In many parts of Canada, the AstraZeneca vaccine is generally being used only for second doses for individuals who have had a first dose of the AstraZeneca vaccine and do not wish to have a second dose of another vaccine. The vaccine is irrelevant to Canadian children, youth, and young adults of child-bearing age, as it was never authorized for use in these population groups.

2. Janssen vaccine (Ad26.COV2.S):

This vaccine is made by Johnson & Johnson. Like the AstraZeneca vaccine, the Johnson & Johnson vaccine uses an adenovirus, albeit a different one. The way this vaccine works is similar to the AstraZeneca vaccine. After injection, cells infected with the adenovirus start to manufacture a spike protein that is very similar to that of the SARS-CoV-2 spike protein. There has been some public acknowledgement that this vaccine might also be associated with blood clots, and Health Canada has noted in their website notices of April 26th, 2021, to healthcare professionals that "[v]ery rare cases of thrombosis in combination with thrombocytopenia, in some cases accompanied by bleeding, have been observed following vaccination with Janssen COVID-19 vaccine. A causal relationship with the vaccine is considered plausible." In considering the request for the Janssen vaccine to be Authorized Under Interim Order, Health Canada yet again acknowledged that "[i]mportant limitations of the data at this time include the lack of information

on the long-term safety and effectiveness of the vaccine, interactions with other vaccines, and the lack of data in sub-populations (*e.g.* pregnant/breastfeeding women, pediatric population <18 years of age, patients with autoimmune or inflammatory disorders, immunocompromised patients and frail patients with comorbidities).” At the timing of writing this article, this vaccine has not been authorized for use in Canadian children, youth, and young adults of child-bearing age.

3. Pfizer BioNTech vaccine (BNT162b2; Comirnaty):

This vaccine relies on technology that, prior to the COVID-19 pandemic, was not previously used in humans, except in small-scale clinical trials (such as a clinical trial of a rabies mRNA vaccine)⁷⁷. The backbone of the Pfizer BioNTech vaccine is a lipid nanoparticle (a small bubble of fat). Inside the nanoparticle is a ‘messenger ribonucleic acid’ (mRNA). This is a tiny piece of genetic material that provides the instructions for a cell to manufacture a modified version of the SARS-CoV-2 spike protein. When these nanoparticles are injected into the body, they are intended to fuse with cells with which they come into contact. When this happens, the mRNA migrates from the lipid nanoparticle and into the cell and the cell ‘machinery’ then uses this mRNA ‘blueprint’ to manufacture the modified version of the SARS-CoV-2 spike protein. This protein is the ‘thing 1’ that provides one of the two signals required for the immune system to become activated. It is not entirely clear what provides ‘thing 2’. However, mRNA vaccines promote inflammation that can cause injury to normal tissue. When cells are injured, they release ‘danger signals’. This might be what is providing the second signal (‘thing 2’) needed to induce an immune response.

Pfizer’s vaccine has been associated with anaphylactic reactions in a small subset of individuals. These are serious allergic reactions that can be life-threatening. At the time of writing this guide, **the Pfizer vaccine is the only one that has received Authorization under Interim Order for Canadian children and adolescents 12 to 15 years of age.** In its decision-making process, Health Canada declared; “Health Canada has conducted a rigorous scientific review of the available medical evidence to assess the safety of the Pfizer-BioNTech COVID-19 vaccine. No major safety concerns have been identified in the data that we reviewed” [emphasis added]. Health Canada also acknowledged that “One limitation of the data at this time is the lack of information on the long-term safety and efficacy of the vaccine. The identified limitations are managed through labelling and the Risk Management Plan. The Phase 3 Study is ongoing and will continue to collect information on the long-term safety and efficacy of the vaccine. There are post-authorization commitments for monitoring the long-term safety and efficacy of Pfizer-BioNTech COVID-19 vaccine.” Specifically related to the authorization for adolescents 12 to 15 years of age, “Health Canada declared, Health Canada has placed terms and conditions on this authorization requiring Pfizer-BioNTech to continue providing information to Health Canada on the safety, efficacy and quality of the vaccine in this younger age group to ensure its benefits continue to be demonstrated once it is on the market.”

4. Moderna vaccine (mRNA 1273 SARS-CoV-2; Spikevax):

The Moderna vaccine also is an mRNA-based vaccine and, therefore, works the same way as Pfizer’s COVID-19 vaccine. This vaccine has also been associated with anaphylactic reactions in a small subset of individuals. On June 7th, 2021, Moderna had filed an application to extend the

Authorization under an Interim Order to adolescents aged 12 to 17 years. At the time of writing this, Health Canada had not issued its decision.

None of Canada's COVID-19 vaccines can, in and of themselves, infect people with the SARS-CoV-2 virus, per se. Rather, these vaccines trigger the cells in a person's own body to manufacture one of the proteins that is a component part of SARS-CoV-2, and all the vaccines cause a person to make a modified version of the spike protein from SARS-CoV-2. The AstraZeneca vaccine contains the manufacturing blueprint for the exact same spike protein as is found on SARS-CoV-2. In contrast, the other three vaccines in use in Canada contain the manufacturing blueprint for a modified version that scientists refer to as the 'prefusion-stabilized spike'. All four vaccines are designed to use the body's internal capability to manufacture the spike protein to then trigger the body's immune response.

What are the known serious adverse events that are associated with COVID-19 vaccines?

Using the United States Vaccine Adverse Event Reporting System (U.S. VAERS), as of June 11th 2021, the 20 most frequently reported adverse events (presented in descending order) were headache, pyrexia (fever), fatigue, chills, pain, nausea, dizziness, pain in extremity, injection site pain, myalgia (muscle pain), injection site erythema (redness), arthralgia (joint stiffness), pruritus (itching), rash, dyspnoea (difficulty breathing), injection site swelling, injection site pruritus (itching), vomiting, and asthenia (weakness). These side effects are common side effects and are similar to those reported in the Phase 3 clinical trials. Although these symptoms can be severe in some people and can result in an inability to perform daily activities, they usually subside over one to three days.

The mRNA vaccines (Pfizer and Moderna) can, in rare cases, cause anaphylaxis. Since this can be potentially fatal, these vaccines are often administered in special vaccine clinics that are staffed with personnel trained to treat people who may experience anaphylactic shock. The reason this problem is thought to be limited to the mRNA vaccines is likely due to a pre-existing allergy against something present in the liposome nanoparticles (the small bubble of fat) that are the part of the vaccine that envelopes the mRNA material. One of the liposome ingredients that might be the culprit is polyethylene glycol (PEG).

Based on data from international regulatory agencies (such as the Norwegian Medicines Agency), the adenovirus-based vaccines (*i.e.*, AstraZeneca and Janssen) have been implicated in causing a very serious type of blood clot (a cerebral venous sinus thrombosis) that is simultaneously associated with a low platelet count and bleeding following vaccination. This is one of the reasons the AstraZeneca vaccine has largely been suspended for use in Canada, with the exception of use for second doses in those who received the AstraZeneca as their first dose and wish to stay with the same vaccine brand.

Are there other serious adverse events associated with COVID-19 vaccines that are being investigated?

Side effects that are rarer, including those that are serious or life-threatening, are still being learned about. For example, the United States Centers for Disease Control and Prevention (CDC) announced, only on June 11th, 2021, that an Emergency Meeting would be held on June 18th 2021 to discuss reports of inflammation of the heart resulting from use of the Pfizer and Moderna vaccines in young males 16 to 24 years of age. It has been approximately six months since the vaccines were authorized under an emergency use in the U.S., and only now is this association being recognized. There are many reasons why it is difficult to identify serious side effects that are rare or that occur only over a longer period of time or in a specific population group or sex. These difficulties are described below.

Difficulty #1: Too Soon to Tell for Sure

Pfizer and Moderna each initiated large, Phase 3 trials that were randomized, double-blind, and placebo-controlled. The placebo group is important because it serves as the reference group and helps in the interpretation of side effects experienced in the vaccine group. At the time that the vaccines were granted emergency use authorization, each company had safety and efficacy data for an average of only two months following the administration of the second vaccine dose; in the study in adolescents, most subjects had safety and efficacy data for either one or two months. According to the original protocols, every individual in the study is supposed to be followed for a total of two years following their second dose.

Difficulty #2: Abandoning the Control Group

The vaccines have been authorized under emergency use in many key countries, globally; and fear-based pressures imposed by public health agencies to vaccinate everyone has triggered study participants to want to know which study group they had been allocated to, so that those in the placebo group could be vaccinated. The studies have therefore been unblinded, meaning there is no longer a placebo group. This means that a rigorous assessment of safety in the context of a well-controlled clinical study is no longer possible, and there must be increased reliance on vaccine post-deployment, passive surveillance systems. Of course, this, itself, is challenging, given that there is uncertainty in both the numerator (the number of vaccine-related adverse events) and the denominator (the number that is typical for that event, otherwise referred to as the “background incidence” of the event). Moreover, it is extremely difficult to prove definitively that an event is caused by (and not just associated with) vaccination when using passive surveillance systems.

Difficulty #3: Under-Reporting of Adverse Events

The problem with passive adverse event reporting systems, which is the type of system that both Canada and the U.S. are relying on, is that there is a notorious problem of adverse event under-reporting. This is because reporting is voluntary; people may be unaware there are ways to report adverse events; people are often discouraged from reporting adverse events; people (including attending physicians) assume the condition is not related to vaccination; or people may not be able to report their adverse events (if they are severely disabled, ill, or deceased). Most disconcerting

is the situation, as we see in Canada, where adverse event reports attempted to be submitted by medical professionals are pre-screened and sometimes rejected by pre-screening authorities. Consequently, adverse event databases can easily fail to identify potential concerns, or underestimate problems to an unknown degree and are, therefore, not a source of accurate numbers to calculate true risk. For example, using the U.S. VAERS, it was estimated that the risk of anaphylaxis was 4.7 per million for the Pfizer vaccine and 2.5 per million for the Moderna vaccine⁷⁸; however, in an active surveillance study of 64,900 healthcare workers who had been vaccinated, the rate was actually 216 per million⁷⁸, representing a potential rate of under-reporting of 46- to 86-fold. Despite these limitations, passive surveillance systems are useful for identifying potential risks that could then be investigated in properly designed safety studies.

Difficulty #4: Lack of Global Consistency and Thoroughness in Defining Events of Special Interest

Using the U.S. VAERS and similar adverse event reporting systems around the world, there is continuous monitoring of adverse events of special interest. But each jurisdiction is left to their own discretion to decide which, if any, particular adverse events of special interest will receive closer scrutiny. For example, the European Medicines Agency has compiled a list of important medical events (IMEs) which are always to be classified as serious (the IME list). The IMEs that are most frequently [reported](#) following COVID-19 vaccination (in descending order) are:

- Fainting (syncope)
- Blood clot(s) in the lungs
- Anaphylactic reaction
- Deep vein thrombosis
- Pneumonia
- Low blood platelet count (thrombocytopenia)
- Blood clot(s) or bleeding in the brain
- Hallucinations
- Cerebral stroke
- Loss of consciousness

Definitive cause-and-effect relationships for these events have not yet been established; it is hoped that with additional surveillance and time, clarity on the role of the vaccines in the cause of these events will be better understood. In the meantime, given that the spike protein is biologically active and there are mechanisms that could potentially explain some of these IMEs (discussed further below), there is good reason for genuine concern.

Why weren't serious adverse events identified before vaccines were rolled out?

Problems like anaphylactic shock (a severe allergic reaction) and potentially fatal blood clots were not identified until most of the experimental COVID-19 vaccines were used widely among the public^{78,79}. Janssen's study of the Johnson & Johnson vaccine did suggest some propensity for blood clotting. As for anaphylactic reactions, people with a history of allergies were excluded from the earlier clinical trials.

Another reason why some problems were not identified earlier is because short-cuts were taken with the traditional approach to vaccine research. Specifically, **the time taken to assess safety**

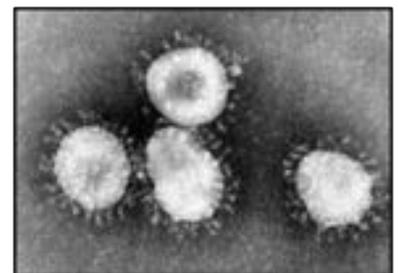
was too short. Instead of taking the usual ~4-10 years to undergo thorough *in vitro* (*i.e.*, benchtop) tests, pre-clinical (*i.e.*, animal) studies, and then sequential clinical testing (*i.e.*, human Phase 1, 2 and 3 trials), COVID-19 vaccines were developed and assessed for safety and efficacy in less than one year. This meant that only very short-term safety scenarios could be evaluated. Of equal concern, **the number of people that were evaluated in clinical trials was too small** to capture rare but dangerous side-effects. This is unfortunate, because we have seen in Canada that rare but serious problems can lead to a vaccine program being suspended. Indeed, in Canada, a risk of blood clots for the AstraZeneca vaccine of 1 out of every [55,000](#) people vaccinated was deemed to be too dangerous, leading to its use being halted. Authorization under Interim Order for COVID-19 vaccines was granted after they were evaluated for a short duration in about 20,000 people. This means these studies could, at best, detect serious side effects that would occur in at least 1 out of every 20,000 people. In other words, the study design included a test population that was too small to identify vaccines that may be too dangerous for Canadians.

A clinical trial was conducted to justify using the Pfizer vaccine in Canadian children and adolescents; was it flawed as well?

Yes. First, it was far too short in duration to have any chance of assessing anything other than short-term harm. Also, in light of the information provided above, one needs to consider the following: only 1,131 adolescents between the ages of 12 and 15 received the vaccine in this [study](#). This means that the study would have only been able to detect a serious side effect that occurs in 1 out of every 1,131 adolescents that are vaccinated; but a 1 in 55,000 risk was deemed to be too dangerous for adults for whom SARS-CoV-2 represents a greater risk. Furthermore, based on the recent observation of increased risk of heart inflammation following immunization with either the Pfizer or Moderna vaccine in young males, it appears serious side effects may be a function of both age and sex. In this regard, the Pfizer study of only 1,131 subjects provides even less robust data...enough to detect a serious gender-differentiating side effect that occurs in one out of approximately 565 (*i.e.*, $1,131 \div 2$) males vaccinated and one out of approximately 565 females vaccinated.

Why was the spike protein from SARS-CoV-2 chosen as a target for the immune system?

The spike protein gives SARS-CoV-2 its 'crown-like' appearance, which means it looks like it has a 'corona'. This protein allows the virus to attach to our cells and then infect them. If antibodies can bind to and 'block' all the spike proteins on the surface of the virus, then it could not infect our cells. Moreover, the binding of antibodies to even a part of the virus can tag it for attack by cells of our immune system. As such, COVID-19 vaccines currently being used in Canada instruct our cells to manufacture the spike protein to trigger our bodies to mount an immune response against this protein with the hope that the ensuing antibodies will get into our lungs and airways and block the virus, should we be infected in the future.



Electron micrograph of a coronavirus

<https://starfishmedical.com/blog/covid-19-point-of-care-diagnostic/>

What should we know about the SARS-CoV2 spike protein?

Before we go any further with the story about COVID-19 vaccines, there is important information that you need to know about the spike protein from SARS-CoV-2.

The spike protein from SARS-CoV-2 has the potential to damage cells in the body

In cases of severe COVID-19, problems can extend well beyond pneumonia and the associated inflammation in the lungs. The disease can progress beyond the lungs and into other parts of the body. In severe infections, SARS-CoV-2 can cause damage to the cardiovascular system (*i.e.*, heart and blood vessels). In fact, some have referred to severe COVID-19 as largely being a [vascular disease](#)⁸⁰⁻⁸². Blood clots, bleeding and/or damage to the heart have all been linked to severe COVID-19. Severe COVID-19 can also cause neurological problems (*i.e.*, damage in the brain). A series of recent scientific publications provide some evidence that this damage throughout the body may not require an intact SARS-CoV-2 particle. Instead, the spike protein from SARS-CoV-2 might be responsible for at least some of the damage that occurs in severe cases of COVID-19⁸³. This is because there are many cells other than those in the lungs and airways that



feature the receptor for the spike protein, known as the ACE2 receptor. Most notably, platelets and cells lining blood vessels can express high concentrations of this receptor. Importantly, autopsies performed on patients who died from severe COVID-19 revealed that free spike protein from SARS-CoV-2, not the intact virus, was responsible for substantial damage throughout the body. Notably, blood vessels in the skin, fat, and the brain were found to express high concentrations of the ACE2 receptor that the spike protein binds to. There was a lot of spike protein found in these tissues, with little to no evidence of the intact virus being present. Indeed, the authors of the study that described these autopsies concluded “COVID-19 represents a viral infection with limited sites of infectious virions but deadly sequelae due to the effective manner in which pseudovirions in the context of released viral proteins activate synergistic microvascular pathways of tissue destruction throughout the body.”⁸⁴ In lay language, proteins like the spike protein, not the intact virus, appear to mediate much of the damage in the body in people who suffer from severe COVID-19. When the spike protein binds to these receptors, there are several events that can take place:

1. Proteins (called ‘complement proteins’) that are part of our innate immune system can get activated, causing inflammation that can damage or destroy the cells lining blood vessels and/or platelets⁸⁵. Platelets that are required for clotting of blood also express ACE2 receptors that can bind with spike protein with dire consequences. Damage and destruction of platelets can cause their numbers to go down (a condition known as “thrombocytopenia”), and if platelet counts get too low and blood vessels are damaged, bleeding cannot be stopped. Therefore, the spike protein can potentiate bleeding.

2. Binding of the spike protein to platelets can also cause the platelets to become activated⁸⁶. Activated platelets tend to clump, which can lead to the formation of clots. There is evidence that the spike protein can interact with other proteins in the blood to promote clotting⁸⁷. As such, the spike protein can promote blood clotting.
3. Spike proteins binding to the cells that line our blood vessels can cause these cells to express proteins (known as ‘caspases’) that can cause the cells to die⁸⁴. This is similar to findings from the 2002-2004 SARS outbreak where the spike protein from the original SARS-CoV could cause cells to die when it was being manufactured inside of them⁸⁸. Dying cells that have been manufacturing the vaccine-encoded spike protein would release free spike protein or portions thereof.
4. Spike proteins binding to the cells that line our blood vessels can cause these cells to over-produce cell-signalling cytokines that can potentially contribute to dangerous ‘cytokine storms’ (overly robust and severe inflammation)^{84,89}.

Of additional concern is the knowledge that the spike protein is capable of dissociating into two parts and these smaller subunits (S1 and S2) can cross the blood-brain barrier where they can potentially cause damage in the brain⁹⁰. Indeed, people who have died from severe COVID-19 with neurological signs were found to have the spike proteins but not the intact virus in their brains⁹¹. These neurological signs could be seen in laboratory studies when spike proteins were injected into the blood of mice.

Conclusion: The spike protein, if it gets into circulation, has the potential to cause damage to the cardiovascular system and other tissues.

Back to the vaccines

Now that there is a clear understanding that the spike protein from SARS-CoV-2 is a dangerous toxin when it gets into the blood and is distributed throughout the body, we can continue with the story about COVID-19 vaccines.

Evidence that mRNA-based COVID-19 vaccines can get distributed throughout the body

When the COVID-19 vaccines were designed, it was not appreciated that the spike protein could potentially damage cells in the body. As a consequence, administration of the current COVID-19 vaccines can put people at risk of damaging their cells, especially if expression of the spike protein is not limited to the vaccine injection site. An assumption was made with these vaccines that has proven to be incorrect. The assumption was that mRNA vaccines, which are a new technology, would behave the same as traditional vaccines. It was thought by many that mRNA vaccines would stay at the injection site and the only other place they would go is to the draining lymph nodes in the immediate vicinity of the injection site. More specifically, it was thought that cells of the immune system would come to the site of injection and create pieces of the virus and take these pieces to the lymph nodes where they would be shown to B and T cells (*i.e.*, B and T lymphocytes).

The B and T cells would then get activated, multiply to large numbers (this is why lymph nodes swell when a person is mounting an immune response) and then head out into the body to search for the pathogen. Notably, B cells are the source of antibodies. Unfortunately, researchers have come to learn that **the mRNA vaccines do not stay in the shoulder muscle**. In fact, **they have the potential to spread far and wide throughout the body via the blood**. Obviously, this is a very serious conclusion to draw, so let's walk through the solid scientific evidence that demonstrates this potential for biodistribution.

A report that Pfizer provided to the Japanese government (see Appendix 1) was published as reference #25 in an article⁹² published in *BMJ* that can be found at this [link](#). In section 2.6.5.5B of the report to the Japanese government there is a table containing lipid nanoparticle biodistribution data. This table shows where their surrogate "vaccine" (*i.e.*, represented in the laboratory test by little bubbles of surrogate fat containing an analytical detection marker) ended up in the body of immunized rats, used in the laboratory as surrogates for humans. A portion of the table is reproduced below. Please review the data so you can get the full picture. I would like to highlight some observations. First, as shown in the blue rectangle that I added to the table, a lot of the surrogate vaccine dose remained at the injection site, as one would expect. Remarkably, however, most of the vaccine dose had gone elsewhere. The right side of the table (shown in the report to the Japanese government but not below) shows that 50-75% of the vaccine dose failed to remain the site of injection. The big question is, where did it go? Looking at the other tissues shows some of the places it went and accumulated. The red rectangle shows that **the surrogate vaccine was circulating in the blood**. There is also evidence that a substantial amount of the vaccine went to places like the spleen (green rectangle), liver (brown rectangle), ovaries (yellow rectangle), adrenal glands (purple rectangle), and bone marrow (orange rectangle). The vaccine went to other places as well, such as testes, lungs, intestines, kidneys, thyroid gland, pituitary gland, uterus, *etc.* **The surrogate vaccine tested in a laboratory setting was widely distributed throughout the laboratory animals' bodies.**

Species (Strain):							
Sex/Number of Animals:	Male and female 3 animals/sex						
Feeding Condition:							
Method of Administration:	i						
Dose:	50 µg [³ H]						
Number of Doses:							
Detection:	Radioactivity counter						
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, 48						
Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL)) (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.151
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.34	2.40	3.77
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112
Heart	0.282	1.01	1.40	0.987	0.790	0.451	0.546
Injection site	128	394	311	338	213	195	165
Kidneys	0.391	1.18	2.05	0.924	0.590	0.420	0.425
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test #

Sample	Total Lipid concentration (µg lipid equivalent/g (or mL)) (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3
Pancreas	0.081	0.207	0.414	0.380	0.204	0.358	0.599
Parotid gland	0.339	0.645	0.868	0.854	0.495	0.478	0.694
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264
Skin	0.013	0.208	0.150	0.145	0.119	0.157	0.253
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456
Whole blood	1.97	4.37	7.40	3.05	1.31	0.909	0.420
Plasma	3.97	8.74	8.90	6.50	2.36	1.78	0.805
Blood Plasma ratio ^a	0.815	0.515	0.550	0.510	0.555	0.530	0.540

Based on the results of this biodistribution test, further tests should have been required to assess the impacts on more tissues and for a longer time before the vaccine was authorized for use, especially in growing children, adolescents, and young adults of child-bearing age. The vaccine manufacturer, researchers and regulatory authorities alike should have also looked more comprehensively at the potential for the test animals to shed the vaccine by assessing saliva, urine, and feces. Note that there was evidence of some trafficking of the vaccine to the salivary gland and bladder, which indicates there is potential for some degree of shedding of the vaccine from the body. Further, the biodistribution of the spike protein that is created by the body after vaccination should be carefully mapped. Studies such as these should be performed in at least two animal models, with one of these not being a rodent model since rodents have levels of ACE2 receptor binding affinity that is far less than that of humans and may, as a result, underestimate the impact of spike protein on humans. There should also have been an evaluation of where the vaccine and the spike protein were going in humans in a very limited Phase 1 clinical safety trial. **This may not have mattered as much if the protein encoded by the mRNA was inert, although the risks of autoimmunity with the deposition of the lipid nanomaterials at different organs are certainly worthy of consideration. But now that we know the spike protein encoded by the mRNA has its own biological activities of concern, there is even greater potential for damage to organs and tissues arising from circulating vaccine material.**

Although not as detailed as the data in the report to the Japanese government, Pfizer's report to the European Medicines Agency states similar findings regarding the broad distribution of their vaccine platform throughout the body. The [report](#) is in Appendix 2. Of great concern is the following excerpt from section 2.3.2 on page 45: **"No traditional pharmacokinetic or biodistribution studies have been performed with the [Pfizer-BioNTech] vaccine candidate BNT162b2"**. If this is the first time this vaccine technology platform has been rolled out for wide

distribution to humans, and if the Japanese biodistribution data showed evidence of spread of the surrogate vaccine material, one must ask **why was this experimental vaccine allowed to be used in people without it having undergone a crucial biodistribution study first?** This would have told us where the vaccine was going in the body before its use in people.

Supporting the need to address uncertainties and concerns regarding the biodistribution of the vaccine and the resulting spike protein is a peer-reviewed scientific paper that has just been accepted for publication. It describes a study in which 13 healthcare workers were assessed for the presence of the spike protein in their blood after receiving Moderna's vaccine (an mRNA vaccine with essentially identical platform technology as the Pfizer-BioNTech vaccine). Notably, the spike protein, (or the portion of it that binds to ACE2 receptor), could be found in the circulation in 3 out of the 13 people (and in 11 out of the 13 people), respectively⁹³. The spike protein could be detected in the blood up to two weeks post-vaccination in most individuals and at 28 days post-vaccination in one individual. Some may argue that the concentration of the protein was low in most of the people studied. However, a protein circulating at a low concentration for up to two or more weeks could accumulate on cells over time as the blood constantly perfuses (*i.e.*, flows through) bodily tissues. Further, the biodistribution studies in the appendices suggest the spike protein could potentially be concentrated in many tissues that would not be evident by looking in blood alone. The possibility also exists that there were spike proteins already bound to ACE2 on the cells lining the blood vessels, but this was not investigated. Regardless, low concentrations of the spike protein in circulation would be expected in this small-scale study. High concentrations of a protein that can cause damage to blood vessels in a large number of people would not be consistent with a low incidence of severe adverse events. Remember, the AstraZeneca vaccination program was suspended in Canada due to a [1:55,000](#) incidence of blood clots. If spike proteins in blood were responsible for a severe side-effect, one would expect to see high concentrations of this protein in only one out of many thousands of people; a phenomenon that would likely not be detected in an analysis of only 13 people. Clearly, more work is needed here to assess the biodistribution of spike proteins in the human body after vaccination.

In a pre-print [article](#) (note: this means the paper has not yet undergone independent scientific peer review), there are data that indicate mRNA can even be detected in breast milk post-vaccination. This aspect of the study was downplayed but provides proof-of-principle that this can happen. Knowing what we now know, it would not be surprising to have the spike protein in the breast milk of some lactating women if they were to be vaccinated. Proteins circulating in the blood usually get concentrated in breast milk. Notably, there have been some adverse events reported of infants experiencing bleeding in their gastrointestinal tracts after suckling from mothers who had received a COVID-19 vaccine. Here are some examples from the U.S. VAERS (I haven't checked for more since May 2021):

Serious Adverse Events Related to Breastfeeding After Receiving a COVID-19 Vaccine

- VAERS ID #945282; a 32-year-old mother had her 2-month-old breastfeeding daughter die seven days after the mother had received the Pfizer-BioNTech vaccine
- VAERS ID #949926; a 34-year-old mother had her four-month-old breastfeeding boy pass blood and mucous in the stools starting two days after the mother had received the Moderna vaccine

- VAERS ID #992676; a 30-year-old mother had her two-month-old breastfeeding boy experience anorexia, spitting up, discoloured bloody feces, vomiting of blood, ulceration of the stomach, and bleeding in the gastrointestinal tract starting two days after the mother had received the Moderna vaccine

There were also other types of adverse events in infants associated with breastfeeding from mothers who had recently received a COVID-19 vaccine. For the sake of brevity, the VAERS ID #s have been listed here; anyone can look them up in the publicly available [VAERS](#) database.

- VAERS ID #s: 903355, 911226, 913968, 913971, 918972, 921052, 927664, 936865, 939409, 974519, 978085, 978485, 984448 (mother) - 984602 (infant), 1049482, 1105816, 1168901, 1171284

There is also a pre-print [article](#) that describes how an adenovirus-based vaccine can result in spike proteins damaging the vascular system. These types of vaccines are currently not being given to children in Canada. The mechanism is different from the mRNA-based vaccines, but the outcome is similar. The authors of this paper have coined an interesting term to describe the effect of a COVID-19 vaccine causing the same damage to the body that SARS-CoV-2 does; they called it “vaccine-induced COVID-19 mimicry syndrome”.

It turns out that the suggested wide distribution of mRNA vaccines throughout the body has a historical precedent, such as for immunizing against influenza for example⁹⁴. However, many people do not realize that lipid nanoparticles were not designed to function as vaccines. They were designed to serve as gene therapies or carry drug cargo throughout the body⁹⁵, including into the brain where attempts could be made to treat diseases such as Alzheimer’s disease, Parkinson’s disease, and brain cancers. Of substantial concern is the use of PEG, which has been associated with anaphylactic shock in some people after receiving a mRNA vaccine. PEG was added to lipid nanoparticles in the early days of drug development to promote much wider distribution throughout the body. Specifically, when PEG is added to lipid nanoparticles, it helps the particles avoid being consumed by cells throughout the body, especially cells of the immune system, that would limit the distribution of the mRNA cargo^{96,97}. Indeed, addition of PEG to lipid nanoparticles was hailed as a breakthrough because “This effect is substantially greater than that observed previously with conventional liposomes and is associated with a more than 5-fold prolongation of liposome circulation time in blood”⁹⁶. In retrospect, it seems that another mistake may have been made in the rush to get these vaccines into people: Arguably, the PEG component should have been removed from the lipid nanoparticle formulation. This likely would have resulted in lipid nanoparticles with a greater tendency to remain at the injection site and be picked up by the very cells of the immune system that we want to induce an immune response.



Conclusion: The assumption that COVID-19 vaccines remain at the injection site (*i.e.* the shoulder muscle) is not borne by the evidence. Laboratory studies have shown that the vaccine itself, and

the spike protein that it encodes, may get into the blood, and be distributed widely throughout the body. Vaccines targeting the spike protein from SARS-CoV-2 were designed to induce antibodies that would bind to this protein to prevent the virus from being able to infect our bodies. The spike protein was supposed to be the 'first thing' that a vaccine must provide; a target for the immune system. We did not appreciate the potential for the spike protein alone to cause damage to cells in the body. We now understand that the current COVID-19 mRNA vaccines have the potential to be distributed throughout the body, thereby potentially and inadvertently inoculating many tissues with a protein that is possibly harmful. If unknown damage is being caused in some organs, this might not be clearly evident until years after vaccination. The data presented here do not provide proof of long-term harm. However, it provides the rationale for asking a number of safety questions. These questions should be thoroughly investigated in safety studies prior to using COVID-19 vaccines in children, adolescents, and young adults of child-bearing age.

A concern beyond circulating spike proteins: the potential for induction of autoimmunity

Some scientists have proposed that the spike protein from SARS-CoV-2 might have portions that are very similar to proteins in our own bodies⁹⁸. If true, inducing immunity against the spike protein could theoretically promote autoimmune disorders. Indeed, two researchers found there was cross-reactivity between antibodies induced against the spike protein and several 'self' proteins⁹⁹. This led to the recommendation almost one year ago to avoid targeting the entire spike protein in vaccines and instead target only portions of the protein that are not similar to proteins in our own bodies. Unfortunately, autoimmune diseases can be insidious and take years for symptoms to become apparent.

The broad distribution of an mRNA vaccine throughout the body implicates other mechanisms that could lead to autoimmune disease. First, the mRNA vaccines promote robust inflammation. This is why many people have sore shoulders after being immunized. Promotion of inflammation in critical tissues, such as the ovaries, after being seeded with the vaccine could have dire consequences. Tissues like the ovaries are not supposed to become inflamed. This is because inflammation causes a lot of bystander damage to normal tissues, which is unwanted in an organ designed for reproduction. Also, the vaccine-encoded spike protein is designed to remain anchored on the surface of the cell that has manufactured it. If antibodies are present, such as would be the case several days after vaccination or natural infection, they could bind to the spike proteins on cells throughout our body, resulting in their destruction. Let's take the ovaries, again, as a theoretical scenario. If they were to undergo any type of tissue destruction, there is the possibility of proteins being released that the immune system has never seen before. This is because our immune systems learn to tolerate 'self' at a very young age. However, organs like the ovaries and testes start to express new proteins during puberty that the immune system has not been tolerized against. If these get released due to tissue damage, this could provide the same two signals that a vaccine needs to activate the immune system; signal 1 (target protein) and signal 2 (damage-associated danger signals). This could result in an autoimmune response against the organ. In this example (ovaries), such damage might not become apparent until years later when attempting to have a baby. This is speculation but is based on a huge body of scientific literature looking at how autoimmune diseases get started. Notably, this could potentially happen in any of the tissues seeded with the vaccine if they start to express the spike protein. This is certainly worthy of

investigation before the mass vaccination of children, adolescents, and young adults of child-bearing age.

Even the fact that the current COVID-19 vaccines cause muscle cells in the shoulder to express the spike protein, is a potential problem. This could potentially result in immune responses being mounted against muscle tissue. This is of particular concern, because [Israel](#) has started to suspect a link between COVID-19 vaccines and inflammation in the heart muscle (a condition known as myocarditis). Indeed, this potential link is being actively [investigated](#) by the European Medicines Agency, as well as by the [U.S. CDC](#). Again, with these kinds of concerns being raised in the global community, one must wonder why these vaccines are pushed so hard upon Canadian youth who are not at high risk of severe COVID-19. It will be a tragedy if we repeat something similar to or even worse than the AstraZeneca vaccine fiasco with our young people.

Why doesn't everyone who gets vaccinated experience a severe side-effect?

The spike protein likely does not get into circulation in every person. Indeed, in the study of 13 people vaccinated with the Moderna vaccine, ten had no evidence of the spike protein and two had no evidence of the S1 subunit (a fragment of the spike protein) in their blood⁹³. Also, it is important to remember that following vaccination, people manufacture the spike protein in their own cells. The amount and quality of mRNA in each dose of the vaccine can vary from batch to batch. The stability of the mRNA is also dependent on its handling as it is very temperature sensitive. So different people will receive different amounts of the active mRNA. People that receive the same amount of mRNA can produce different amounts of the spike protein depending on how metabolically active their cells are. And there are likely numerous other factors, including body size, *etc.* All of this could contribute to substantial variability in the concentration of spike proteins that a person produces. Notably, a standard vaccine injection might be expected to have a different impact in a 75-pound youth than in a 200-pound adult. The adverse events that we know about seem relatively rare. Some adverse events may go undetected. For example, knowing that the spike protein gets into circulation and knowing that it can kill platelets, it would not be surprising if most people have some loss of platelets after getting vaccinated. Also, platelets could pick up the mRNA from the circulating lipid nanoparticles and then display the spike protein on their surface, which would tag them for destruction by the ensuing antibody response. However, platelet counts are not being routinely monitored after people leave vaccination clinics, nor have the vaccine companies publicly released their data showing platelet counts post-immunization. Indeed, in a first-in-human study of BNT162b1, an earlier prototype of the Pfizer BioNTech BNT162b2 vaccine in use today, that encoded the S1 subunit of the spike protein (which contains the portion of the spike protein that binds to ACE2 receptors, called the receptor binding domain), platelet numbers dropped following vaccination in both the young and older adults studied¹⁰⁰. Unfortunately, clinical chemistry and haematology values following vaccination with the BNT162b2 vaccine, which is the one currently being used to vaccinate people, were not published in Pfizer's first-in-human study¹⁰¹.

One would be unaware if they were experiencing a loss of platelets unless their platelet count became dangerously low and they suffered trauma that would cause bleeding. Of greater concern is the potential for serious adverse events that we may not know about for quite some time. For

example, damage to the ovaries or testicles might result in infertility that would not become apparent until attempting to have children. The oocytes that are present in the ovaries of newborn baby girls represent that female's life-long fixed supply of oocytes, which are the precursor of eggs. These oocytes cannot reproduce or regenerate if damaged or destroyed. Damage to the uterus could potentiate spontaneous abortions or miscarriages during pregnancy. The fact is, there is a clearly established set of biological mechanisms that raise numerous legitimate scientific concerns about COVID-19 vaccines. **We can't simply hope that none of these concerns end up being realized.** Instead, we must return to following the scientific method. We should stop the roll-out of the vaccination program for children, youth and young adults of child-bearing age, and ask the manufacturers of COVID-19 vaccines to take the time to conduct the proper biodistribution and safety studies to answer these emerging questions, and then conduct an accurate re-evaluation of the risk of COVID-19 versus the risks associated with the experimental COVID-19 vaccines.

Is the Pfizer BioNTech vaccine losing its effectiveness?

The stated purpose of vaccinating children, youth, and young adults of child-bearing age is to protect them from infection and reduce the risk of them transmitting SARS-CoV-2 to older adults. Therefore, it is important to note that the current COVID-19 vaccines fail to induce what we call 'sterilizing immunity'. This means that vaccinated individuals can still get infected with SARS-CoV-2, potentially become ill, and potentially transmit the virus to others. This is why vaccinated individuals are not exempt from lockdown policies and are still encouraged to wear masks. Importantly, there is evidence that the 'Delta variant' of SARS-CoV-2 has changed enough to be able to start evading the immunity conferred by the Pfizer BioNTech vaccine¹⁰². Indeed, the earlier 'South African' variant rendered AstraZeneca's vaccine only 10% effective¹⁰³. With new variants on the horizon that will almost inevitably be able to bypass vaccine-induced immunity, this raises another question about whether the potential risks associated with the current vaccines are worth the minimal protection they will confer in the long-term to children, youth, and young adults of child-bearing age.

The Pfizer BioNTech vaccine might cause an excessive number of serious side-effects in young Canadians

As noted previously, Pfizer conducted an extremely small and very short-term clinical trial to test their vaccine in adolescents between the ages of 12-15 years. The results were reported in a [fact sheet](#) to the U.S. Food and Drug Administration. In this document, Pfizer defined severe adverse events as follows:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may

jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes listed above

No deaths occurred in this small study, but Pfizer did note the following on page 27 of their fact sheet: “Serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.1% of placebo recipients.” Much larger numbers of adolescents would have to be studied to provide conclusive evidence, but these limited data suggest the risk of serious adverse events may have been 0.3% higher in the vaccinated group (not statistically significant in this small study).

As discussed previously, adverse events of special interest are being monitored, although the thoroughness is questionable, and the transparency of such activity is spotty at best. For example, the European Medicines Agency has compiled a list of important medical events (IMEs) which are always to be classified as serious (the IME list). The IMEs that are most frequently reported following COVID-19 vaccination include (in descending order):

- Fainting (syncope)
- Blood clot in the lungs
- Anaphylactic reaction
- Deep vein thrombosis
- Pneumonia
- Low blood platelet count (thrombocytopenia)
- Blood clots or bleeding in the brain
- Hallucinations
- Cerebral stroke
- Loss of consciousness

As the number of adolescents studied in the Pfizer trial was so small, it remains unclear whether adolescents also will experience these IMEs. It is not appropriate or ethical to experiment with youth, especially when their risk of severe COVID-19 is so low.

What options are we left with if we pause the vaccination roll-out for children, adolescents, and young adults of child-bearing age?

Canada abandoned the original goal of learning to live with SARS-CoV-2 after the initial 2-3-week ‘flattening of the curve’ of daily cases of COVID-19 early in the year 2020. A massive amount of scientific data about COVID-19 has been compiled over the past 16 months. But we have not been following the accumulating science. It can direct us towards what one of my colleagues likes to call a ‘rapid but soft landing.’ The purpose of this guide was not to build a detailed exit strategy. However, I have also been closely following the scientific literature about strategies that can be used to effectively treat COVID-19, especially if they are implemented as an early out-patient, at-home treatment before the disease progresses to a level requiring hospitalization. Some, but all too few Canadian physicians, are aware of, or using, these early at-home treatment protocols. These protocols include safe and highly effective drugs like ivermectin, fluvoxamine, budesonide, zinc, melatonin, vitamin C, vitamin D, and many others. Several cocktails of approved drugs have proven to be particularly effective and are described in a variety of websites including TreatEarly.org, c19protocols.com, and FLCCC.net. There is now an

avalanche of scientific data in support of these treatment options, but this digresses into an area beyond the scope of this guide. Unfortunately, the use of these effective therapies has never been promoted in Canada even though they could have prevented a lot of sickness and deaths and would have reduced the burden on intensive care units. Many people do not realize that the Interim Order or emergency use authorization of COVID-19 vaccines would have been contraindicated if there was acknowledgement of effective treatment strategies. This rule is in place to protect Canadians from being experimented on when there are viable alternatives that are known to be safe. However, it is never too late to do the right thing. Canada panicked and threw out pandemic preparedness plans at all its public institutions. Sometimes poor decisions occur when being made during a crisis and in the absence of established guidelines. It is time to move on. By promoting widespread use of effective treatments for COVID-19, Canada can safely narrow its experimental vaccination program and call for the science to catch up before subjecting our children, adolescents, and young adults of child-bearing age to potential harm.

Concluding remarks

Looking back through this report, it is clear that there are too many warning signals to ignore. Each individual signal may present a particular level of uncertainty, but when all the signals are considered together, the alert is deafening and must not be ignored. We must halt the vaccination of our children, adolescents, and young adults of child-bearing age. This can be done safely and expeditiously because:

- The risk of severe and potentially lethal COVID-19 in these specific populations is so low that we need to be very certain that risks associated with mass vaccination are not higher;
- Asymptomatic members of this population are not a substantial risk for passing COVID-19 to others; and
- There are effective early-treatment strategies and considerations for the very few children, adolescents, and young adults of child-bearing age who may be at risk of developing severe COVID-19.

Our younger generations of Canadians are our treasures and our future. Let's not put their futures at unnecessary risk by forcing upon them experimental vaccines that present newly identified and still-to-be-clarified dangers. Proof-of-principle now exists to demonstrate the current crop of vaccines may be dangerous. This risk, no matter how theoretical, must be further investigated and all concerns put to rest prior to the vaccination of our youth. It's time to sort out the science and reduce the pressures on parents and their children so they can make truly informed decisions. It is time to pass the torch from the pharmaceutical companies and hand it to the leaders and innovators among our community of physicians and researchers who have the skills, knowledge, and experience to optimize excellent treatment strategies encompassing repurposed drugs that can be deployed to reduce the future casualties of this war against COVID-19.

12. Increased Risk for Those with Pre-Existing Immunity Against the Spike Protein

Of major concern is information arising from three recent scientific studies all showing that vaccine-induced adverse events (*i.e.*, unwanted side-effects) are more severe in people who are forced to be vaccinated after having recovered from COVID-19 and acquiring naturally induced immunity to SARS-CoV-2¹⁰⁴⁻¹⁰⁶. Indeed, the science clearly demonstrates that naturally acquired immunity against SARS-CoV-2 is more broadly protective, more durable, and more appropriate with respect to the type of antibody response at the site of SARS-CoV-2 infection in the lung and airways than vaccine-induced immunity.

Knowing that naturally acquired protection is routinely developed in COVID-19-recovered patients, should automatically set aside any mandated need for vaccination in this population.

Recent published studies have indicated that about a third of the population in the US has already acquired natural immunity, and serological studies performed in Canada indicate much higher levels of natural immunity in our country. As such, mandating COVID-19 vaccines with no knowledge of the immunity status of an individual would be completely inappropriate and could be dangerous. Therefore, mandated vaccination should not be instituted.

Instead, organizations should consider offering testing for evidence of immunity against SARS-CoV-2. This would equip the organization, their leaders, members, and their family members, with solid evidence to guide personal choices about COVID-19 vaccines.

Remember, the goal is not to vaccinate as many people per se. Instead, it is to achieve protective immunity against SARS-CoV-2 in a maximum number of people. Vaccines represent a tool to potentially help achieve this for those without natural immunity.

It is also important to note that some people are non-responders to vaccines, meaning that they fail to generate a protective immune response after receiving their injections. Thus, having evidence of immunity, or lack thereof, among both the vaccinated and unvaccinated would allow both groups to make fully informed decisions about how to best manage their health.

13. Questionable Efficacy and Safety Outcomes for Pfizer-BioNTech's BNT162b2 mRNA COVID-19 Vaccine Through Six Months

Pfizer/BioNTech recently published an update of the efficacy and safety data for their mRNA-based COVID-19 vaccine out to six months since it was rolled out to the public. The paper was rife with issues, including major conflicts of interest and a large quantity of troubling results reserved for the supplementary data section, which is separate from the main paper and often not viewed by readers. Dr. Bridle, along with four collaborators carefully assessed the main and supplementary data. They concluded that the reliability and clinical relevance of the six-month

follow-up efficacy & safety claims outlined in the publication are highly questionable. Here is the letter that they wrote to be submitted to the editor of the journal in which the paper was published...

Letter to the Editor of the *New England Journal of Medicine* (NEJM): Response to the Thomas *et al.* (2021) NEJM Publication

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We are writing with concerns regarding the recent article by Thomas *et al* reporting on the safety and efficacy of the BNT162b2 mRNA coronavirus disease (Covid-19) vaccine through six months, which was published in the *New England Journal of Medicine* on September 15, 2021.¹⁰⁷ This study which assessed the BNT162b2 in healthy individuals concluded that, “through 6 month follow up, despite a gradual decline in vaccine efficacy, that BNT162b2 had a favorable safety profile and was highly efficacious at preventing COVID-19.” We would like to address concerns regarding the reported safety and efficacy of these findings.

Efficacy

With regards to efficacy, the study reported that the vaccine reduced the relative risk of contracting symptomatic reverse-transcriptase-polymerase chain reaction (PCR)-confirmed COVID-19 relative to placebo by 91.3% (77 vs 850 cases) and severe symptomatic PCR-confirmed COVID-19 relative to placebo by 96.7% (1 vs 30 severe cases).¹⁰⁷ However, we feel that the authors failed to discuss important limitations of these findings.

First, the prespecified analysis was to report on safety and efficacy of the phase II – III portion of the BNT162b2 trial assessing outcomes among participants ≥ 16 years of age at six months follow-up after immunization. In a trial amendment, a cohort of adolescents aged 12 to 15 years was added to the phase III study for which there was a shorter follow-up period. Authors, however, chose to combine the original adult dataset providing efficacy outcomes after a six month follow up with that of this cohort, thereby departing from the pre-specified analysis without providing a reasonable explanation for doing so. Moreover, authors reported that vaccine efficacy waned over time.¹⁰⁷ By combining the older and younger datasets, authors obfuscated the efficacy

of the older group at six months. We kindly request that authors appropriately qualify their conclusion to clearly indicate the post-hoc nature of this analysis as well as explicitly state the two reporting time periods in their conclusion.

Second, when discussing findings, authors did not mention that a larger proportion of participants on the placebo arm discontinued the trial compared to the vaccine arm; 40% more after the first dose (271 vs 380 participants) and 63% more after the second dose (167 vs 273 participants). Discontinuations consisted mostly of “no longer meeting the eligibility criteria” and “voluntary withdrawals”. These imbalances, which was in the order of the number of primary end-point events (77 and 850, for vaccine and placebo, respectively) calls into question the reliability of these findings. We kindly request that authors disclose the details related to the nature of these losses and discuss the impact they may have had on overall findings.

Third, authors indicated that testing for the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was done with the Cepheid Xpert Xpress SARS-CoV-2 RT-PCR, presumably according to United States Food and Drug Administration-approved specifications, which at the time the study was using the test at a cycle threshold of up to 45.¹⁰⁸ It is now widely recognized that the PCR test used at a threshold higher than 20-30 cycles cannot reliably detect an active COVID-19 infection.¹⁰⁹⁻¹¹¹ If the PCR test is not reliably detecting active infections, the clinical relevance of these findings is brought strongly into question. We kindly request that authors discuss the implications of these findings on study outcomes, report non-laboratory confirmed symptomatic events, and adjust their conclusions to acknowledge the potential lack of clinical relevance, “the vaccine was very efficacious at lowering symptomatic laboratory confirmed cases although it is unclear whether this indicates a reduction in unconfirmed SARS-CoV-2 symptoms and infection rates”. Further, it would be helpful if the authors could explain why the gold-standard functional virology assay, looking for cytopathic effect in permissive cells, was not used in parallel with PCR testing.

Fourth, we noted an absence of systematic testing and an objective testing framework for SARS-CoV-2 in this study. In this study, it was left to the discretion of the investigator to send a patient presenting with COVID-like symptoms for laboratory confirmation of a SARS-CoV-2 infection, a task which is particularly difficult given that the majority of vaccine adverse effects present as COVID-like symptoms. This lack of systematic testing introduced a concerning level of variability and subjectivity associated with the identification of both symptomatic cases and disease severity.^{112,113} We kindly ask that authors discuss the implications of this lack of objective and systematic virological assessment on their study findings.

Finally, given inclusion of adolescents in the study population, we noted very little discussion of death, the most clinically relevant endpoint of this trial. A close inspection of the publication supplement showed that there was a numerically greater number of deaths in the vaccine arm (n=15 vs n=14 in the placebo arm during the blinded period), and five additional deaths in vaccine recipients after unblinding (two of which were initially allocated to the placebo arm), and nearly half of the deaths reported during the blinded period in the vaccine arm were cardiovascular events (n=7; four due cardiac arrest, one cardiac failure congestive, one cardiorespiratory arrest, one hypertensive heart disease). Authors state that, “None of these deaths

were considered to be related to BNT162b2”, but do not describe how they came to that conclusion. There is real-world evidence to support an association between cardiovascular adverse events and the vaccines.¹¹⁴⁻¹¹⁸ Given the seriousness of these adverse events, we kindly ask that authors provide a detailed description of how they arrived at their conclusions and request that authors recommend that all ongoing study protocols investigating BNT162b2, especially in children be immediately amended to include systematic clinical and sub-clinical monitoring of cardiovascular health.

Safety

The authors concluded their article by stating that BNT162b2 shows a, “favorable safety profile”, and in their abstract state, “that BNT162b2 continued to be safe and have an acceptable adverse-event profile”. However, the study supplement reported a considerably higher rate of treatment-related adverse events and any severe adverse event among vaccine recipients, presented as COVID-like symptoms. If the design of this trial was to argue that COVID symptoms are unfavorable and clinically relevant, how is it that an increase in COVID-like adverse effects among the vaccinated group is considered favorable?

In order to better compare the benefits and risks of this vaccine, we calculated absolute and relative risk reductions/increases (ARR/ARI and RRR/RRI, respectively) associated with the vaccine seven days after the second dose (*i.e.*, corresponding to full vaccination for those in the vaccine arm) in the eligible population for each relevant safety and efficacy event analysis, and applied a simple chi-square calculator to assess the significance of the difference in event numbers between arms (Table 1)¹¹⁹. Our findings showed that the increase in adverse events observed in vaccine recipients (RRI 298.3% and ARI of 17.9%; $p < .00001$) was greater than the reduction in COVID-19 cases observed in fully vaccinated individuals (RRR 90.9% and ARR 3.7%; $p < .00001$).

Table 1. Differences in efficacy and safety events in eligible populations reported in the 6-month update of the BNT162b2 mRNA Covid-19 Vaccine

Event	BNT162b2 (n)	Placebo (n)	Absolute Difference (p-value)	Absolute Risk Change* (%)	Relative Risk Change* (%)
Total Randomized Adults and Adolescents (n)	23,219	23,210			
Cases in Adults and Adolescents 7 days after 2 nd dose [§]	77	850	-773 (p<.00001)	-3.7	-90.9
COVID-19 symptoms + PCR					
Any Treatment-Related Adverse Event Adults [#]	5,241	1,311	+3,930 (p<.00001)	+17.9	+298.3
Any Severe Event Adults [/]	278	187	+91 (p=.00002)	+0.4	+48.7
Severe Cases in Fully Vaccinated Adults ^{&}	1	23	-22 (p<.00001)	-0.1	-95.6
COVID symptoms + PCR					

Severe Adverse Events in Adults					
Prevents daily routine activity or requires intervention or worse	262	150	+112 (p<.00001)	+0.5	+71.4
Deaths during placebo-controlled period [additional deaths during open-label period in vaccine recipients or those that only received placebo] [%]	15 [+5]	14 [NR]	+1 [+5] (p=.9)	+0.005 [+0.022]	+7.1 [+35.7]
Deaths due to cardiac events [^]	7	4	+3		

[?] Significance figures (p-values) estimated using chi-square calculator available at <https://www.socscistatistics.com/tests/chisquare>. P-values are without the Yates correction. This procedure was applied following the framework used by Classen (2021) in their analysis of “All Cause Severe Morbidity” based on data from the initial reports of the vaccine Phase III trials¹¹⁹

* Absolute and relative risk change calculations were performed using the common statistical definition, i.e. number of events relative to total number of eligible patients for each event analysis reported;¹²⁰ vaccine efficacy estimates reported at source used total surveillance time as denominator, however, this value is not available for all the events analyzed

[§] ≥7 Days after dose 2 among participants without evidence of previous infection

[#] Assessed by the investigator as related to investigational product

[/] In calculations combining efficacy and safety events, the number of patients randomized that received any dose of vaccine or placebo was used as the study population in the statistical calculations, following the framework used by Classen (2021) in their analysis of “All Cause Severe Morbidity”.¹¹⁹ Differences in the total (event-incident) population (randomized vs efficacy vs safety) used as denominator are relatively small and are expected to have minimal impact on the relative differences between arms

[&] ≥7 Days after dose 2

[%] During the open-label period, 3 participants in the BNT162b2 group and 2 in the original placebo group who received BNT162b2 after unblinding died

[^] Those with reported cause of death due to: cardiac arrest, cardiac failure congestive, cardiorespiratory arrest, hypertensive heart disease, or myocardial infarction

A similar pattern was seen when it came to severe adverse events. Although the study claimed that “vaccine efficacy against severe disease was 96.7%”. Table S6 reports a relative vaccine efficacy against severe disease of 95.7% among fully vaccinated individuals translating to an ARR of approximately 0.1%. However, the vaccine was associated with a significant RRI in severe adverse events of 71.4% and an ARI of 0.5% among vaccine recipients overall (p<0.00001). When the two groups were pooled to determine the likelihood of experiencing any severe event,¹¹⁹ there was an overall increase in severe events among vaccine recipients compared with placebo (RRI of 48.7% and ARI of 0.4%, p=0.00002). Given the increase in severe events in the vaccine compared to the placebo arm we kindly request that the authors revise their conclusion to state, “the vaccine was associated with a concerning and clinically significant increase in severe events relative to placebo”.

The authors stated that most participants randomized to the placebo arm of the trial have now been vaccinated, thereby ending the placebo-controlled period of the trial. This cross-over, which occurred sometime after 2.5 months, but before six months median follow up, precludes any insight into the long-term effects of these vaccines, which is supposed to be carried out for two years. Given the increases in short-term severe events associated with these vaccines (RRI of 48.7% and ARI of 0.4%) and increase in the number of cardiac deaths, we kindly request that authors provide a detailed discussion of severe adverse events along with a discussion of their long-term implications.

This study was conducted in predominantly healthy adults and shows questionable results concerning short-term safety and a diminishing long-term efficacy. These findings do not support the use of these vaccines in this population or in any other population, especially those who are more susceptible to adverse outcomes, such as those with co-morbidities of a cardiovascular nature and the frail elderly. Safety data also does not support further investigation in populations at risk of loss of multiple quality life years including pregnant females and their unborn children, adolescents, as well as children; we call for an immediate halt to the use and investigation of these vaccines in any of these populations.

Conflicts of Interest

An examination of the second supplement revealed a concerning level of direct conflict of interest in the preparation of this article (Table 2). The article was supported by BioNTech and Pfizer, the corresponding author, Judith Absalon, and last author owned shares in Pfizer, and the first author had been a consultant for Pfizer. Of the 29 other authors 21 (66%) were employees of Pfizer or BioNtech and 26 (81%) had some kind of Pfizer/BioNtech-related conflict of interest. Given the involvement of so many parties with conflicts of interest in the preparation of this publication, the weight of these findings for the Global community, and the mischaracterization of the safety profile as “favorable”, we request that the *New England Journal of Medicine* disclose the names and conflicts of interest of journal reviewers who should have conducted a more rigorous review of the manuscript.

Table 2. Conflicts of interest (COI) related to Pfizer/BioNtech	
Title	Author
Corresponding author	Judith Absalon: Pfizer employment+stock
First author	Stephen Thomas: Pfizer consultancy
Last author	Kathrin Jansen: Pfizer employment+stock
Other 29 authors (66% employees, 81% had some COI)	Pfizer/BNT employment+stock n=15; Pfizer/BNT employment (without stock) n=4; Pfizer grant/contract n=3; Pfizer clinical trial n=1; Other company consultancy n=1; No COI n=5

Conclusion: The reliability and clinical relevance of the six month follow-up efficacy & safety claims of BNT162b2 outlined in this publication have been brought strongly into question due to the combining of study cohorts with two different follow up periods, the imbalances in

people lost to follow up, the lack of systematic testing using a tool unable to reliably detect active infection, the relative and absolute increase in severe adverse events along with a numerical increase in death associated with the vaccine. Given the impact that these findings will have on the global community, we request that the authors address the requested revisions as a priority, and request that the dataset be made available for independent analysis.

14. The Effects of COVID-19 Vaccines on Pregnant Females and Their Developing Fetuses and Neonates are Unknown

Promotion of administering COVID-19 inoculations to pregnant females has been based on assumptions of safety due to a lack of data demonstrating that it is contraindicated. This has been a preposterous approach. **A lack of data demonstrating harm is not indicative of safety.** The scientific process and safety of the public demands that manufacturers of vaccines and drugs thoroughly demonstrate the safety of their products prior to their rollout into target populations. This has not been done in the context of COVID-19 inoculations for pregnant females. Indeed, in an article published in the extremely low impact *Journal of Obstetrics and Gynaecology Canada* (impact factor = 0.893; most scientists will not consider publishing a paper in a journal with an impact factor <2; impact factors provide an objective assessment of the quality and global impact [or lack thereof] of published data), justifications used by the authors included statements like “Patients who fear increased risk of miscarriage, congenital malformation, preterm delivery, or neonatal infection should be reassured that inactivated vaccines, such as the influenza vaccine, are frequently administered during pregnancy and have minimal risk of adverse events.”¹²¹ It cannot be emphasized enough how preposterous a statement like this is. The current COVID-19 inoculations are novel technologies that are very different from traditional vaccine technologies such as inactivated vaccines. This is akin to comparing apples to oranges and is a completely inappropriate argument to make, especially when the safety of mothers and their children are at stake. The authors go on to state: “Although none of the vaccines currently in use have included pregnant patients in their clinical trials, the rate of serious adverse effects in study populations has been quite low.” It is completely inappropriate to assume a novel medical technology is going to be safe in a unique demographic because serious harms to a different demographic seemed to be relatively low. Here is another statement that has been typical of how physicians have been viewing COVID-19 inoculations in the context of pregnant females: “Although clinical trial data do not yet exist to verify the safety of COVID-19 vaccine use in pregnancy, precedent from past immunization efforts and the present pandemic provide strong support for vaccination.” This is akin to questioning why we should bother evaluating any new medical intervention prior to rolling it out into the public. This kind of philosophy leads to rhetorical questions such as: “If drugs have been successfully used in the past and there is a pressing current need, why bother waiting for safety data from clinical trials prior to testing them in the general public?”

Remarkably, The Society of Obstetricians and Gynaecologists of Canada issued a statement on December 18, 2020 to promote the use of COVID-19 inoculations in pregnant and lactating (breast-feeding) females. This was a mere eight days after the United States Food and Drug Administration met to authorize the Pfizer-BioNTech inoculation for emergency use only. This statement was updated on May 25, 2021. Notably, the supporting evidence section of the statement

begins with the statement “Most pregnant individuals who become infected with SARS-CoV-2 will have mild-to-moderate symptoms and many can be asymptomatic.”; in other words, it is not a substantial problem for most pregnant females. The statement then focuses on what were believed to be legitimate but rare serious complications from infection of a pregnant female with SARS-CoV-2. The major problem with the statement from The Society of Obstetricians and Gynaecologists of Canada and the opinions expressed in articles such as the one published in the *Journal of Obstetrics and Gynaecology Canada* is that they are based almost entirely on assumptions and have failed to follow the progression of the ever-accumulating science.

A landmark study about the safety of COVID-19 vaccination in pregnant females was published by Shimabukuro, *et. al.* in the very high-impact *New England Journal of Medicine* in June 2021¹²². This study claimed there was no difference in the rates of spontaneous abortions (loss of fetuses) among vaccinated versus unvaccinated pregnant females. This was heralded as the missing safety data that was needed to truly justify policies for vaccinating pregnant females. There were two key problems, though. 1. The authors admitted “Preliminary findings did not show obvious safety signals”. The research was preliminary in nature and, therefore, not conclusive. Also, the study was designed in a way that only obvious, not subtle, safety signals could be detected. However, the second problem was much worse: 2. The authors made a very simple mathematical error that completely altered the conclusions of the study. To make such a simple error seems egregious considering the number of authors who wrote, revised, and approved the manuscript, and when one considers that the authorship represented the United States Centres for Disease Control. **Because of this major error, the authors were required to publish a correction.** Unfortunately, the correction was done quietly, with little fanfare. This was in stark contrast to the massive publicity garnered by the original published manuscript. As such, relatively few people are aware that the authors had to retract their assertion of safety of the COVID-19 inoculations in pregnant females. Indeed, **the authors had to admit that they had no idea what the denominator should be for a simple equation involving division. This means that this paper no longer makes the claim that COVID-19 inoculations appear safe in pregnant females. This key foundation for arguing safety was removed by the authors.** This can be confirmed by reading the published [correction](#), in which the key admission is “No denominator was available to calculate a risk estimate for spontaneous abortions”¹²³. The back-story to how this came about is as follows: Dr. Bridle is a collaborator with several other scientists who authored a letter (Dr. Bridle was not one of the authors) that was submitted to the editor of the *New England Journal of Medicine*. In this letter, Dr. Bridle’s collaborators pointed out the mathematical error. For some reason, the editor refused to publish the letter but did ask the authors to re-evaluate their findings. This led to the published erratum.

Dr. Bridle was one of seven co-authors of a paper showing a dearth of evidence that current COVID-19 inoculations are safe for developing fetuses and neonates. It also highlights why there could be risk of harms and why, therefore, **it is not okay to assume that COVID-19 inoculations will be safe in pregnant females.** This paper was submitted to the scientific journal *Vaccines*, which requested minor revisions following the peer review process. The revised and resubmitted version follows...

Maternal COVID-19 vaccination and potential impact on fetal and neonatal development

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Abstract

Vaccines have been developed at “warp speed” to combat the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus. Although they are considered the best approach to prevent mortality, when assessing the safety of these vaccines, pregnant women were not included in the clinical trials. Thus, vaccine safety for this demographic, as well as the developing fetus and neonate, remains to be determined. A global effort has been underway to encourage pregnant women to get vaccinated despite the uncertain risk posed to them and their offspring. Given this, *post-hoc* data collection, potentially for years, will be required to determine the outcomes of COVID-19 and vaccination on the next generation. While most COVID-19 vaccine reactions include injection site erythema, pain, swelling, fatigue, headache, fever and lymphadenopathy, these reactions may also be sufficient to affect fetal/neonatal development. In this review, we have explored components of the first-generation viral vector and mRNA COVID-19 vaccines that are believed to contribute to adverse reactions and may negatively impact fetal and neonatal development. We have followed with a discussion of the potential for using an ovine model to explore long-term outcomes of COVID-19 vaccination during the prenatal and neonatal periods.

Keywords: COVID-19, SARS-CoV-2, vaccines, fetal development, neonatal development

Introduction

Vaccines are a key strategy for preventing and controlling endemic and emerging diseases of both humans and livestock. In the case of COVID-19, which is caused by the zoonotic SARS-CoV-2 coronavirus, vaccines have been designed and produced at “warp speed” to combat the pandemic. Never before have vaccines been developed and made it to Phase III clinical trials in such a short period of time. The viral vector “Sputnik V” vaccine was the first to be registered in August 2020. The Oxford/AstraZeneca viral vector vaccine was later approved for use in the UK vaccination program in December 2020, and that same month the Pfizer-BioNTech mRNA vaccine was issued “emergency use authorization” by the US Food and Drug Administration and was approved for individuals 16 years of age and older in May 2021.

As of October 23, 2021, four different COVID-19 vaccines have been approved for use in Canada: Oxford/AstraZeneca’s Vaxzevria, Pfizer-BioNTech’s Comirnaty, Moderna’s Spikevax, and Johnson & Johnson’s Janssen (1). At this time, approximately 77% of the Canadian population

that was 12 years or older had received at least one dose, and 84% was fully vaccinated; most receiving the Pfizer-BioNTech and Moderna vaccines. Approximately 10% had received combinations of different vaccines, despite warnings against this “dangerous trend” by the World Health Organization (WHO) due to lack of immunogenicity and safety data (2).

In terms of females, approximately 79% of Canadian females had received at least one dose and 75% were fully vaccinated. Females mount a stronger immune response to vaccination than males, which can also make them more susceptible to adverse vaccine reactions (AVR) (3). The number of COVID-19 vaccinated pregnant women in Canada is currently unknown, but it can be approximated using the numbers of births in Canada from 2001-2020 (4). If we estimate 370,000 births per year, one can conservatively approximate 243,581 pregnant Canadian women received at least one COVID-19 vaccine dose and 231,248 were fully vaccinated within the 10-month vaccine rollout period based on the percentages of vaccinated females above. There is a concerted global effort underway to encourage pregnant women to get vaccinated despite the lack of safety data for this demographic (5); the rationale being that pregnant women who get COVID-19 are more likely to be more critically ill and have adverse fetal/neonatal outcomes (6). However, this rationale is not supported by all studies (7).

In the USA, 133,000 participants of the V-safe COVID-19 Vaccine Pregnancy Registry have indicated that they were pregnant at the time of vaccination, and the US Centers for Disease Control and Prevention (CDC) is currently enrolling eligible participants and analyzing data (i.e. pregnancy outcomes like miscarriage and stillbirth, pregnancy complications like preeclampsia and gestational diabetes, and problems with the newborn like preterm delivery, poor growth or birth defects) to better understand how COVID-19 vaccination may affect pregnant women (8). A widely cited preliminary study of the V-safe and Vaccine Adverse Event Reporting System (VAERS) data suggested that COVID-19 mRNA vaccines were safe for pregnant women (9); however, errors were found in their analysis (10), and a follow-up re-analysis of the data revealed cumulative incidence of spontaneous abortion to be 7-8 times higher than the original author’s calculations, which was statistically higher than the typical average for pregnancy loss during the equivalent time period (11). While this post-hoc data analysis of extreme outcomes will be very important for assessing vaccine safety during pregnancy, it does not include more subtle multi-organ developmental changes that would be expected to occur in the fetus during an AVR, and these could lead to increased risk of disease according to the Developmental Origins of Health and Disease (DOHaD) Hypothesis (12). We have actually been advised to, “feel positive about feeling bad”, after receiving a COVID-19 vaccine (13). However, the desired goal of these vaccines, to drive an anti-viral cell-mediated immune response against SARS-CoV-2 (i.e. the pro-inflammatory cytokines tumor necrosis factor (TNF) α , interleukin (IL)-1, IL-6, and Type I and II interferons (IFNs)), can also lead to adverse fetal outcomes (14,15).

Lipid nanoparticles (LNPs) in the COVID-19 mRNA vaccines

COVID-19 vaccine development has truly been unprecedented. Not only have vaccines been rapidly produced and approved for use, but this is the first time a coronavirus vaccine has ever been attempted for use on humans. Moreover, vaccines against infectious pathogens have not previously been created using the novel technologies that were used to develop the current emergency use COVID-19 vaccines. The mRNA vaccine platforms (Pfizer-BioNTech and

Moderna) contain a genetically modified mRNA sequence encoding the immunogenic SARS-CoV-2 spike protein, which is used by the virus to invade host cells. They also contain a novel lipid nanoparticle (LNP) carrier system that allows for efficient endocytosis of the mRNA cargo by host cells. These LNPs possess adjuvant-like properties, both inflammatory and mRNA stabilizing, which is why conventional adjuvants are not required for these vaccines (16). Nevertheless, the RNAs are not very stable during storage below 80°C, and rapidly degrade at body temperature. The LNPs are comprised of ionizable cationic lipids, phospholipids, cholesterol and polyethylene glycols (PEGs), which are used to control the LNP size (60-100 nm), prolong circulation time and prevent LNP aggregation during vaccine storage (17). Concern was raised years ago regarding the safety of LNPs due to their biodistribution. For example, they were found to disperse to the ovaries in experimental mice (18). Pfizer's own pharmacokinetic studies of a surrogate vaccine containing ALC0315 and ALC0159 LNPs demonstrated that they dispersed over a 48-hr period to many rat endocrine and immune organs including the ovaries, adrenals, bone marrow, liver and spleen (19).

Very little is known about how LNP particle components are metabolized by the human body. Thus, further research must be completed, or information on studies from the companies that manufacture LNP components must be made available on Safety Data Sheets, to indicate how these LNPs degrade into smaller catabolites. Research must also be conducted on how LNP components and their catabolites are distributed, retained and excreted. A critical component of the LNPs in both mRNA vaccines is the pegylated lipid composed of a PEG unit with an average molecular mass of 2000 Da, DMG2000 in the Moderna and ALC-0159 in the Pfizer-BioNTech vaccines. Interestingly, smaller PEG molecules have been studied as a possible means for both inducing retinopathy and as a means for drug delivery to the eye. C57BL/6 mice were administered an intra-ocular injection of PEG8 to induce choroid neovascularization (CNV) after complement activation (20), and may serve as a model for studying macular degeneration of the retina. Dutch belted rabbits injected with PEG400 were reported to have retinal degeneration and atrophy 5 days post injection (21). Both of these studies demonstrate that small sized PEGs were found to be toxic and, though helpful as a model for disease, indicate pegylated lipids are an unsuitable method for intraocular drug delivery. As a follow up to this, two recent case reports published in the USA reveal a possible association with mRNA vaccines and damage to the retina. Subramony *et al.* (22) for example, reported a case of bi-lateral retinal detachment in a healthy 22-year old after vaccination with the Moderna mRNA vaccine. This individual had no health issues, but upon ophthalmologic exam, was determined to have lattice degeneration. Post-vitreous retinal detachment is common in >50-year olds due to the liquefied vitreous pulling away from the retina, but not in younger patients. Lattice degeneration by itself in this individual is unlikely to cause a retinal detachment, thus some other mechanism must have caused the retina to detach around this area of lattice. Fowler *et al.* (23) reported acute onset central serous retinopathy in a 33-year old healthy male post Pfizer-BioNTech vaccination. Given the known factors that cause acute central serous retinopathy, the author speculated on few possible mechanisms as to why this occurred including increased serum cortisol and free extracellular RNA that can cause increased permeability of the choroid endothelial cells, but also suggested that PEG may be involved, and mentioned that fact PEG8 was shown in mice to induce central serous retinopathy via the complement pathway. Without evidence of how catabolites of PEG in COVID-19 vaccines circulate and are excreted, one could hypothesize that PEG2000 molecules are broken down into

smaller sizes, which could permit them to enter into the vasculature of immune-privileged tissues such as the eye and cause pathology.

LNPs are bioactive and the possibility of immunotoxicity has been raised. The innate immune system for example, is activated when phagocytic cells (i.e. dendritic cells, macrophages, Kupffer cells, monocytes, mast cells and granulocytes) come into contact with LNPs, which are recognized as danger signals by host cell toll-like receptors (TLRs). Ligation of LNPs to these TLRs triggers the induction and release of abnormally high levels of pro-inflammatory and anti-inflammatory cytokines, referred to as cytokine release syndrome. LNPs can also activate serum complement, resulting in complement activation-related pseudoallergy (CARPA), which can lead to anaphylactic shock (24). A recent pre-print study demonstrated that, when LNPs were injected intradermally into mice, inflammatory, pro-apoptotic, necroptotic and IFN gene pathways were induced, and when these LNPs were administered intranasal, 80% of mice died within 24 hours (25).

PEGs have been previously used in both cancer immunotherapies and to deliver cytotoxins throughout the body. They have also been used to dampen cytokine and complement activation triggered by LNPs, but an optimal concentration of PEG is required to both maximize LNP protection from the immune system and ensure the LNP cargo remains bioactive (24). PEGs were thought to have inert characteristics. However, it is now widely appreciated that they possess potent immunogenic properties. Exposure to PEG can result in the production of anti-PEG immunoglobulin (Ig)M and IgG, which can activate the complement system and result in anaphylaxis (26). Anaphylaxis is one AVR that is associated with the COVID-19 mRNA vaccines (27), and for the Pfizer-BioNTech vaccine, the risk is 1:100,000 (28). Since PEG is commonly used in consumer products, a considerable number of people may have already been sensitized to PEG and may therefore have pre-existing anti-PEG antibodies prior to COVID-19 vaccination (24). Following endocytosis of the LNPs, PEGs can also freely interact with IgE antibodies that are bound to Fc receptors on mast cells and granulocytes; this can lead to Fc cross-linking that immediately triggers cellular degranulation, also resulting in anaphylaxis (29). While anaphylaxis during pregnancy is typically a rare event, a recent study reported severe outcomes for infants from mothers with anaphylaxis (30), which should alert us to potential fetal/neonatal outcomes resulting from vaccine-induced maternal anaphylaxis.

Viral vector COVID-19 vaccines

The COVID-19 viral vector vaccines (Oxford/AstraZeneca, Janssen, and Sputnik V) rely on adenovirus DNA vectors as carriers for the genetic information coding for the SARS-CoV-2 spike protein. Following intramuscular injection, the adenovirus invades host cells via receptor-mediated endocytosis. Its DNA is carried to the nucleus, and the host cell machinery then transcribes and translates it into spike protein. Since typically 30 or more mRNA copies can be transcribed from a single DNA copy of gene, this provides for marked amplification of total spike protein than can be produced from the RNA-based vaccines.

The most commonly described side effects following the Oxford/AstraZeneca vaccination are injection site erythema, pain, swelling, fatigue, headache, fever and lymphadenopathy. However, in March 2021, vaccine-induced prothrombotic immune thrombocytopenia (VIPIT),

also referred to as thrombosis-thrombocytopenia-syndrome (TTS) or vaccine-induced immune thrombotic thrombocytopenia (VITT), was first reported for the Oxford/AstraZeneca vaccine. This should not be surprising, since thrombocytopenia has been consistently reported as an outcome of administering adenovirus vectors (31). In April 2021, similar reports started to appear for the Janssen vaccine. Females less than 60 years of age are at greatest risk of VITT within 5-30 days post vaccination, and the estimated risk is 1:25,000 and 1:500,000 for the Oxford/AstraZeneca and Janssen vaccines, respectively (32). In light of this AVR, many countries temporarily halted use of these vaccines, but they were later reinstated, because the risk of COVID-19 was deemed greater than the risk of VITT. A number of hypotheses have been proposed to explain potential mechanisms of VITT including antibodies acting against platelet factor 4 (PF4), interaction between the adenovirus and platelets, cross-reactivity of SARS-CoV-2 spike protein with PF4 (i.e. molecular mimicry), interaction between spike protein and platelets, and platelet expression of adenoviral proteins (33). With regards to pregnancy, a case study of immune thrombocytopenia was reported in a woman with mild COVID-19, and her newborn daughter who was COVID-19 free, also experienced a decrease in platelet count that was resolved within 3 weeks postpartum (34). In another study, a young COVID-19 positive woman, who delivered a stillbirth at 29 weeks into gestation, was also diagnosed with thrombotic thrombocytopenic purpura (35). Interestingly, new onset immune thrombocytopenia post-mild COVID-19 has been reported during the pandemic (36), and also following Pfizer-BioNTech vaccination (37), which indicates that the etiology of this condition is more complex than the adenoviral vectors alone.

Rare neurological manifestations, such as Guillain-Barre syndrome (GBS), have also been reported to be associated with the COVID-19 adenovirus vector vaccines (38–42). GBS is an acute inflammatory, demyelinating polyneuropathy characterized by progressive muscle weakness that is often self-resolving. However, in severe cases where respiratory muscle is compromised, it can be life-threatening and patients will require assisted mechanical ventilation (43), which has been reported to increase risk of premature birth (44). GBS is most commonly triggered by molecular mimicry following a gastrointestinal or respiratory illness. Mohkhedkar *et al.* (45) recently provided evidence to support involvement of molecular mimicry in COVID-19 by identifying autoantibodies in cerebral spinal fluid from a GBS diagnosed patient with COVID-19. It has also been proposed that pro-inflammatory cytokines and hypoxia may also contribute to COVID-19 related neuronal damage (42).

In addition to concerns about the adenovirus vectors, the Oxford/AstraZeneca vaccine also contains polysorbate 80 (Tween 80), which helps stabilize the vaccine. This synthetic non-ionic surfactant has been previously used in various drug formulations (46). However, polysorbate 80 is cross-reactive with PEG, so anti-PEG antibodies may also trigger an IgE-mediated hypersensitivity reaction to polysorbate 80 (27,47).

Lastly, concern has been raised about the potential fate of foreign DNA in human cells, sourced from either an adenovirus vector, or reverse-transcribed mRNA coding the spike protein. While this is theoretically possible based on gene therapies, the likelihood of SARS-CoV-2 mRNA being reverse transcribed into DNA and then integrating within the host genome is equally plausible during COVID-19 (48); thus, the benefits of the COVID-19 vaccines for now are thought to outweigh the potential risk of DNA integration (49).

Bioactivity of the SARS-CoV-2 spike protein

The main host target receptor for SARS-CoV-2 spike protein is angiotensin-converting enzyme 2 (ACE2), which is involved in maintaining blood pressure and vascular remodeling, and is expressed on adipocytes (50), other cells at mucosal surfaces and in the vasculature, heart, kidneys, pancreas and brain (51). ACE2 is also expressed within placental tissues (52), and is involved in regulating fetal myocardial growth, and lung and brain development (53). A recent pre-print study showed that blocking the ACE2 with an anti-ACE2 antibody reduced placental SARS-CoV-2 infection (54). This is one of a number of studies that have demonstrated the placenta is susceptible to SARS-CoV-2 (53,55), and may also be responsive to spike protein, which has been identified at low concentrations in plasma from recipients of the Moderna vaccine (56).

A large number of studies have provided evidence that the SARS-CoV-2 spike protein is bioactive, and ligation of the spike protein to ACE2 explains some of its bioactivity. A study by Lei *et al.* (57) for example, demonstrated that the spike protein down-regulated ACE2 on Syrian hamster vascular endothelial cells, which led to inhibited mitochondrial function and cell damage. In a later *in vitro* study, however, the spike protein was shown to up-regulate bronchial epithelial cell ACE2 expression via activation of the Type I IFN signaling pathway (58). These two studies indicate that the effect of spike protein on ACE2 expression is tissue or species specific. A recent study using mice and human umbilical cord blood demonstrated that ligation of recombinant spike protein to ACE2 can activate Nlrp3 inflammasome assembly resulting in uncontrolled inflammation that led to pyroptotic cell death (59). Ropa *et al.* (60) demonstrated that hematopoietic stem cells from human umbilical cord blood express ACE2 and were adversely affected by spike protein in terms of their ability to proliferate and expand into progenitor cells. Ropa *et al.* proposed that this could explain the reduced numbers of circulating lymphocytes and platelets that are observed in COVID-19 patients (60). Using wild type and transgenic mice expressing human ACE2, Biancatelli *et al.* (61) recently demonstrated that the intratracheal administration of the spike protein S1 subunit induced alveolar inflammation and acute lung injury, and altered lung vascular permeability leading to an ACE2-dependent systemic cytokine storm. Suzuki *et al.* recently demonstrated that the spike protein S1 subunit (Val-16-Gln-690), but not the ACE2 receptor binding domain (Arg-319-Phe-541), elicited mitogen-activated protein kinase (MEK/ERK) signaling in human pulmonary artery smooth muscle and endothelial cells (62). These authors proposed that this growth factor/hormone-like cell signaling contributes to the hyperplasia and/or hypertrophy of vascular smooth muscle and endothelial cells in patients with COVID-19 and possibly may also explain some AVRs associated with the COVID-19 vaccines (62). By combining their knowledge of the SARS-CoV-2 spike protein, and the work of Chen *et al.* (63) on SARS-CoV-1 spike protein conducted on human pneumocytes, Suzuki proposed that the spike protein functionally converts ACE2 from a peptidase to a functional cell membrane signaling receptor (Figure 1).

A number of studies have shown that the spike protein also possesses ACE2-independent bioactivity. Nader *et al.* (64) for example, found that in addition to ACE2, SARS-CoV-2 can also attach to, invade and damage host cells via $\alpha V\beta 3$ integrin adhesion molecules, which are highly expressed on vascular endothelial cells. These authors demonstrated that an arginine-glycine-aspartic acid mutation (RGD motif) in the spike protein has uniquely allowed SARS-CoV-2 to acquire this function. Since the RGD motif is located adjacent to the ACE2 receptor binding motif

(Figure 1), this could allow SARS-CoV-2 to bind to cells lacking ACE2 and potentially enhance binding to cells expressing both ACE2 and $\alpha V\beta 3$ integrin. Interestingly, $\alpha V\beta 3$ integrins are also expressed on platelets and contribute to platelet activation and aggregation (65). Shen *et al.* showed that SARS-CoV-2 interacts with platelets to influence their function and promote dysregulated coagulation (66), and they proposed an ACE2-independent mechanism because the expression of ACE2 is uncertain on platelets and their progenitor megakaryocytes (67). Perhaps, $\alpha V\beta 3$ integrin is involved in SARS-CoV-2 interaction with platelets.

In silico analysis of the S1 subunit of the SARS-CoV-2 spike protein has revealed molecular docking sites for TLRs including TLR1, TLR4 and TLR6, and interaction with spike protein was the strongest for TLR4 (68) (Figure 1). An *in vitro* study performed by Shirato and Kizaki (69) demonstrated that the spike protein S1 subunit induced murine peritoneal macrophages to secrete pro-inflammatory cytokines via TLR4 signaling and the response was attenuated using a TLR4 antagonist. TLR4 is also highly expressed on platelets, and when bacterial lipopolysaccharide (LPS) binds to TLR4, it can result in thrombocytopenia and the accumulation of platelets in the lungs (70). Ouyang *et al.* (71) recently demonstrated that SARS-CoV-2 spike protein can also bind to bacterial LPS, and this spike protein-LPS interaction was shown to boost monocyte NF- κ B activation and cytokine responses *in vitro*, and NF- κ B activation *in vivo* (72). Petruk *et al.* predicted the LPS interacting region to be within the proximity of the spike protein S1/S2 furin cleavage site (Figure 1) and proposed that spike protein-LPS interactions may in part explain the increased risk of severe COVID-19 due to comorbidities.

The SARS-CoV-2 spike protein can also interact with other proteins. Grobbelaar *et al.* (73) demonstrated that when the spike protein S1 subunit was added to platelet poor plasma, it interacted with and structurally modified plasma proteins β and γ fibrinogen, complement 3 and prothrombin, which made them more resistant to trypsinization. These authors proposed that this may contribute to hypercoagulation associated with COVID-19 and may impair clot breakdown during fibrinolysis (Figure 1). The SARS-CoV-2 spike protein can also bind with high affinity to glycosylated human serum albumin. This may allow SARS-CoV-2 to evade detection of its receptor-binding domain (RBD) by neutralizing antibodies (Figure 1); however, it can also lead to albumin depletion and may contribute to fluid tissue-vascular imbalance that can give rise to septic shock (74). Also found within the RBD of SARS-CoV-2 and SARS-CoV-1 spike proteins, is a “toxin-like” epitope that shares homology to snake venom α -bungarotoxin (75), which is a highly specific blocker of nicotinic acetylcholine receptors. Lagoumintzis *et al.* (75), hypothesize that the spike protein may block the cholinergic anti-inflammatory pathway allowing for uncontrolled inflammation to occur during COVID-19.

The SARS-CoV-2 spike protein can also bind to the b1b2 domain of the neuropilin-1 receptor (NRP-1) (76), which normally interacts with vascular endothelial growth factor-A (VEGF-A) in neurons. ACE2 is not present in most neurons (77), even though reports of neurological symptoms are common in COVID-19 patients (78). Interestingly, interaction between the polybasic 682RRAR685 amino acid sequence, termed the “C-end rule” (CendR) motif (Figure 1), with NRP-1 potentiates SARS-CoV-2 entry into host cells (79). This CendR motif is not conserved in either SARS-CoV-1 or Middle East Respiratory Syndrome coronavirus (MERS-CoV), and it is hypothesized that a “silencing” of pain through subversion of VEGF-A/NRP-1 signaling may underlie increased disease transmission in asymptomatic individuals (80).

There are three other regions of interest within the spike protein RBD that may also contribute to spike protein bioactivity. The first region is predicted with high probability to be an allergenic sequence (29). This region could therefore contribute to anaphylaxis in some patients that have received viral vector and/or mRNA COVID-19 vaccines. The second RBD region of interest potentially allows the spike protein to bind to amyloid-forming heparin binding proteins, which could lead to accelerated aggregation of amyloid proteins within the brain (81). This supports Classen's concern that COVID-19 vaccines could potentially induce prion disease (82). The third region of interest within the RBD contains seven predicted molecular sites that share similarity to different toxins or virulence factors from 12 different bacterial species, 2 malarial parasites and influenza A (83) (Figure 1).

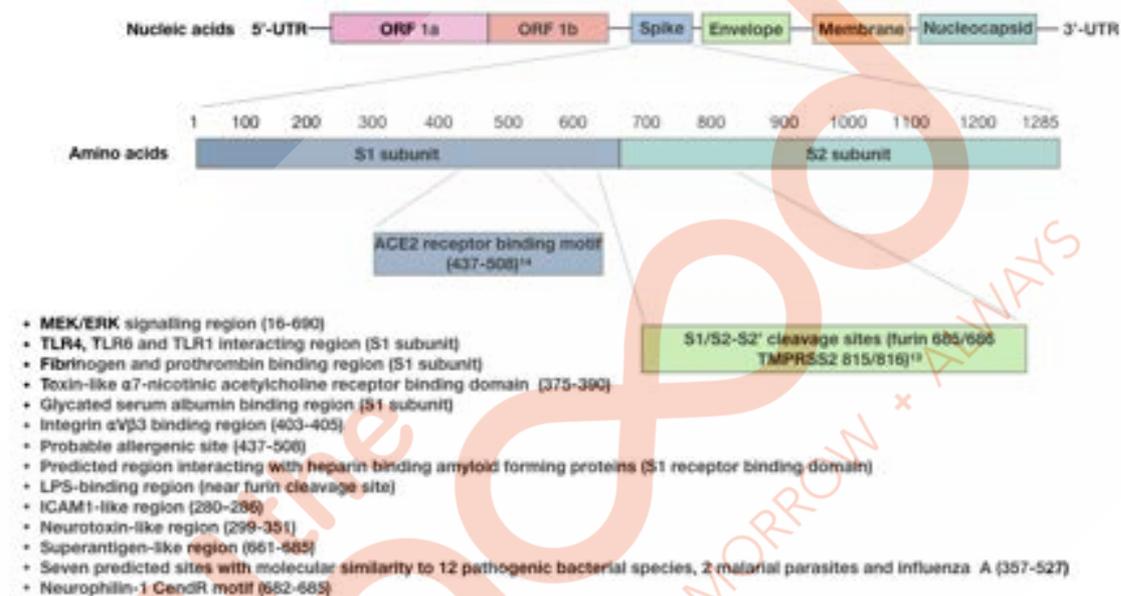


Figure 1. Sites within the SARS-CoV-2 spike protein S1 subunit and receptor binding domain showing confirmed or predicted bioactivity.

There is one final aspect of the spike protein that warrants consideration regarding its bioactivity, and this stems from the hypothesis that COVID-19-associated multi-system inflammatory syndrome in children (MIS-C) and the cytokine storm observed in adult patients with severe COVID-19 is mediated by spike protein superantigenic activity. Rivas *et al.* (84) have built on this hypothesis, first by drawing parallels between these two COVID-19 conditions and toxic shock syndrome (TSS). The superantigen *Staphylococcus* Enterotoxin B (SEB) associated with TSS is a biotoxin that causes polyclonal T-cell activation and proliferation, which leads to massive production of pro-inflammatory cytokines. These researchers used structure-based computer modelling to discover a SEB-like sequence (glutamic acid661-arginine685) near the spike protein S1/S2 cleavage site that exhibits high binding affinity to both the T-cell receptor (TCR) β chain and co-stimulatory molecule CD28 (85) (Figure 1). They also identified several neurotoxin-like sequences within the spike protein; one (threonine299-tyrosine351) also displayed high tendency to bind to the TCR, and another is an ICAM1-like region (aparginine280-

threonine286) that is predicted to stabilize interaction between the spike protein and the TCR. These researchers also demonstrated TCRV/β skewing of the T cell response in COVID-19 patients with more severe and hyper-inflammatory clinical courses, which is consistent with spike protein superantigen activity. Additionally, they showed that the SARS-CoV-2 mutation aspartic acid839tyrosine predictably enhanced binding affinity of the spike protein to the TCR, and later this group also provided evidence that a repurposed anti-SEB antibody could prevent SARS-CoV-2 infection *in vitro* (86).

Collectively, the diverse bioactivity of the SARS-CoV-2 spike protein makes this an ideal target for the immune system to neutralize the virus, and all the current COVID-19 vaccine platforms have focused on the spike protein because it is highly immunogenic (87). However, we should also be cognizant of these bioactive properties when designing COVID-19 vaccines to ensure that only nontoxic immunogenic portions of the spike protein are expressed, and that their expression is both temporally and spatially limited and does not provide selection pressure driving viral mutation. The mRNA vaccines were designed to allow a host cell to express the spike protein in its cell membrane (88), and the expression of the spike protein throughout the body is dependent on the biodistribution of LNPs, which primarily relocate to the spleen and liver, but have also been found in various other tissues (16,19). We currently have no idea how long spike proteins are expressed by different host cells and in what tissues spike protein expression can occur because biodistribution studies on the spike protein have not been carried out to date (19). The mRNA sequence has also been modified by manufacturers with the addition of proline residues at positions 986 and 987, which could allow them to reside longer in the plasma membrane (16). A recent pre-print by Patterson *et al.* (89) indicated that a subset of monocytes contained SARS-CoV-2 S1 mRNA and protein as long as 15 months post-acute infection. This raises the possibility of spike protein being expressed by maternal immune cells in colostrum and milk from COVID-19 positive mothers, thus, the biodistribution of spike mRNA and protein could be especially relevant during lactation. A recent study by Golan *et al.* (90) suggested that biodistribution of mRNA to milk during lactation is not a concern, as none was detected in milk from 6 mothers 4-48 hours post Pfizer-BioNTech and Moderna vaccination. However, a study demonstrated that following COVID-19 mRNA vaccination, exosomes expressing spike protein could be detected in plasma up to 4 months post vaccination (91), which is concerning because we, and others (92,93), have shown that exosomes can be shed in bodily fluids such as colostrum and milk.

Lastly, Zhang *et al.* (48) have provided evidence that SARS-CoV-2 sequences can become integrated into human genomic DNA, and Seneff and Nigh speculated that retrotransposons in sperm and embryos could theoretically copy and paste SARS-CoV-2 cDNA into the fetal genome resulting in the expression of spike protein that could render the neonatal immune system defenseless to mount an immune response to a subsequent SARS-CoV-2 infection due to immune tolerance to viral proteins (16).

The SARS-CoV-2 spike protein triggers autoimmune responses

Autoimmune diseases can be triggered by viral infections and some vaccines, and are more common to females (94). There is mounting evidence to support the hypothesis that SARS-CoV-2 infection is a risk factor for autoimmune disease in predisposed people (95–98). Autoimmune diseases manifest as hyper-stimulated immune responses against autoantigens, which are normally

tolerated by the immune system. The proposed mechanisms of autoimmune response during SARS-CoV-2 infection have been previously discussed (98,99) and include molecular mimicry, bystander activation, epitope spreading, and polyclonal lymphocyte activation by SARS-CoV-2 superantigens. Molecular mimicry describes structural similarities between SARS-CoV-2 antigens and autoantigens that are recognized by immune cells (i.e. cytotoxic T cells) and immunoglobulins (i.e. autoantibodies and antiphospholipid antibodies) at cross-reactive epitopes. When autoantigens are targeted by these effectors, this can lead to immune-mediated tissue damage, and if autoreactive memory B-cells and T-cells are generated, this can lead to chronic disease. Bystander activation involves immune-mediated tissue damage resulting from a nonspecific and over-reactive antiviral innate immune response, such as the cytokine storm that has been described in severely impacted COVID-19 patients. In this case, tissue and cellular components become exposed during damage, and are then ingested by phagocytic cells and presented as autoantigens to autoreactive T helper and cytotoxic T cells, which contribute to ongoing immune-mediated pathology. Epitope spreading refers to ongoing sensitization to autoantigens as the disease progresses, which can lead to progressive and chronic disease. A recent study by Zuo *et al.* (100) implicated anti-NET antibodies as potential contributors of COVID-19 thromboinflammation; NETs are neutrophil extracellular traps that are produced by hyperactive neutrophils that have either come into contact with SARS-CoV-2, or have been activated platelets and prothrombotic antibodies. These NETs are cytotoxic to pulmonary endothelial cells, and Zuo *et al.* discovered that anti-NET antibodies contribute to NET stabilization, which may impair their clearance and exacerbate thromboinflammation. Very recently, NETs were also implicated in VIPIT following the Oxford/AstraZeneca vaccine (101), but the potential involvement of anti-NET antibodies remains to be determined.

SARS-CoV-2 spike protein superantigen activity was discussed earlier. Superantigens are known to trigger the cytokine storm that can lead to immune-mediated multiple organ dysfunction syndrome, and this is often followed by immune suppression that can lead to persistent infection (102). Superantigens such as SEB have been shown to exacerbate autoimmune disorders (i.e. experimental autoimmune encephalomyelitis and experimental multiple sclerosis) in mice models (103). Recently, Jacobs proposed that long-COVID could be due in part to SARS-CoV-2 superantigen mediated immune suppression leading to persistent systemic SARS-CoV-2 infection (99). In terms of pregnancy, prenatal exposure of rats to SEB was shown to attenuate the development and function of regulatory T cells in adult offspring (104), and alter behaviour (i.e. increased anxiety and locomotion) of mice offspring (105).

Among the proposed mechanisms contributing to autoimmune response during COVID-19, molecular mimicry has recently taken the front stage. A number of studies have found homologies between SARS-CoV-2 amino acid and human protein amino acid residues (106,107), and more specifically between the spike protein and human proteins (108–110). Additionally, some of these cross-reactive regions were immunogenic epitopes, meaning that they can bind to MHC I or II molecules on antigen-presenting cells thereby activating autoreactive B and T cells that elicit an autoimmune response. Martínez *et al.* (109) for example, identified common host-like motifs on the SARS-CoV-1 and SARS-CoV-2 spike proteins that were nested in B and T cell epitopes. Morsy and Morsy also identified SARS-CoV-2 spike protein epitopes for MHC I and II molecules that were cross-reactive with the homeobox protein 2.1 (NKX2-1) and ATP-binding cassette sub-family A member 3 (ABCA3) lung proteins (110). Kanduc and Shoenfeld searched for overlapping SARS-CoV-2 spike protein hexa- and hepta-peptides across mammalian

proteomes and found a large number of matches within the human proteome; these authors stated that this is evidence of molecular mimicry contributing to SARS-CoV-2-associated diseases (108). Dotan *et al.* (111) also recently identified 41 immunogenic penta-peptides within the SARS-CoV-2 spike protein that are shared with 27 human proteins related to oogenesis, placentation and/or decidualization, implicating molecular mimicry as a potential contributor to female infertility. Vojdani and Kharrazian also demonstrated that anti-SARS-CoV-2 human IgG monoclonal antibodies cross-reacted with 28 out of 55 human tissue antigens derived from various tissues (i.e. mucosal and blood-brain barrier, thyroid, central nervous system, muscle and connective tissue), and BLAST searches revealed similarities and homologies between the SARS-CoV-2 spike protein and human proteins (112). In terms of the COVID-19 vaccines, molecular mimicry has also been implicated in myocarditis, an AVR associated with the COVID-19 mRNA vaccines (113). Huynh *et al.* (114) also recently identified autoantibodies as the potential cause of VIPIT; these autoantibodies were found to bind to PF4 and allowed for Fc receptor mediated activation of platelets, which could initiate coagulation leading to thrombocytopenia and thrombosis. These findings have raised concern over the possibility that anti-SARS-CoV-2 spike protein antibodies may be responsible for VIPIT. Greinacher A *et al.* (115) investigated this hypothesis and found that SARS-CoV-2 spike protein and PF4 share at least one similar epitope. However, when they used purified anti-PF4 antibodies from patients with VIPIT, none of the anti-PF4 antibodies cross-reacted with SARS-CoV-2 spike protein. They therefore concluded that the vaccine induced immune response against the SARS-CoV-2 spike protein was not the trigger causing VIPIT.

Others have implicated antiphospholipid antibodies in both COVID-19 and VIPIT related thrombosis. APA are present in 1-5% of healthy people and are associated with risk of autoimmune antiphospholipid syndrome (APS), which is the most common form of thrombophilia, and is more common in young women. APS during pregnancy is risk factor for poor maternal and fetal outcomes such as pregnancy-induced hypertension, fetal loss, placental abruption, abortion, thrombosis, preterm delivery, pulmonary embolism, neonatal mortality, fetal growth restriction, premature infants and increased neonatal admission to intensive care units (116). Antiphospholipid antibodies are a heterogeneous group of autoantibodies that recognize anionic phospholipids and protein-phospholipid aggregates and are used as a diagnostic biomarker of APS. Bacterial, viral and fungal infections can elicit the production of antiphospholipid antibodies, and molecular mimicry is the proposed mechanism (117). For example, human β 2-glycoprotein I, which contains a highly immunogenic five domain glycoprotein, displays homology to several microbial peptides (118). Anti- β 2-glycoprotein I antibodies have been detected in COVID-19 patients, and anti- β 2-glycoprotein I antibodies are considered to be the most pathogenic antiphospholipid antibodies in APS (117). β 2-glycoprotein I is able to bind to endothelial cells and anti-cardiolipin antibodies, which can result in APA induced endothelial cell damage (118). Zussman *et al.* (119) recently demonstrated that antiphospholipid antibodies were able to bind to placental mitochondria leading to ROS production. These authors proposed that APA binding to β 2-glycoprotein I and cardiolipin in mitochondrial membranes contributes to oxidative stress and placental dysfunction. Antiphospholipid antibodies are also generated in response to vaccination, most commonly reported for influenza vaccines (120). Martirosyan *et al.* reviewed cases of paediatric Henoch-Schonlein purpura and lupus associated with influenza vaccine and suggested that long-term effects such as thrombosis could be expected, since antiphospholipid antibodies remained elevated in some lupus patients for at least 6 months post vaccination (120). In the case of COVID-19 and

COVID-19 vaccine-related AVRs, the role of antiphospholipid antibodies remains controversial and more data are needed to establish potential cause-effect relationships (121).

Very recently, anti-idiotypic antibodies were also proposed as an autoimmune response following SARS-CoV-2 infection (122). In this study, Arthur *et al.* detected ACE2 autoantibodies in convalescent plasma from previously infected patients, which were also correlated with anti-spike protein RBD antibody levels. Since patients having ACE2 autoantibodies also had less plasma ACE2 activity, these authors hypothesized that the ACE2 autoantibodies were anti-idiotypic antibodies that could interfere with ACE2 function and contribute to post-acute sequelae of SARS-CoV-2 infection (PASC, or “long-COVID”). We are unaware of ACE2 autoantibody levels being assessed following COVID-19 vaccination so this warrants further investigation. Collectively, the above autoimmune responses triggered by infection with SARS-CoV-2 or the COVID-19 vaccines suggest potential negative outcomes on fetal and neonatal development, and this should be explored in future studies. As with APS, a cytokine storm and thromboinflammation are of concern, as is the potential for autoantibody responses that could target fetal/neonatal proteins.

The SARS-CoV-2 spike protein and antibody-dependent enhancement

While antibodies have a number of important effector activities against SARS-CoV-2, including limiting viral attachment to epithelial cells and viral neutralization, non-neutralizing antibodies that enhance viral entry into host cells can sometimes also be generated; this immunological phenomenon is referred to as antibody-dependent enhancement (ADE). Since the early days of COVID-19 pandemic, concern was raised about the possibility of ADE occurring because it was reported that both SARS-CoV-1 and MERS-CoV infect various animal models via ADE (123,124). Ricke (124) proposed that SARS-CoV-2 may leverage Fc receptors for host cell invasion, and this may contribute to the cytokine storm leading to adult multi-system inflammatory syndrome, and also infant MIS-C, the latter presumably being mediated by passive transfer of maternal anti-SARS-CoV-2 antibodies that have become bound to Fc receptors on infant mast cells, or macrophages (125). While the potential risk of this type of ADE occurring in response to COVID-19 vaccines remains unknown, experience with SARS-CoV-1 spike protein vaccines demonstrates it is indeed a possibility and warrants further investigation (124).

A second type of ADE involves non-neutralizing antibodies binding to and then eliciting conformational changes to viral proteins that can lead to enhanced viral adhesion to host cells (123). Liu *et al.* (126) recently screened a panel of anti-SARS-CoV-2 spike protein monoclonal antibodies derived from COVID-19 patients and found that some of these antibodies that bound to the N-terminal domain of the spike protein induced open confirmation of the RBD, which enhanced binding capacity of the spike protein to ACE2 and infectivity of SARS-CoV-2. Interestingly, these infection enhancing antibodies were identified in both uninfected and infected blood donors and were detected a high levels in severe COVID-19 patients; their presence in uninfected people implies these individuals may be at risk of severe COVID-19 if they later become infected with SARS-CoV-2 (126). Another recent study suggested that people may be at risk of infection by the SARS-CoV-2 Delta variant if they were vaccinated against the Wuhan strain spike sequence because the Delta variant is well recognized by infection enhancing antibodies targeting the N-terminal domain of the spike protein (127).

A number of murine studies have demonstrated that non-neutralizing maternal antibodies can increase risk of neonatal disease. For example, pregnant mice infected with different strains of Dengue virus (DENV) displayed maternal anti-DENV IgG that was passively transferred during gestation and enhanced severity of offspring disease (i.e. hepatocyte vacuolation, vascular leakage, lymphopenia and thrombocytopenia) following infection with the heterotypic strain (128), and breast feeding was shown to extend the window of ADE (129). In terms of anti-SARS-CoV-2 antibodies, passive transfer of anti-SARS-CoV-2 neutralizing antibodies has been detected in milk samples collected from women with COVID-19 (130), but non-neutralizing antibodies were not assessed. Anti-spike protein antibodies (IgG and IgA) have also been detected in milk samples from lactating mothers who were vaccinated with SARS-CoV-2 mRNA vaccines (131), however, their neutralization/non-neutralization status was not assessed. Therefore, we have no data to determine whether or not passive transfer of ADE can occur during SARS-CoV-2 infection or COVID-19 vaccination and this warrants further investigation.

Using an ovine model to study long-term outcomes of maternal COVID-19 vaccination

Assessing long-term outcomes of vaccination to pregnant women and their offspring under the DOHaD paradigm is difficult. Humans have a long-life span and a generation interval between 26-30 years. Differences in gender and genetics contribute to variation in the immune response, and environmental factors such as socioeconomic status, comorbidities, diet, exercise and vices act as interacting variables.

Large animal models such as sheep offer numerous advantages for DOHaD research. Sheep have a generation interval <1.5 years, a long gestation period of 145 days, and their fetal size and rate of development is comparable to humans (132). The ovine respiratory and cardiovascular systems are physiologically similar to humans, which make them an ideal model for studying respiratory diseases, neonatal lung development and xenotransplantation (133). Pregnant sheep have been used to study connections between maternal allergy and offspring lung development and risk of allergy (134,135). Sheep are also considered ideal models for studying neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases(136), and due to their susceptibility to scrapie, are widely used to study prion disease (137,138). Sheep are also a well-recognized biomedical model for studying immunology (139), vaccine development and safety (140,141), and have been extensively used by our group and others to study the impact of maternal inflammation during pregnancy on offspring development (142). We have shown for example, that transient inflammation, lasting approximately 6 hours, elicited by an immune challenge with *Escherichia coli* LPS endotoxin at gestation day 135 is sufficient to alter male and female offspring immune responsiveness at 4.5 months of age (143), and neuroendocrine responsiveness at 5.5 months of age (144,145). Using this endotoxin model, we have explored candidate protein and miRNA biomarkers for assessing the acute-phase response (APR) to immune challenge (146,147), and characterized variation in the APR at the population level (148), which is a moderately heritable phenotype (149).

As this pandemic continues to evolve, there are many unknowns with regards to COVID-19 and DOHaD. For example, what will be the outcomes of newborn babies born to mothers having COVID-19 during pregnancy? (150). Also, what will be the outcome of offspring from mothers

who received COVID-19 vaccines (151), and will this depend on gestational stage of exposure? With recent evidence of decreased vaccine efficacy against new SARS-CoV-2 variants (152), and immunity waning over time (153), addressing vaccine safety during pregnancy is becoming increasingly important as efforts are already underway in some countries to administer more booster immunizations. Since epigenetic mechanisms are believed to contribute to risk of DOHaD (154), a systems biology approach to addressing these questions is warranted, and we believe that the ovine model offers unique advantages for assessing the long-term impact of maternal COVID-19 vaccination on offspring health. Spike protein biodistribution studies can be performed during pregnancy and lactation by harvesting various tissues after euthanasia, and vaccine protocols can be mixed (*i.e.*, primary immunization with Pfizer-BioNTech followed by booster immunization with Moderna) to assess efficacy and safety of mixed vaccines. Offspring health can be assessed in terms of neonatal growth, gut development, and neuroendocrine-immune system function. If phenotypic changes are observed, then mRNA, microRNA and circularRNA sequencing can be performed using different tissues to better understand potential epigenetic changes brought on by maternal vaccination. Since there is evidence that SARS-CoV-2 spike protein is capable of binding to ovine ACE2 (155), and ovine respiratory organ cultures are susceptible to SARS-CoV-2 infection (156), this model species could also be used to investigate potential impact of molecular mimicry and ADE on neonatal health.

Conclusion: In closing, we currently have no data to assess the outcome of maternal COVID-19 vaccination on offspring health, and this may take years to generate. We believe that the ovine model can be used to rapidly assess potential concerns about administering COVID-19 vaccines during pregnancy and knowledge gained will help us to predict potential health outcomes to human offspring, which could lead to the development of treatments to help mitigate potential adverse outcomes.

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(Note: due to time constraints, these could not be reformatted to be included in the list that appears at the end of this expert report)

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15. Early Messaging About Pregnancy Increasing the Risk of Severe COVID-19 was Incorrect

Another key message underpinning policy for using COVID-19 inoculations in pregnant females has been the perception that they are at enhanced risk of severe outcomes should be get infected with SARS-CoV-2. Two studies conducted early during the declared COVID-19 pandemic concluded that pregnant females were at enhanced risk of serious consequences of COVID-19 than those who were not pregnant. This formed the basis for policies promoting rushed vaccination of pregnant females despite a dearth of safety data, especially long-term. It also led to the inclusion of pregnant females in COVID-19 vaccine mandates. However, as demonstrated by more recent and more reliable studies, these two early studies have been shown to be flawed. Specific details can be found in the following article, which Dr. Bridle co-authored along with five collaborators. This paper will be submitted to a peer-reviewed scientific journal...

Risks of Severe COVID-19 in Pregnant Females

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Since the declaration of the pandemic caused by severe acute respiratory syndrome-coronavirus-2, several studies have retrospectively and prospectively investigated the severity of the coronavirus disease that was first identified in 2019 (COVID-19) in pregnant females using data from multiple types of medical databases. Current government health policy was established from a retrospective analysis of electronically reported data submitted to the United States Centres for Disease Control (CDC) using standard case report forms, or from the National Notifiable Diseases Surveillance System (NNDSS), that showed symptomatic pregnant females were at increased risk of severe disease compared with non-pregnant females.¹ Since then, however, three additional comparative, dual cohort studies have been released that shed new light on the CDC's analysis.^{2,3}

What do COVID-19 registries tell us of the risk of severe disease in pregnant females?

The NNDSS has been utilized to aggregate and track COVID-19 cases in the United States. This information, along with data from the Response Pregnancy and Infant Linked Outcomes Team (CDC analysis), was used to perform the largest and most well-recognized assessment of COVID-19 risk among pregnant females. This retrospective registry analysis published by **Zambrano *et al.*** in November 2020 analyzed 23,434 pregnant and 386,028 non-pregnant females 15 to 44 years of age with symptomatic COVID-19 recorded in the NNDSS from January 22 to October 3, 2020.¹ Differences in intensive care unit (ICU) admissions, invasive ventilation and death between pregnant and non-pregnant women were assessed. When outcomes were adjusted for cardiovascular and chronic lung disease, age and diabetes, adjusted risk ratios (aRR) for serious events were significantly higher for symptomatic pregnant females compared with symptomatic non-pregnant females, including ICU admittance (aRR = 3.0 (95% confidence interval [CI], 2.6–3.49); 1.05% vs. 0.39%), invasive ventilation (aRR = 2.9 (95% CI, 2.2–3.8); 0.29% vs 0.11%) and death (aRR = 1.7 (95% CI, 1.2–2.4); 0.15% vs. 0.12%). The analysis showed that older females (aged 35 to 44 years) were at a particular risk of severe outcomes, with a nearly four-fold increased risk of invasive ventilation and two-fold increased risk of death compared with non-pregnant females. Authors concluded that although the absolute risk of severe disease was low for symptomatic pregnant females, the risk was significantly higher than for symptomatic non-pregnant females.

Similar outcomes were seen in a second large retrospective analysis using data from the COVID-19 National Data Registry of Mexico published by **Martinez-Portilla *et al.*** in February 2021.⁴ This study included 5,183 pregnant and 175,905 non-pregnant females aged 15 to 45 years with symptomatic COVID-19. The primary outcome was death, with rates of pneumonia, intubation, and ICU admission as secondary outcomes. A propensity score-matched analysis was conducted to control for underlying conditions (chronic obstructive pulmonary disease, asthma, smoking, hypertension, cardiovascular disease, obesity, diabetes, chronic renal disease, immunosuppression, age, language, nationality, and level of health insurance). Unadjusted

outcomes did not show increased risk of death for symptomatic pregnant versus symptomatic non-pregnant females (1.5% vs. 1.5%, OR = 1.01, 95% CI 0.80 to 1.26, P=0.935), although ICU admittance was higher (13.0% vs. 6.9%, OR = 2.03 95% CI 1.69 to 2.44, P<0.001) and invasive ventilation was significantly lower in the pregnant cohort (8.1% vs. 9.9%, OR = 0.80, 95% CI 0.64 to 0.99, P=0.044). Matched analysis, however, showed a significantly higher mortality rate in pregnant versus non-pregnant females (1.5% vs. 0.8%, OR=1.84; 95%CI 1.26 to 2.69, P=0.001) and ICU admissions (13.0% vs. 7.4%, OR=1.86, 95% CI 1.41 to 2.45, P<0.001). Authors concluded that pregnancy was a risk factor for death and ICU admission in symptomatic SARS-CoV-2-infected females of reproductive age after adjusting for differences in baseline risk factors.

Although helpful for identifying potential correlations, retrospective registry analyses are limited by incomplete data, imbalances in baseline factors, and ascertainment bias that can confound outcomes. Although COVID-19 registry analyses represent a rich repository of COVID-19 data, it should be recognized that these registries tend to capture outcomes of symptomatic COVID-19 cases and do not account for the many asymptomatic or mildly symptomatic cases in individuals who opted out of testing and recovered at home. Additionally, as these databases are designed to capture COVID-19 data, ancillary data such as pregnancy status and hospital outcomes will be more limited. For instance, the analysis by **Zambrano *et al.*** used most often to guide current policy had pregnancy status data available for only 36% of the 1,300,938 women potentially eligible for inclusion.¹ Furthermore, data on ICU admission status was only available for 22% to 24% of eligible women in this study and for only 8.2% of eligible individuals in the analysis by **Martinez-Portilla *et al.***^{1,4} Considering that these databases are designed for symptomatic COVID-19, they should be interpreted with caution when drawing conclusions on the risk for individuals with asymptomatic disease and for those who are pregnant.

Imbalances in baseline factors are also a concern when retrospectively analyzing registry data. **Zambrano *et al.*** used a multi-variate analysis and **Martinez-Portilla *et al.*** used propensity score matching to address this issue.^{1,4} Both analyses failed to recognize that pregnancy is also a well-recognized risk factor for increased morbidity and mortality.^{5,6} In an observational cohort study SARS-CoV-2-positive pregnant females, 24% of ICU admittances were for an indication other than COVID-19 and two out of six deaths were not deemed related to COVID-19 (for a rate of COVID-19-related mortality of 0.3%).⁷ The analysis by **Zambrano *et al.*** also failed to adjust for severe obesity, another well-recognized risk factor for poor outcomes, which was twice as common among the pregnant versus non-pregnant study group (2.2% vs. 1.1%).¹ Although **Martinez-Portilla *et al.*** considered a wider range of factors in their analysis, this approach is typically limited by the potential for unmeasured variables that can affect outcomes.^{8,9} These studies also tend to be poorly implemented in the medical literature and their reliability is difficult to assess in the absence of sensitivity analyses.⁸⁻¹⁰ The influence of these limitations and other factors, known to be strongly associated with severe outcomes, that define high-risk subgroups and that may be driving the overall effect (for example, older pregnant females had a four- and two-fold greater risk of invasive ventilation and death, respectively, relative to non-pregnant females in the **Zambrano *et al.*** study¹) may partially or fully explain the reported increased risk in pregnant females, underscoring the importance of well-controlled randomized trials to confirm findings.

Hospital database analyses of pregnant females with symptomatic COVID-19

Hospital databases provide a more complete picture of pregnancy status and hospitalization outcomes for risk evaluation. **Knight *et al.*** and **Pineles *et al.*** recently published retrospective analyses of hospital databases to assess the risk of severe COVID-19 among hospitalized pregnant females.^{2,3} **Knight *et al.*** analyzed data from the COVID-19 Clinical Information Network (CO-CIN) including over 300 National Health Service hospitals across the United Kingdom (UK), the UK Obstetric Surveillance System (UKOSS), and from the 'Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK' (MBRRACE-UK) Confidential Enquiry into Maternal Deaths surveillance system.² COVID-19 events were assessed in 1,134 pregnant females and 6,810 non-pregnant females and males aged 20-39 years who were hospitalized with COVID-19. The dataset was over 94% complete for COVID-19 status, pregnancy status and relevant outcomes (ventilation, ICU admissions, and death rates). Unlike the CDC analysis, the CO-CIN study found lower rates of ICU admission (11.4% vs. 23.5%), invasive ventilation (3.7% vs. 8.8%) and death (0.8% vs. 3.1%) among symptomatic pregnant females versus non-pregnant females. Similar outcomes were seen in the overall study cohort which also included asymptomatic patients. **Pineles *et al.***³ conducted a large analysis of an all-payer hospital network data repository from 853 hospitals that captured 20% of all United States hospitalizations to determine the risk of severe outcomes for females hospitalized with COVID-19 or viral pneumonia. The study showed that in-hospital deaths occurred less frequently among pregnant ($n=1,062$) compared with non-pregnant females ($n=9,815$) (8 vs. 35 per 1000) and that pregnant females tended to be younger and less likely to have co-morbidities.³ Overall, recently published cohort analyses relying on databases that provided more complete pregnancy and hospitalization outcome data failed to confirm an increased risk of ICU admittance, invasive ventilation, and/or mortality for pregnant females compared with non-pregnant persons hospitalized for COVID-19. Finally, a prospective cohort study of the UKOSS representing all 194 obstetrics units was conducted by **Knight *et al.*** This group identified 427 pregnant females hospitalized between March 1 and April 14, 2020 that tested positive for SARS-CoV-2 after becoming symptomatic.¹¹ They found that the estimated incidence of admission to a hospital with symptomatic COVID-19 was low (4.9 per 1,000 pregnancies) and that most females did not need critical care (90%) and were healthy discharges (93%). They did note, however, that the majority of hospitalized females were black or of other ethnic minorities (56%), overweight or obese (69%), older than 36 years (34%) and/or had pre-existing comorbidities (34%).

Medical database analyses of asymptomatic pregnant females who tested positive for SARS-CoV-2

Single cohort studies of asymptomatic patients provide important insights into rates of positivity for SARS-CoV-2 infections and outcomes among pregnant females. A number of small retrospective studies of obstetrics units conducting universal testing for SARS-CoV-2 were published by **Woods, Sutton and Maru *et al.*** and showed that the vast majority of those testing positive were asymptomatic ($n = 33$ to 46 , 72% to 98%).¹²⁻¹⁴ **Delahoy and Cruz-Lemini *et al.*** conducted retrospective reviews of hospital databases to determine the risk of severe outcomes from COVID-19 among pregnant females and neonates hospitalized with what was presumed to

be COVID-19. They analyzed the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET), which included 598 hospitalized pregnant females who had tested positive for SARS-CoV-2. The study found that the majority of pregnant females were asymptomatic (54.5%)¹⁵ and required no ICU admissions or invasive ventilation requirements, with no deaths reported. **Cruz-Lemini et al.** of the Spanish Obstetric Emergency Group prospectively screened 11,728 pregnant females admitted to 42 hospitals, including a small fraction of SARS-CoV-2-positive patients ($n=279$, 2.4%) and among these those with asymptomatic infections ($n=174$, 62%). They found no significant differences in neonatal outcomes from asymptomatic pregnant females with positive SARS-CoV-2 tests compared with those testing negative for the infection ($n=430$), with the exception of pre-labor rupture of membranes at term.¹⁶ The authors concluded that “Pregnant asymptomatic females testing positive for COVID-19 [technically, SARS-CoV-2] at admission for delivery should be reassured by their healthcare workers.” Studies that include outcomes among females with asymptomatic infections show that the majority of pregnant females remain asymptomatic and that these females and their neonates are not at an increased risk of severe outcomes from COVID-19.

Conclusions: The CDC analysis suggested a higher risk of severe COVID-19 outcomes such as ICU admittance, invasive ventilation, and death among symptomatic pregnant females, although the overall risk was low. Outcomes from this analysis should be interpreted with caution as they are based on limited pregnancy status and hospital outcome data and did not fully control for baseline factors such as severe obesity which is a well-known risk factor for severe COVID-19 outcomes. Our review of studies assessing the risk of severe COVID-19 outcomes among pregnant females underscores the importance of not ascribing causation based on association and appropriately extrapolating outcomes, in addition to the importance of properly controlled trials to confirm findings prior to policy implementation. Finally, and perhaps most importantly, these studies do not account for the role of prophylaxis using safe and effective therapies like hydroxychloroquine, which can help mitigate severe COVID-19 outcomes.¹⁷ Although it is reasonable to adopt greater caution given the substantial global health issue that COVID-19 represents, **available data fail to definitively support the claim that pregnant females are at increased risk for developing severe COVID-19 outcomes.**

Overall conclusion: Having closely monitored the accumulation of data about COVID-19 and COVID-19 inoculations in pregnant females, Dr. Bridle has come to the following conclusions: 1. The sum of the data indicate that pregnant females are not at enhanced risk of severe outcomes from infection with SARS-CoV-2 compared to non-pregnant females. Also, pregnant females fall into an age range for which the risks of the most severe outcomes of infection with SARS-CoV-2 are extremely low. As such, **COVID-19 vaccines should not be mandated for pregnant females.** 2. There are numerous legitimate scientific concerns about the safety of COVID-19 inoculations for developing fetuses and neonates. And this is with a notable absence of potential long-term safety issues that have yet to be evaluated. Not only is there a dearth of clinical evidence of safety for fetuses and neonates, but key safety studies were also not conducted, and some were conducted incorrectly during the pre-clinical phase of development of the COVID-19 inoculations. For example, in the pre-clinical fertility toxicology studies for the Pfizer/BioNTech inoculation, only females were inoculated (*i.e.*, there was no evaluation of

potential impacts on male fertility). Also, the studies were conducted in rats, which are an inappropriate model for evaluating the safety of inoculations that induce host cell-mediated expression of the spike protein from SARS-CoV-2. This is because the cells of rats express what is called a low-affinity ACE2 receptor, unlike other species such as humans that express the high-affinity receptor. This means that the spike protein cannot efficiently ‘grab onto’ cells in rats. Indeed, this is supported by the fact that rats are inherently resistant to infection with SARS-CoV-2 and do not develop COVID-19 even after intentional delivery of SARS-CoV-2 into their respiratory tract. It is also notable that the risk of death due to COVID-19 in Canadian neonates is statistically equivalent to zero. This is likely due to the natural protection conferred by the fact that cells lining their respiratory tracts express much lower concentrations of the receptor used by SARS-CoV-2 to facilitate infection as compared to adults. As such, **for the safety of fetuses and neonates, a basic risk/potential risk-benefit analysis does not support mandating COVID-19 inoculations for pregnant or breast-feeding females.**

16. Those with Naturally Acquired Immunity Don’t Need to be Vaccinated and are at Greater Risk of Harm if Vaccinated

Dr. Bridle was one of seven co-authors of a paper in which the qualitative and quantitative aspects of naturally acquired versus vaccine-induced immunity against SARS-CoV-2 were compared...

Which is Better for Future COVID-19 Prevention: Immunity Following Natural Infection or Vaccine-Induced Immunity?

A review of a collection of 15 studies compiled by Daniel Horowitz at TheBlaze.com - all credit to Horowitz with additional references and commentary prepared for the Canadian Covid Care Alliance (<https://www.canadiancovidcarealliance.org/>)

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1) ***Discrete Immune Response Signature to SARS-CoV-2 mRNA Vaccination versus Infection*** | New York University, May 3, 2021¹²⁴

The authors of this study examined the contrast between vaccine-induced immunity and immunity from SARS-CoV-2 infection as it relates to stimulating innate host defense as well as B- and T-cell immunity. It is relevant to note that the appropriate combination of innate and adaptive host defense mechanisms generally generates more durable adaptive immunity than antibodies alone. The authors concluded, "In COVID-19 patients, immune responses were characterized by a highly augmented interferon response which was largely absent in vaccine recipients. Increased interferon signalling likely contributed to the observed dramatic up regulation of cytotoxic genes in the peripheral T cells and innate-like lymphocytes in patients but not in immunized subjects."

Other authors established that early in the pandemic, the interferon class of cytokines were important in control of viral replication and in making the appropriate transition from innate to adaptive immune responses.¹²⁵

The study by Ivanova *et al.*¹²⁴ - currently still a preprint - further notes, "Analysis of B and T cell receptor repertoires revealed that while the majority of clonal B and T cells in COVID-19 patients were effector cells, in vaccine recipients clonally expanded cells were primarily circulating memory cells." Horowitz suggests this could indicate that, "Natural immunity conveys much more innate immunity, while the vaccine mainly stimulates adaptive immunity." The authors write in the discussion that, "**We observed the presence of cytotoxic CD4 T cells in COVID-19 patients that were largely absent in healthy volunteers following immunization.** While hyper-activation of inflammatory responses and cytotoxic cells may contribute to immunopathology in severe illness, in mild and moderate disease, **these features are indicative of protective immune responses and resolution of infection.**"

These authors also point out that, "COVID-19 patients had a striking expansion of antibody-producing plasmablasts, with evidence of clonal cells in this cluster. However, **we did not detect appreciable expansion of plasmablasts in circulation of individuals immunized with SARS-CoV-2 BNT162b2 mRNA vaccine**, despite a robust antibody response." Plasmablasts are the cells specialized to go on to produce large amounts of antibodies.

It is important to understand that **not all antibodies are created equal**. Some can neutralize viruses and others do not. Some antibodies are more important at mucosal surfaces, such as IgA which can be found in the upper respiratory tract. Antibodies of the IgG class are found lower in the respiratory tract and play a more important role than IgA at that location. Since natural exposure to SARS-CoV-2 is via the upper respiratory tract, which later can move down to lower regions of the tract, this has a propensity to generate both IgA in the upper track and IgG antibodies in the lower airway to various components of the virus. Conversely, intramuscular vaccination is known to preferentially generate IgG, but not necessarily mucosal IgA. Consequently, upon re-exposure, people who have previously been exposed to the live virus will quickly generate a robust and broad-based set of innate and adaptive immune responses, both IgA and IgG, along with other cellular responses. This is why immunity following natural exposure is durable, often lasting the duration of the declared pandemic as discussed in various reports below. In contrast, **vaccine-induced immunity is clearly shorter term and must lack the breadth of immunity following natural**

exposure since the response is limited only to the viral spike (S) protein. Consequently, multiple vaccine boosters have been necessary. Testing for evidence of immunity following natural infection would negate the need for vaccination, spare vaccine doses, and certainly multiple booster shots. Although not part of this paper, another important consideration is that with natural exposure, the polyclonal antibody response will allow for the generation of a wide variety of memory cells. When the virus mutates, the immune response can respond with expansion of appropriate neutralizing effector cells. In contrast, vaccination will elicit a much smaller diversity of memory cells that are more likely to result in antibody-dependent enhancement, often due to non-neutralizing antibodies that actually facilitate the uptake of virus into the host cells as the virus mutates.

To summarize, **the results of this paper demonstrate distinct differences in the quality, quantity, location, and the overall nature of the innate and adaptive immune responses generated following vaccination versus natural infection.** Understanding these differences is important to determine who needs to be vaccinated and for designing better vaccines that more closely mimic the responses of immunity following natural infection, for example mucosal delivery systems. It has always been the goal of immunologists and vaccinologists to design vaccines that mimic the protective and durable immunity found in those who successfully recovered from natural infections.

2) ***SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans* | Washington University, St. Louis, Missouri, May 24, 2021, published in Nature¹²⁶**

As Horowitz states, the media has been promoting the idea that if antibody levels wane, it means immunity is weakening, as we are indeed seeing with the vaccines today. But as author Ewen Callaway writes in a Nature News article entitled, Had COVID? You'll probably make antibodies for a lifetime,¹²⁷ as he highlights the paper by Turner *et al.*, **“People who recover (even) from mild COVID-19 have bone-marrow cells that can churn out antibodies for decades.”**

More specifically, Turner *et al.*¹²⁶ explained in the primary research article that, “After a new infection, short-lived cells called plasmablasts are an early source of antibodies. But these cells recede soon after a virus is cleared from the body, and other, longer-lasting cells make antibodies: memory B cells patrol the blood for reinfection, while bone marrow plasma cells (BMPCs) hide away in bones, trickling out antibodies for decades” as needed. Turner and colleagues conclude in the discussion section of the paper, **“Overall, our data provide strong evidence that SARS-CoV-2 infection in humans robustly establishes the two arms of humoral immune memory: long-lived bone marrow plasma cells (BMPCs) and memory B-cells.”** This means that even though antibody levels will eventually wane, there are long-lived cells in the bone marrow that have memory of the virus and can quickly produce the needed antibodies against the virus upon re-infection.

Horowitz then went on to correctly point out, “It's therefore not surprising that early on in the pandemic, an in-vitro study in Singapore published in Nature found **immunity against SARS-CoV-2 to last even 17 years later from SARS-1-infected patients who never previously had COVID-19.**”¹²⁸ This paper by Le Bert *et al.* looked specifically at T-cell responses against the structural nucleocapsid (N) protein of the virus and found both CD4 and CD8 T cells that recognized multiple regions of the N-protein. The CD4 and CD8 T-cells are cells critical in generating both

helper and cytotoxic T-cell responses. The authors conclude, “Thus, infection with betacoronaviruses induces multi-specific and long-lasting immunity against the structural N protein.”

3) *Necessity of COVID-19 vaccination in previously infected individuals* | Cleveland Clinic, June 19, 2021¹²⁹

Howowitz then talked about a study involving **1,359 previously SARS-CoV-2 infected health care workers** in the Cleveland Clinic system, where “**not a single one of them was re-infected 10 months into the pandemic**, despite some of these individuals being around COVID-positive patients more than the regular population.”

The idea of reinfection with SARS-CoV-2 is a contentious one, being dependent on individual health status and stress levels, but most studies indicate that reinfection is rare and the immunity following natural infection is highly protective even against any new variants to date. A large study of UK health workers discussed by Nature News in January 2021 concluded that, “The data suggest that repeat infections are rare — they occurred in less than 1% of about 6,600 participants who had already been ill with COVID-19.”¹³⁰ In the original paper published by Hall *et al.* in the Lancet¹³¹, the authors interpreted their findings as follows, “A previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection. **This study shows that previous infection with SARS-CoV-2 induces effective immunity to future infections in most individuals.**” Further, a May 2021 paper published in the Lancet’s *EClinicalMedicine* elaborates that, “based on current evidence, we hypothesize that antibodies to both S and N-proteins after natural infection may persist for longer than previously thought, thereby providing evidence of sustainability that may influence post-pandemic planning.”¹³² Their hypothesis was indeed correct since the authors, “demonstrated a sustained positivity rate of antibodies against the SARS-CoV-2 spike protein past ten months post-PCR confirmed COVID-19 infection using data from over 39,000 patients, with linear trends indicating a substantial population half-life.”

In immunology anything is possible, but not everything is probable. Therefore, although a few people have shown to test positive more than once for SARS-CoV-2, these occurrences appear rare.¹³⁰ They may indicate a true reinfection, or a false positive PCR test, or may even be due to SARS-CoV-2 RNA integration into the host genome later expressed in human cells, although the latter needs to be confirmed *in vivo*.¹³³

Cumulatively, these studies indicate that there is no need of further vaccination or advantage of vaccinating those previously infected with SARS-CoV-2. Although vaccination following natural infection may increase antibody titers to the spike protein, this is not required for further protection. Additionally, as discussed above the responses induced by the vaccine are distinct from that of natural infection and much less durable. Further, amplification of naturally induced antibody responses by vaccination cannot be recommended in the absence of long-term safety studies. This is important because overly robust antibody responses can predispose people to unwanted autoimmune sequelae.

- 4) ***Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells*** | Fred Hutchinson Cancer Research Center, Seattle/Emory University, Washington, July 14, 2021, published in *Cell Medicine*¹³⁴

The study found that most recovered patients produced durable antibodies, memory B cells, and durable polyfunctional CD4 and CD8 T cells that target multiple parts of the virus. Horowitz concluded, "Taken together, these results suggest that **broad and effective immunity may persist long-term in recovered COVID-19 patients.**" Horowitz, in support of the growing body of literature, stated, "unlike with the vaccines, **no boosters are required to assist natural immunity.**"

- 5) ***Single cell profiling of T and B cell repertoires following SARS-CoV-2 mRNA vaccine*** | University of California, Irvine, July 21, 2021¹³⁵

Horowitz quotes the authors conclusion on their preprint paper - "**Natural infection induced expansion of larger CD8 T cell clones occupied distinct clusters, likely due to the recognition of a broader set of viral epitopes presented by the virus not seen in the mRNA vaccine.**" This makes sense given that following vaccination, a person is only exposed to the viral spike protein; whereas, following natural infection the person is exposed to all components of the virus giving the individual the opportunity to make a much broader immune response using multiple T cell clones that recognize various parts (epitopes) of viral antigens. This becomes highly pertinent when a person comes in contact with the virus for a second time, since even if the spike protein has been altered producing a variant of concern (VOC), the immune system still can activate other clones against the membrane protein for example, as well as other components of the virus.

In fact, each infected person can have antibodies generated against hundreds of epitopes in the virus. VOC's typically differ by less than 0.5% from other strains in their overall protein structures. Moreover, the actual regions in which the mutations associated with the common VOC's are located do not appear to be particularly immunogenic in patients that recovered from COVID-19.¹³ Consequently, the mutations in the known VOC's should not really impact overall immunity following natural exposure to the virus.

- 6) ***mRNA vaccine-induced T cells respond identically to SARS-CoV-2 variants of concern but differ in longevity and homing properties depending on prior infection status*** | University of California, San Francisco, May 12, 2021^{136,137}

This preprint article concluded that, "**In infection-naïve individuals, the second (vaccine) dose boosted the quantity but not quality of the T cell response, while in convalescents (recovered individuals), the second dose helped neither.** Spike protein-specific T cells from convalescent vaccinees differed strikingly from those of infection-naïve vaccinees, with phenotypic features suggesting superior long-term persistence and ability to home to the respiratory tract including the nasopharynx." This reiterates the findings of Ivanova¹²⁴ and further supports that the nature of the immunity generated following natural infection is distinct from that following vaccination.

Horowitz correctly explains that, “Given that we know the virus spreads through the nasopharynx, **the fact that natural infection conveys much stronger mucosal immunity makes it clear that the previously infected are much safer to be around than infection-naïve people with the vaccine.** The fact that this study artfully couched the choices between vaccinated naive people and vaccinated recovered rather than just plain recovered doesn't change the fact that **it's the prior infection, not the vaccine, conveying mucosal immunity.** In fact, studies now show that **infected vaccinated people contain just as much viral load in their nasopharynx as those unvaccinated,** a clearly unmistakable conclusion from the **virus spreading equally or in greater amounts among the vaccinated**”.¹³⁸ The CDC also recognized in its July 28, 2021 report that, “preliminary evidence suggests that fully vaccinated people who do become infected with the Delta variant can be infectious and can spread the virus to others”¹³⁹; this is now commonly acknowledged.

It is relevant to mention at this point that **there are also risks associated with the current nucleic acid vaccines against SARS-CoV-2.** These have been recently discussed in several papers, including one by Kostoff *et al.*¹⁴⁰ in *Toxicological Reports* entitled, “Why are we vaccinating children against COVID-19”. These authors stated, “A novel *best-case scenario* cost-benefit analysis showed *very conservatively* that there are **five times the number of deaths attributable to each inoculation versus those attributable to COVID-19** in the most vulnerable 65+ demographic. The risk of death from COVID-19 decreases drastically as age decreases, and the longer-term effects of the inoculations on lower age groups will increase their risk-benefit ratio, perhaps substantially.” Similarly, a paper by Walach and colleagues, which appeared in *Science, Public Health Policy and the Law*, calculated the Number Needed to Vaccinate (NNTV) to prevent one death from a field study.¹⁴¹ They used the Adverse Drug Reactions database of the Dutch National Register (Lareb) to extract the number of cases reporting severe side-effects and the number of cases reporting fatal side-effects and concluded that for six deaths prevented by vaccination, approximately four deaths were reported to Dutch Lareb that occurred after vaccination, yielding a potential risk/benefit ratio of 2:3. Their overall conclusion was that, “**these data indicate a lack of clear (vaccine) benefit,** which should cause governments to rethink their vaccination policy.” The Ontario Civil Liberties Association has concluded the same in a recent Open Letter to Public Health by Canadian virologist, Dr. John Zwaagstra, posted on their website September 21, 2021.¹⁴²

7) **Large-scale study of antibody titer decay following BNT162b2 mRNA vaccine or SARS-CoV-2 infection** | Israeli researchers, August 22, 2021¹⁴³

Regarding this preprint paper, Horowitz says, “Aside from more robust T cell and memory B cell immunity, which is at least as important as antibody levels, Israeli researchers found that **antibodies wane slower among those with prior infection.** Specifically, “In vaccinated subjects, antibody titers decreased by up to 40% each subsequent month while in convalescents they decreased by less than 5% per month.” This supports the studies mentioned above which show evidence of long-term antibody producing cells following natural infection that are not necessarily found post-vaccination.

8) **Quantifying the risk of SARS-CoV-2 reinfection over time** | Irish researchers, published in Wiley Review, May 18, 2021¹⁴⁴

In this study, the researchers conducted a review of 11 cohort studies with over **600,000 total recovered COVID-19 patients** who were followed up for more than 10 months. Horowitz provided the key finding, stating that **unlike the vaccine, after about four to six months, they found "no study reporting an increase in the risk of reinfection over time."**

- 9) ***SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy*** | Cornell University, Doha, Qatar, published in the Lancet, April 27, 2021¹⁴⁵

Horowitz describes this study as, “one of the only studies that analyzed the population-level risk of reinfection based on whole genome sequencing in a subset of patients with supporting evidence of reinfection. Researchers estimate the risk at 0.66 per 10,000 person-weeks”. Most importantly, **the study found no evidence of waning of immunity for over seven months of the follow-up period.** The few reinfections that did occur, "were less severe than primary infections," and "only one reinfection was severe, two were moderate, and none were critical or fatal." Also, unlike many vaccinated breakthrough infections in recent weeks that have been very symptomatic, "most reinfections were diagnosed incidentally through random or routine testing, or through contact tracing."

- 10) ***Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel*** | Israeli researchers, April 24, 2021¹⁴⁶

As Horowitz explained, “Several months ago, **Israeli researchers studied 6.3 million Israelis and their COVID status and were able to confirm only one death in the entire country of someone who supposedly already had the virus, and he was over 80 years old.**” Horowitz contrasted that to the hospitalization and deaths now reported in the vaccinated in Israel. There are other studies in Israel, Vietnam and elsewhere confirming breakthrough infections despite full vaccination. For example, the study of Vietnamese health care workers concluded, “**Breakthrough Delta variant infections are associated with high viral loads, prolonged PCR positivity, and low levels of vaccine-induced neutralizing antibodies,** explaining the transmission between the vaccinated people.”¹⁴⁷ In this study, the viral loads in the vaccinated people with COVID-19 with the Delta variant were estimated to be 251-times higher than in unvaccinated people previously diagnosed with COVID-19 a year before with earlier strains.¹⁴⁷

- 11) ***Live virus neutralisation testing in convalescent patients and subjects vaccinated against 19A, 20B, 20I/501Y.V1 and 20H/501Y.V2 isolates of SARS-CoV-2*** | French researchers, May 11, 2021¹⁴⁸

Horowitz described in this preprint article, “Researchers tested blood samples from health care workers who never had the virus but got both Pfizer shots against blood samples from those health care workers who had a previous mild infection and a third group of patients who had a serious case of COVID.” The authors state that they found, "No neutralization escape could be feared concerning the two variants of concern [Alpha and Beta] in both populations of those previously infected.”¹⁴⁸ However, the authors state, “The reduced neutralizing response observed towards the 20H/501Y.V2 (variant 2) in comparison with the 19A (initial strain) and 20I/501Y.V1 (variant 1) isolates in fully immunized subjects with the BNT162b2 vaccine is a striking finding of

the study.”¹⁴⁸ In other words, **the virus neutralizing capacity of the antibodies in the previously infected were minimally impacted by the variants** examined in this study compared to the vaccinated where viral neutralization to certain variants was substantially reduced.

12) *Highly functional virus-specific cellular immune response in asymptomatic SARS-CoV-2 infection* | Duke-NUS Medical School, Singapore, published in *Journal of Experimental Medicine*¹⁴⁹

Horowitz posed the question that many people are asking, “If they got only an asymptomatic infection, are they less protected against future infection than those who suffered infection with more evident symptoms?” This research study by le Bert¹⁴⁹ showed the opposite to be true. **"Asymptomatic SARS-CoV-2-infected individuals are not characterized by weak antiviral immunity; on the contrary, they mount a highly functional virus-specific cellular immune response,"** Horowitz pointed out, “If anything, they found that those with asymptomatic infection only had signs of non-inflammatory cytokines, which means that **the body is primed to deal with the virus without producing that dangerous inflammatory response that is killing so many hospitalized with the virus.**” The fact that asymptomatic people infected with SARS-CoV-2 recovered with minimal disease clearly demonstrates a high degree of immunological responsiveness in these individuals in the first place. Likewise, anyone who fully recovers from SARS-CoV-2 ultimately has had to develop an effective immune response to overcome the viral infection. In vaccinated people, the effectiveness of the induced immunity remains equivocal until tested, due to large variability in the antibody and T-cell responses amongst individuals, especially when narrowly focused on a single viral protein.

13) *SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells* | Korean researchers, published in *Nature Communications* on June 30, 2021¹⁵⁰

Horowitz highlighted this paper by Jung *et al.*¹⁵⁰ by saying, “The authors found that the T cells created from convalescent patients had "stem-cell like" qualities. After studying SARS-CoV-2-specific memory T cells in **recovered patients** who had the virus in varying degrees of severity, the authors concluded that **long-term "SARS-CoV-2-specific T cell memory is successfully maintained regardless of the severity of COVID-19."**

14) *Anti-SARS-CoV-2 Receptor Binding Domain Antibody Evolution after mRNA Vaccination* | Rockefeller University, July 29, 2021¹⁵¹

In agreement with the other papers referenced here, Horowitz made a remark about this preprint article by Cho *et al.*¹⁵¹ He stated, “The researchers note that far from suffering waning immunity, memory B cells in those with prior infection **express increasingly broad and potent antibodies that are resistant to mutations found in variants of concern.**” They concluded that, **"memory antibodies selected over time by natural infection have greater potency and breadth than antibodies elicited by vaccination."**

- 15) ***Differential effects of the second SARS-CoV-2 mRNA vaccine dose on T cell immunity in naïve and COVID-19-recovered individuals*** | Researchers from Madrid and Mount Sinai, New York, March 22, 2021¹⁵²

In this published article by Lozano-Ojalvo *et al.*¹⁵² cited by Horowitz, he concluded, “Until now, we have established that natural immunity provides better adaptive B cell and innate T cell responses that last longer and work for the variants as compared to the vaccines. Moreover, those with prior infection are at greater risk for bad side effects from the vaccines, rendering the campaign to vaccinate the previously infected both unnecessary and dangerous. But the final question is: **Do the vaccines possibly harm the superior T cell immunity built up from prior infection?**”

Immunologists from Mount Sinai in New York and Hospital La Paz in Madrid have raised serious concerns about this question. In a shocking discovery, after monitoring a group of vaccinated people both with and without prior infection, they found, **"in individuals with a pre-existing immunity against SARS-CoV-2, the second vaccine dose not only failed to boost humoral immunity but determines a contraction of the spike-specific T cell response."** They also noted that other research has shown, **"the second vaccination dose appears to exert a detrimental effect in the overall magnitude of the spike-specific humoral response in COVID-19 recovered individuals."**

CONCLUSION and FURTHER READING

We would be remiss not to mention several other key studies demonstrating the value of immunity following natural infection with SARS-CoV-2 that are published in reputable peer-reviewed journals. These include the early studies of Sette and Crotty that showed that CD4 T cells, CD8 T cells, and neutralizing antibodies all contributed to control of SARS-CoV-2 in non-hospitalized and hospitalized patients with COVID-19.¹⁵³

A Canadian study also demonstrated that 90% of healthy adults tested in the Greater Vancouver area had antibodies or cross-reactive antibodies to various components of the virus using a highly sensitive multiplex array.¹⁵⁴ This evidence of immunity in non-vaccinated Canadians was recently substantiated in a small pilot study of unvaccinated individuals between June-August 2021 residing in South Western Ontario using the same assay.¹⁵⁵

Another study by Braun *et al.* showed that both healthy donors and patients with COVID-19 have SARS-CoV-2 reactive T-cells.¹⁵⁶ The study concluded, “the presence of spike-protein cross-reactive T cells in a considerable fraction of the general population may affect the dynamics of the current pandemic and has important implications for the design and analysis of upcoming trials investigating COVID-19 vaccines.”

A recently published study by Wang *et al.* also showed **stable B-cell immunity six to 12 months following infection.**¹⁵⁷ The authors reported, “In the absence of vaccination, antibody reactivity to the receptor binding domain (RBD) of SARS-CoV-2, neutralizing activity and the number of RBD-specific memory B cells remain relatively stable between 6 and 12 months after infection. They did however see increases in antibodies to the viral spike protein following vaccination of these individuals, which would be expected. However, keep in mind as explained

above, the nature of vaccine-induced immune responses is not the same as that following natural infection. In fact, when all the evidence is considered, there appears to be no additional protective benefit from vaccinating those previously recovered from COVID-19. **This would impose an unnecessary risk of vaccination.** Whether vaccinating those previously immune from natural infection reduces or enhances the clonal diversity against SARS-CoV-2 remains controversial. This may differ depending on whether or not the studies examined B or T cell clones. Either way, the functionality and location of the clones post-vaccination would be critical to know when addressing this question.

Collectively, the current literature unequivocally demonstrates protective immunity following natural infection with SARS-CoV-2 that is durable and long lasting. Therefore, there is no need for mandated vaccination of individuals with previous SARS-CoV-2 infection, particularly in those with proof of previous immunity based on evidence of antibody or T-cell responses. This becomes increasingly important now that it is clear that both fully and partially vaccinated people, without prior viral exposure, can become infected and transmit the pathogen.

It is also important to accurately classify people based on their prior vaccine exposure. It is not reasonable to classify individuals as completely unvaccinated simply because they have not yet received the full series or the next booster in the series. Therefore, a standard system needs to be adopted to identify people who have received one, two or even three shots, and the timing of those injections. Maximum immune responses will be mounted differently depending on whether this is the first or subsequent exposure to the virus or the vaccine. More rapid anamnestic (memory) responses are generally generated on subsequent exposures. It is important to keep in mind that the timing of maximal immune responses will differ from the reported timing of vaccine injury, and these timelines should not be confused. For example, immediate hypersensitivity reactions (*e.g.*, anaphylaxis) can occur within minutes of exposure to a foreign substance, intermediate reactions can occur hours to days later, and long-term reactions may occur even years later. These timelines are distinct from the normal acquired immune responses which generally peak 7-21 days following primary exposure and 3-7 days following secondary exposure. The exact timeline of the response can vary somewhat depending on the antibody isotype (*e.g.*, IgM versus IgG), the antigenic dose, the route of injection, and the genetics of the host. It is pertinent to mention here that the actual dose of spike antigen given with the current nucleic acid vaccines is essentially unknown. The amount of nucleic acid (DNA or mRNA) delivered is known but because each person generates the foreign protein within their own cells after nucleic acid delivery, the amount of spike protein made by each individual can differ depending on age, gender, body metabolism and so on. This is in contrast to traditional vaccines where the amount of foreign protein in each dose is precisely known.

Moreover, as described earlier, vaccination of individuals with established immunity may place them at greater risk of vaccine injury. From a societal perspective to help end the SARS-CoV-2 pandemic, the establishment of immunity from natural acquisition plays an important role given the scope and durability of these immune responses. The relevance of natural immunity needs to be fully recognized and accepted by society as one of the valid means of achieving protection as has long been the case with other infectious diseases. Natural immunity has several protective advantages as outlined above and also reduces the vaccine implementation costs which are solely relying on extensive and repeated vaccinations. The various societal damages associated with recurring lockdowns of the population must also be considered. Safe and selective vaccination of

those at the highest risks of severe COVID-19 and the adoption of a myriad of effective early treatment protocols is the most logical course of action at this time.

Finally, **the spread of the virus in unvaccinated people recovered from COVID-19 is highly unlikely** given their broad and durable immunity shown to date. As such, **it makes sense to abandon the notion of separating society into two groups based on variable vaccination status.** Individuals have the right to consent to medical treatments that align with their needs and preferences, and the COVID-19 vaccines are no different. **We propose a multi-faceted path forward that fully embraces the underlying immunology** demonstrated in the above series of articles, as well as integrating preventative and early treatment protocols into outpatient and healthcare systems to best care for and serve patients in Canada.

Original article: <https://www.theblaze.com/op-ed/horowitz-15-studies-that-indicate-natural-immunity-from-prior-infection-is-more-robust-than-the-covid-vaccines>, Daniel Horowitz is senior editor¹⁵⁸.

17. COVID-19 Vaccines May Have the Potential to Cause Long-Term Neurological Disease

Dr. Bridle was one of three co-authors of a manuscript that was recently submitted to a peer-reviewed scientific journal...

How Does Severe Acute Respiratory Syndrome-Coronavirus-2 Affect the Brain and its Implications for the Vaccines Currently in Use

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Abstract: This mini review focuses on the mechanisms of how severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) affects the brain, with an emphasis on the role of the spike protein in patients with neurological symptoms. Following infection, patients with a history of neurological complications may be at a higher risk of developing long-term neurological conditions associated with the α -synuclein prion, such as Parkinson's disease and Lewy body dementia. Compelling evidence has been published to indicate that the spike protein, generated from the vaccines currently being employed, are not only able to cross the blood-brain barrier, but may cause inflammation and/or blood clots in the brain. Notwithstanding, the long-term implications for these subjects may be identical to that of patients exhibiting neurological complications as a result of being infected with SARS-CoV-2. However, further studies are needed before a definitive conclusion can be made.

Keywords: severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), cytokines, spike protein, blood-brain barrier (BBB), angiotensin-converting enzyme-2 (ACE2), Parkinson's disease, Lewy body dementia, good laboratory practice (GLP).

1. Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is the causative agent of the novel coronavirus disease that emerged in 2019 (COVID-19), which prompted the declaration of a global pandemic that has persisted for more than a year. As of May 12, 2021, there have been more than 160 million cases; 3.3 million deaths, and 138 million recoveries. COVID-19 is primarily being considered a respiratory disease. However, unlike the common flu, other organs including the brain, are also severely affected in some patients [1]. Evidence shows that SARS-CoV-2 has the ability to affect the brain directly, with a new set of symptoms: loss of smell and taste, severe headaches, debilitating fatigue, trouble thinking clearly (brain fog), seizures, stroke, and various degrees of paralysis [2]. A number of reliable studies have already been published on this topic and are referenced in this article. Several revealing patient case histories and results from pre-clinical studies will be used to explain the mechanisms involved.

2. Lessons Learnt from Similar Coronaviruses

The first coronavirus to affect humans was the common cold in 1965. Since then, there was the SARS-CoV (the virus that causes SARS) out-break in 2002 followed by the MERS-CoV (the virus that causes MERS) out-break ten years later (Figure 1). At the time these out-breaks had caused worldwide concern with case fatality rates of 9.5% and 34.4% for the SARS and MERS, respectively [3]. Although the fatality rates were higher than that for SARS-CoV-2, the infections were contained. So, what do these previous infections have in common with SARS-CoV-2?

MERS-CoV binds to the DPP4 receptor (also known as CD26). What made MERS so deadly was the fact that the receptor to which the virus binds is involved in the regulation of T-cells. The results of which are no less than catastrophic. T-cells are inhibited from binding to the CD26 receptor, resulting in a delayed adaptive immune response which forces the body to maintain its innate immune response, resulting with the patient having a fever, and initiating a severe inflammatory reaction making the condition worse [4]. The adaptive immune response being suppressed, plus an over reactive innate response gives rise to a poor prognosis (Table 1).

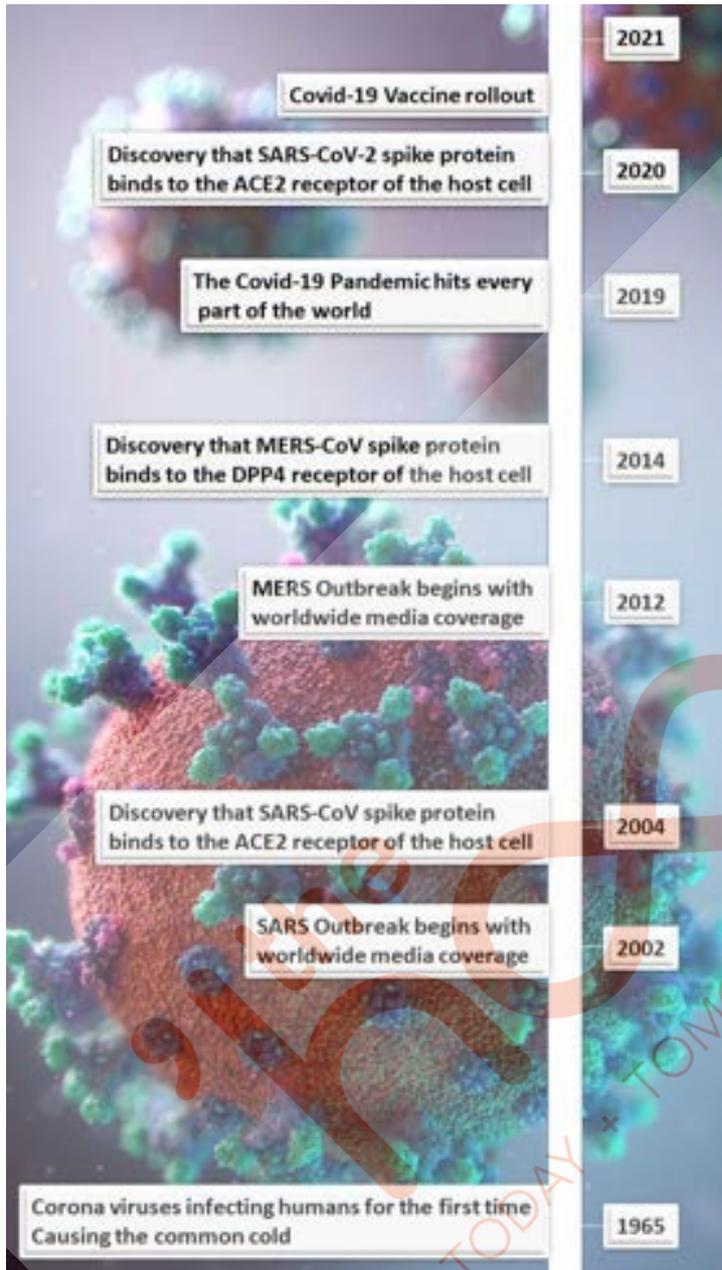


Figure 1. Timeline of Corona Viruses and Spike Protein Receptor Targets

Table 1. Characteristics of severe acute respiratory syndrome-coronavirus (SARS-CoV), Middle East respiratory syndrome-coronavirus (MERS-CoV), and SARS-CoV-2

Corona Virus	Host Cell Target Receptor	Clinical Symptoms	DeathRate (%)
SARS-CoV	Angiotensin-converting enzyme 2 (ACE2)	Fever, Tiredness, Chills, Muscle aches, Dry cough, Difficulty breathing, Diarrhea	9.5
MERS-CoV	Dipeptidyl peptidase 4	Fever, Cough, Shortness of breath	34.4
SARS-CoV-2	ACE2	Fever, Dry cough, Chills, Difficulty breathing, Tiredness, Body aches, Headaches, Loss of taste or smell, Sore throat, Diarrhea	2.3

Both SARS-CoV and SARS-CoV-2 target the same receptor (ACE2) on host cells, and this is probably the reason why the clinical symptoms are similar (Table 1). With SARS and to a lesser extent with COVID-19, patients can feel well one moment, then over a short period of time go downhill with breathing problems requiring oxygen and hospitalization. To gain an insight as to what might be going on in these patients, we need to consider the role of the angiotensin-rennin system that regulates blood pressure and fluid balance. So, when the spike protein of SARS-CoV-2 binds the ACE receptor, the body control mechanism is disrupted causing a buildup of fluid in the lungs, leading to pneumonia and respiratory failure [4]. This is a clear example where the virus is causing the body to work against itself, and the difficulty that physicians are faced with, when it comes to effective treatment.

Therefore, it can be concluded that the spike protein of the virus plays a key role in the pathogenesis of these diseases. These examples also illustrate the need to determine the molecular basis of disease, to facilitate effective treatments.

3. SARS-CoV-2 and Neurological Symptoms

Often one of the first symptoms of COVID-19 is the loss of smell and taste. With the olfactory nerve anatomically close to the brain, this nerve pathway is the ideal means for the SARS-CoV-2 to enter the brain in the early stages of the disease [5]. Nonetheless, there is an alternative route by which SARS-CoV-2 can enter the brain as the disease progresses [5]. The spike proteins of the SARS-Cov-2 virus bind to the angiotensin-converting enzyme 2 (ACE2) receptors expressed by the endothelial cells of the brain's vasculature and invade the cells, enabled by the enzyme transmembrane protease serine-2. The viral damage to the endothelial cells initiates the inflammatory reaction, activating neutrophils, and macrophages in the blood, as well as microglia and astrocytes in the brain. Endothelial damage and the direct activation of platelets by SARS-CoV-2 via spike protein/ACE2 interactions [6] can also promote the formation of micro-thrombi, which in turn can develop into blood clots. Thus, with this destabilization of the blood-

brain barrier (BBB) caused by the cytokines in conjunction with the chemokine, monocyte chemoattractant protein-1, SARS-CoV-2 can then freely pass through the BBB.

Notably, many of the neurological symptoms associated with COVID-19 are due to hypoxia, cytokine storms, and blood clots, all of which contribute to damaging neurons in the brain. Debilitating fatigue, depression, anxiety, psychosis, brain fog, seizures, and stroke are some of these symptoms. Evidence obtained from brain biopsies of patients that had been diagnosed with COVID-19 also showed that SARS-CoV-2 was able to target and replicate in the neurons themselves [7].

4. COVID-19 and Possible Connection with Parkinson's Disease

Based upon other viral infections affecting the brain, it has been suggested that SARS-CoV-2 infection of the central nervous system may lead to long-term neurological consequences for some patients [8]. A pre-print entitled "SARS-CoV-2 causes brain inflammation and induces Lewy body formation in macaques [9]", emphasizes this concern. In this study, the treatment group, four male rhesus and four male cynomolgus monkeys, were experimentally infected with SARS-CoV-2. The control group was comprised of two male rhesus and two male cynomolgus monkeys. The monkeys experienced asymptomatic infections and were euthanized between five to six weeks post-infection, and their brain tissues stained for Lewy bodies by immunohistochemistry. Formation of intracellular Lewy bodies were observed in the midbrain region of the caudate nucleus of all eight of the infected monkeys, while Lewy bodies were absent in the brains of all monkeys in the control group. These results provided compelling evidence that SARS-CoV-2 has the ability to initiate α -synuclein misfolding and is therefore responsible for Lewy body formation in SARS-CoV-2-infected monkeys.

Should the same misfolding of α -synuclein (i.e., α -synuclein prion), its aggregation, and the formation of Lewy bodies occur in the brains of patients who had previously recovered from SARS-CoV-2, this could potentially lead to neurodegenerative diseases such as Parkinson's disease and Lewy body dementia years if not decades later. It is therefore essential to provide follow-up for patients diagnosed with COVID-19 who exhibit neurological complications post-infection [10].

5. Pathology Attributed to the SARS-CoV-2 Spike Protein

Let us consider the spike protein itself. The experimental vaccines that have currently received emergency use authorization to reduce the severity of COVID-19 employ either mRNA or DNA to transfect human cells to produce the spike protein, which then becomes the antigen to be targeted by the body's immune system.

Confirmation that the spike protein does cross the BBB was evidence from an in vitro study [11] suggesting that purified spike proteins from SARS-CoV-2 have the ability to initiate the pro-inflammatory response in endothelial cells in the brain, thereby destabilizing the BBB. Secondly, an in-vivo study in mice, demonstrated that the S1 sub-unit of the spike protein readily crosses the BBB entering the brain parenchyma, after iodinated S1 sub-unit was administered intravenously to male mice [12]. Connecting these phenomena to the vaccine administration site, which is the deltoid muscle, was the remarkable observation that the spike protein S1 sub-unit was detectable in the systemic circulation up to approximately two weeks post-immunization in eleven out of thirteen health care workers [13].

It was demonstrated that the spike protein S1 sub-unit alone is responsible for initiating pro-inflammatory responses via Toll-like receptor 4-mediated signaling [14]. In addition, the spike

protein alone when bound to ACE2 on the surface of platelets, can regulate platelet function, which in turn results in blood clot formation [6]. So, it is evident that the spike protein is responsible for key aspects of the pathogenesis observed following infection with SARS-CoV-2.

6. What are the Implications for the COVID-19 Vaccines Currently Being Used?

During the pandemic, vaccine manufacturers focused mainly on assessing the efficacy of their products [15-17]. However, following experience with other corona virus as mentioned earlier, it was already known that the spike proteins are largely responsible for the observed pathology. Therefore, a theoretical scenario exists that a certain proportion of people receiving the COVID-19 vaccine, likely from among those with neurological side-effects (e.g., severe headaches), may exhibit neurological symptoms of synucleinopathies diagnosed as Parkinson's disease and/or Lewy body dementia up to two to three decades post-immunization. In the U.S. Food and Drug Administration's briefing document, Pfizer stated the following with respect to their COVID-19 vaccine: "Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of nearly 44,000 participants over the period of follow up at this time. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals [15]." The other manufacturers made similar statements. Obviously, the pharmaceutical industry has taken it upon themselves to initiate active and passive safety surveillance during this post-authorization period. On the 23rd August 2021, BioNTech Manufacturing GmbH (in partnership with Pfizer Inc.) has received US FDA's BLA authorization (STN: BL 125742/0) for their COVID-19 mRNA vaccine BNT162b2, now marketed as "Comirnaty" [18].

7. Discussion

Few would have thought, when the COVID-19 pandemic was declared in early 2020, labeled as a respiratory illness, that discussion would progress to the question of serious neurological consequences. We have already recognized the need to closely monitor patients who have neurological complications, and to screen for α -synuclein prions. Of interest is the mode of action of the COVID-19 vaccines currently used, where the end product is the SARS-CoV-2 spike protein; the intended target being the antigen-presenting cells of the immune system. However, there are indications that the spike protein generated by these vaccines may have off-target effects. There is no evidence that distribution, and/or toxicokinetic studies were performed. With this in mind, it would be prudent to follow-up subjects who had experienced neurological side-effects as a result of the COVID-19 vaccines in addition to the hospitalized patients with COVID-19 who had neurological complications. With the COVID-19 vaccines, an assumption was made that the spike protein produced in the host cells would not be shed into the systemic circulation. Therefore, additional evidence is required to determine the toxicity and distribution of the spike protein. Perhaps a standard 28-day study to GLP could be initiated, that not only mimics the concentration that gets into plasma post-vaccination [13], but also exceeds it to provide a good safety margin in a suitable species. Other regulated studies may also be deemed appropriate to fill the knowledge gap. Until such definitive studies are done, and the results substantiated, it lends consideration for caution when deciding whether to administer the vaccines to younger age groups.

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(Note: due to time constraints, these could not be reformatted to be included in the list that appears at the end of this expert report)

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18. Vitamin D as a Preventative Measure for COVID-19

The science underpinning validated treatments and preventive measures has exploded over the past year. My original report described in detail, the overwhelming science in support of the use of ivermectin as an effective early treatment strategy for reducing severity of disease, reducing admissions to hospital, especially intensive care units, and for preventing deaths. Indeed, since my first report, a peer-reviewed scientific [article](#) was published that summarizes the cutting-edge data regarding the effective use of drug combination therapies. This paper is entitled “Early Ambulatory Multidrug Therapy Reduces Hospitalization and Death in High-Risk Patients with SARS-CoV-2”¹⁵⁹. There are also simple preventative measures that are available, including supplementation with vitamin D.

As an immunologist, I routinely teach the benefits of vitamin D in the context of the function of the immune system. Indeed, my students find it very interesting to have the subject introduced in the historical context of sanatoriums that were used during outbreaks of tuberculosis. As an example, two of my lecture slides are shown in figure 9. They describe the mechanism whereby vitamin D, provided by sunlight-mediated production in the skin or via diet, is an essential molecule to promote killing of the tuberculosis-causing bacterium by macrophages, which are a major component of our innate immune system. Notably, the bacterium that causes tuberculosis is an intracellular pathogen, like SARS-CoV-2, highlighting the relevance of this mechanism used by macrophages in the context of viral diseases such as COVID-19. Remarkably, federal Health Minister Patty Hajdu publicly [dismissed](#) vitamin D as playing a role in protection against infectious diseases such as that caused in some people by SARS-CoV-2¹⁶⁰. It is troubling to see a non-scientist with broad-reaching control over the health of Canadians readily dismiss a basic, fundamental immunological fact that is based on decades of high-quality scientific research. Indeed, there are 77 peer-reviewed scientific articles that demonstrate the importance of vitamin D to the proper functioning of the human immune system to kill SARS-CoV-2: ¹⁶¹⁻²¹⁵. Note that each one of these papers deals specifically with COVID-19 and there are many more articles that are currently in pre-print version or undergoing the scientific peer review process. These studies clearly demonstrate that vitamin D insufficiency follows a seasonal trend in northern countries such as Canada. This is due to a lack of exposure to sunlight, which allows vitamin D to be

naturally produced in the skin. These studies also show that vitamin D sufficiency is strongly associated with lower risk of developing COVID-19, less severity of COVID-19, reduced hospital admissions, faster recovery if admitted to a hospital, and, importantly, a reduced risk of COVID-19-induced death. The broader literature showing the benefits of vitamin D supplementation in the general context of intracellular pathogens is massive. It is shocking that such a large body of scientific evidence has been ignored and/or dismissed by public health officials in Canada. Unfortunately, this aversion to following the weight of the science has likely been very costly to Canadians. Recommending proper supplementation with vitamin D, especially during the 'low vitamin D' season that spans mid-Fall to mid-Spring would have been an extremely simple and inexpensive strategy to promote the health of Canadians during the declared pandemic. According to the massive body of scientific evidence, public health officials, by not promoting the use of vitamin D, have caused Canadians to miss an effective preventive strategy. As a result, Canadians have suffered substantially greater COVID-19-induced morbidities and mortalities. Indeed, many proactive physicians were trying to [promote](#) this²¹⁶. None of this science is novel for infectious respiratory pathogens. The benefits of vitamin D supplementation are even better defined in the context of annual outbreaks of [influenza viruses](#)^{217,218}. It is imperative that public health officials stop blinding themselves to the overwhelming scientific evidence that demonstrates there are multiple, effective natural (e.g., vitamin D) and drug-based strategies for preventing and effectively treating COVID-19.

Conclusion: Vitamin D is a nutrient that is essential for a person's immune system to function properly. It plays a plethora of roles in the context of immune responses to viruses. It is well-established among immunologists that a key driver of the classic 'cold and flu' season in northern climates is the coinciding reduction in levels of vitamin D since the primary natural source is production in the skin upon exposure to strong sunlight. Both the intensity and duration of sunlight decrease dramatically from mid-Fall to mid-Spring in Canada. This has been taught for decades in immunology classes across Canada. This can easily be compensated for by supplementing one's diet with vitamin D. Importantly, even during the summer months, many people have relatively low concentrations of vitamin D, and this can be influenced by how much clothing is worn, whether sunblock is used, and the colour of skin (people with darker skin tend to produce lower amounts of vitamin D). As such, many Canadians could likely benefit from vitamin D supplementation year-round. Individuals can pay to have a simple blood test done to evaluate the concentration of vitamin D in their circulation. The fact that the Canadian government not only failed to promote this during the declared pandemic, but discouraged it is egregious. As an immunologist, I speculate that Canadian morbidities and mortalities would have been reduced throughout the declared pandemic had vitamin D supplementation been encouraged. Some may argue that a randomized control trial was not done to prove a benefit of vitamin D in the specific context of SARS-CoV-2 infections. However, such trials are extremely expensive, time-consuming, and unnecessary in a case such as this. Vitamin D is as essential to the immune system as spark plugs are to a race car. One does not need to place a race car that is missing a spark plug at the starting line of the Indy 500 to prove that it would have been beneficial to have the spark plug. Failing to encourage Canadians to take vitamin D supplements was one of the major errors made in the management of the COVID-19 pandemic.

Figure 9 : Two Lecture Slides Used in a Basic Immunology Course to Teach the Importance of Vitamin D in the Effector Functions of Macrophages

Tuberculosis:

M. tuberculosis survives in alveolar macrophages

Tizard, Veterinary Immunology, W.B. Saunders Company

- Immunity to *Mycobacterium tuberculosis* is governed in many species by the availability of vitamin D
- M. tuberculosis* is detected on macrophages by TLR 1/2
- TLR1/2 signaling up-regulates the expression of vitamin D receptors on macrophages
- Binding of vitamin D to this receptor up-regulates vitamin D hydroxylase, which in turn increases production of the antibacterial cathelicidins that kill *M. tuberculosis*.

Sanatoriums and the Treatment of Tuberculosis

Swiss Alps

Waverley Hills Sanatorium, Waverley Hills, KY

The Cottage Sanatorium, Lake Muskoka, Ontario
(Canada's first TB treatment facility)

Treatment: sunlight (i.e. heliotherapy [vitamin D]), fresh air and nutritious food (rich in vitamin D).

Tizard, Veterinary Immunology, W.B. Saunders Company; <http://www.afflu.com/article/17263/haunted-hospital>; <http://www.long.ca/16/164/history/sanatoriums/page.html>; http://www.archives.gov.on.ca/en/explorers/online/health_records/tuberculosis.aspx

19. An Oppressive Environment for Disseminating Balanced Scientific Information That Restricts Availability of Expert Witnesses

In preparing this report I pondered the question of how free I have been made to feel to disseminate frank, science-based assessments of COVID-19 policies imposed by the government of Ontario. This is a critical question since freedom of speech and engagement in respectful scientific debates are supposed to be hallmarks of democracies. Unfortunately, I have experienced some substantial intimidation over the past year while attempting, as a public servant, to address questions posed to me by the media, other scientists, physicians and other health care professionals, and members of the lay public. I will provide two examples here. In doing so, it is important to note that I do not feel comfortable naming the two individuals at the heart of these incidents for fear of potential reprisals that could have a negative impact on the remainder of my professional career. I understand this may be construed, therefore, as circumstantial evidence. However, I recognize that I am providing this information under oath and am stating that I am telling the truth, the whole truth, and nothing but the truth. Incident #1: a senior member of the administration of my university held a 30-minute on-line meeting in which I was berated for the duration in front of two of my colleagues. I was told that my media engagements were being monitored and it was recommended that I consider withdrawing from some of these activities and think about the impact of my statements in the context of the public health narrative that has dominated the COVID-19 pandemic. Incident #2: in a recent on-line department meeting at my university, I was told to be very careful about my public messaging by a senior colleague in front of all my faculty colleagues, including my Chair, the staff and graduate student representatives, and the Dean of my college who was a guest. Both these incidents, especially the first, made me feel like the tenets of academic freedom and freedom of speech had been deliberately crushed. Indeed, these tenets were critical factors in my career choice. This type of intimidation has caused excessive stress, including making me lose many hours of sleep. For a while afterwards, I was even second-guessing some of my messaging during media interviews, wondering if senior members of my administration would approve or disapprove. Indeed, my academic institution has become a poisoned work environment where the unvaccinated are vilified and coerced at every turn. The degree of censorship by the mainstream media is frightening. I was invited by a Member of Parliament to speak at an official press conference on Parliament Hill. No members of the mainstream media showed up and the resulting Cable Public Affairs Channel video was actually shut-down mid-way through a live-stream on YouTube. The video, which shattered all previous records for viewership was also censored. Although I have proof of robust and broad-based immunity to SARS-CoV-2, this was not conferred via two needles in my shoulder. As such, I have been banned from my university's campus, and I have been threatened with a reduction in my salary, effective this upcoming winter semester. These examples demonstrate that open scientific dialogues seem to be no longer welcome in Ontario.

After giving a short radio [interview](#) to a lay audience on May 27, 2021, a public smear campaign was initiated, including a slanderous website, a fake Twitter account, and harassment in the workplace. Nobody involved in the establishment of the smear campaign reached out to me to discuss the science underpinning my expert opinions.

Most of the harassment against me began after ‘fact checkers’ cherry-picked this one short radio interview that I gave to a lay audience. Some have accused me of only giving half the story in that interview. They were most kind; I was only able to reveal ~0.5% of the story. It is unfair to critique a tiny portion of one’s arguments that were presented off-the-cuff to a lay audience with no opportunity for me to respond in real-time. Notably, **I have rebutted every single one of the ‘fact checks’ that I am aware of** in various public interviews. Here is one example that some of my colleagues on my campus and many others beyond have repeatedly misused while harassing me in social media...

One of the many issues that I have raised with the vaccines is that should a reasonable concentration of the free spike protein get into systemic circulation, it could potentially harm the endothelial cells lining our blood vessels. I cited this study: <https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.121.318902>. The authors were contacted, and they claimed I had misinterpreted the study. They said that spike-specific antibodies would mop up any spike proteins in the blood, thereby protecting the blood vessels. They argued that this demonstrated that vaccinating people against the spike protein is a good thing. However, the authors are not immunologists and they failed to recognize the limitations of their own study in drawing these kinds of conclusions. Specifically, they did not recognize that in a naïve individual receiving a mRNA-based COVID-19 vaccine, there are no antibodies; either pre-existing in the host, or in the vaccine formulation. In fact, it will take many days for the antibody response to be induced and for titers to begin reaching substantial concentrations. This leaves a large window of time in which any free spike proteins could exert their biological functions/harm in the body before there are any antibodies to neutralize them. Worse, most of the spike proteins should be expressed by our own cells. In that case, the antibodies will target and kill them in a form of autoimmunity. The authors of the paper forgot that their model was in the context of natural infection, where vaccination would precede exposure to SARS-CoV-2. In that case, I agree that there would be pre-existing antibodies that could neutralize spike proteins of viral origin entering the circulation. This was perceived to be one of the ‘strongest’ arguments used by others to try to discredit me. The reality is that it is completely incorrect and represents an embarrassing misinterpretation by the authors of the original paper and the many ‘fact-checkers’ that believed them without question. My institution has allowed colleagues to harass me endlessly for many consecutive months. They have lied about me, called me many names, and have even accused me of being responsible for deaths.



Of note, was the front page of one of Canada’s major newspapers, shown in figure 10.

Figure 10

My workplace has become a poisoned environment where the bullying, harassment, and hatred against me have been incessant. Are you ever going to put an end to the childish and irrational behaviours being demonstrated by our colleagues? I have received thousands of emails from around the world that indicate the university should be embarrassed and ashamed to allow such childish behaviour from faculty members to go unchecked in front of the public. I have invested a decade of my life into the University of Guelph. I have conducted myself professionally and worked to an exceptionally high standard. I have consistently received excellent ratings for my research, teaching, and service. I have received rave reviews from students for my teaching. I have received prestigious research and teaching awards. I have brought funding to our campus from agencies that had never partnered with the University of Guelph in our institution's history. I have brought in ~\$1 million-worth of equipment to improve our infrastructure, *etc.* I am a man of integrity and a devoted public servant. I want to make Canada a better place for my family and for my fellow Canadians. The University of Guelph is a public institution. My salary is covered by taxpayers. This declared pandemic involves science that is in my 'wheelhouse'. Since the beginning, I have made myself available to answer questions coming from the public in a fashion that is unbiased and based solidly on the ever-exploding scientific literature. My approach has not changed. Has some of it contradicted the very narrow public health narrative carried by mainstream media? Yes. Does that make it wrong? No. I will stand by my track record. Scientists and physicians need to be able to speak freely about topics in their areas of expertise. Without this, the potential pool of expert witnesses to ensure that Canada's courts function properly will continue to be compromised. This has direct relevance for lawyers trying to get experts to opine on the topic of COVID-19 vaccine mandates. Too many experts are too afraid to share their opinions.

Unfortunately, I have seen many other scientists, physicians and other regulated professionals feel uncomfortable to freely express their views about COVID-19 due to fear of reprisal. This instillation of fear to speak openly has recently been amplified by the release of a notice from the [Ontario College of Physicians and Surgeons](#)²¹⁹. Among many fears that it has instilled, is a fear to provide balanced fact-based information to patients about COVID-19 vaccines. For example, many physicians and surgeons now feel uncomfortable relaying information about emerging safety concerns surrounding the vaccines for fear that it may be misconstrued by the Ontario College of Physicians and Surgeons as promoting anti-vaxxer sentiments. This is in direct contradiction of the commitment and requirement to obtain fully informed consent prior to the administration of an experimental vaccine. Personally, I am in a somewhat privileged position to speak openly about COVID-19 because I am a tenured faculty member at an academic institution. However, as already stated, I was not spared from intimidation. Indeed, my fears include the potential for reprisals from colleagues and/or administrators who have some control over the publication of scientific manuscripts and/or the awarding of research funding. My research program depends on my ability to secure grants and publish results. Notably, much of the scientific review process is performed with relative anonymity. The bullying of expert professionals in Canada is being noticed by the [public](#)²²⁰. With free-speakers among the expert scientific and medical community largely limited to professors with tenure and retired physicians, who feel very uncomfortable themselves, the pool experts that are available to challenge the current public health narrative is extremely limited. My concern is that this is causing intimidation of potential witnesses and could prejudice any legal proceedings related to COVID-19. I meet weekly with a group that has grown to approximately

50 scientists, physicians and other health professions across Canada to discuss issues related to COVID-19. This group recently formed, and its membership is growing quickly. I have heard many stories from members of this group about them feeling frightened to express opinions about COVID-19-related health policies. Indeed, me and only two other colleagues have agreed to serve as the ‘voices and faces’ of this group when it is organized enough to begin disseminating balanced scientific information to the public. Sadly, most of the membership feel it is essential that they shield themselves from the public eye to avoid reprisals. Although it was done at very short notice, to demonstrate that the extent of this problem extends beyond myself, I received the following comments from colleagues across Canada:

“With respect to intimidation or suppression, I have been lucky. The main incidence I can think of related to a University of British Columbia Senate Meeting. As a senator, during a meeting earlier this year when the University was contemplating having face-to-face class again in September 2021, I applauded the intent of the senior administration for taking this action, and described the very low risk that this posed to our students and staff. After the meeting, I was notified by the Dean of Graduate and Post-doctoral Studies, Dr. Susan Porter, by e-mail that I should not have said what I had, and that I might be violating scholastic integrity in the university by mentioning work that was unpublished and not peer-reviewed (the work was accepted and published in JCI Insights about 2 weeks later). She contacted the clerk that recorded the minutes of the Senate Meeting and asked by my remarks be struck from the public record. This was done, but I did not make a point of disputing this, since my comments had been heard already by the full Senate.” Dr. Stephen Pelech, Professor of Neurology, Department of Medicine, University of British Columbia

“I had posted something on my Facebook page only urging people to do their own research and questions things to make the decision that is best for them. It went to my dept. head then the chief of staff wrote a letter to our Dept. Basically telling us to keep in line. I’ve also been spoken to as was reported to our chief of staff (he said off the record) but he told me in no uncertain terms to not speak of anything against public health at work otherwise he would have to let the college look into it.”

An anonymous anesthesiologist (for fear of reprisals)

Please see figure 11 on the next three pages for a letter that intimidated another colleague...

Figure 11: A three-page letter sent to a physician colleague from their licensing body. The physician requested anonymity for fear of reprisals.



April 20, 2021

CPSA#

Hello Dr. ,

Thank you for speaking with me on April 14, 2021 to discuss concerns referred to us by a member of the public at , your practice, regarding a lack of adherence to COVID-19 guidance from the [Chief Medical Officer of Health](#) or from CPSA to [physicians](#) and [facilities](#). We appreciate your patience as we work with you, Alberta Health Services and other partners to navigate this very fluid situation.

The specific concern was as follows:

- Lack of adherence to the recommendations and guidelines provided by the CMOH to reduce risk of transmission of COVID -19
- Providing reading material to patients that did not follow the current advice provided to the public by the CMOH and current recommendations to reduce the risk of transmission of COVID -19
- Making statements to patients that implied that the current use of hospital facilities were not at capacity and the danger of overwhelming the health system were overstated

It is CPSA's expectation that physician's organize their practice to ensure they are following guidance provided by Alberta Health, CPSA, Alberta Health Services, and professional organizations. Physicians are advised to:

- follow all [public health orders](#) from the Chief Medical Officer of Health.
- follow CPSA guidance on [re-opening practice](#) and [IPAC guidelines](#) during Alberta's COVID-19 [relaunch strategy](#).
- consult with AHS COVID-19 [information for community physicians](#), including [FAQs](#) and current PPE distribution.

Figure 11 (continued):

- consult with other CPSA resources for [physicians](#) and [facilities](#) during COVID-19, including advice on virtual care.

Safety is a priority for everyone and we must all take action to decrease risk of exposure to COVID-19, to patients and staff alike. We ask that you modify your practice to ensure you meet current guidelines during this dynamic situation. In follow-up to your conversation with CPSA, we have noted the following in regards to the original concerns:

- you have indicated that your practice is following all the recommendations and guidelines provided by the CMOH, CPSA and AHS, including screening, appropriate distancing, use of masks when providing direct patient care, hand sanitizer availability, plexiglass to protect staff and patients, use of telephone visits to minimize in person visits where possible and appropriate cleaning processes
- you have purchased an air purifier to help ensure safety for your staff and patients
- you have provided patients with information regarding the effectiveness of masks in reducing the risk of transmission of COVID 19 as well as the potential risks of long term use of masks
- it was your intention to provide information to allow patients to make informed decisions about the effectiveness and safety of this public health measure
- it was not your intention to increase patient anxieties or fears by providing this information
- you did not intentionally encourage patients to act contrary to the current public health orders
- you have indicated that your personal experience with patients who have contracted COVID 19 is limited and may have influenced your perception of the significance of the pandemic
- your practice focuses on a holistic approach to patient medical concerns with an emphasis on lifestyle choices to enhance personal health and improve immune responses
- it is our expectation that physicians will not make comments or provide advice to encourage the public to act contrary to public health orders and recommendations
- we expect physicians to be guided by the laws, code of ethics and professional conduct, or regulatory standards when offering these opinions
- you have indicated that it was not your intention to not comply with this expectation
- as we discussed, in this time of uncertainty it is possible that patients may be suffering from an information overload and find information that jeopardizes their sense of safety to be very distressing
- you may wish to consider how such information is provided and if it is in the best interest of the patient to be presented with further uncertainty and inconsistencies
- you have indicated that you will provide me with the information you have provided to patients and I look forward to receiving this information

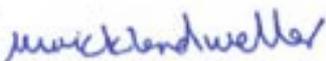
Figure 11 (continued):

- I have forwarded you several links that talk about the effectiveness and safety of masking that may be helpful to you going forward

We recognize this is an extremely difficult time for patients and physicians. It is uncertain how the next several months will unfold. If you need any support, please do not hesitate to contact us. We are here to answer questions and support you in navigating through these complex times.

Please be aware that failure to comply with direction from the Chief Medical Officer of Health will be referred to CPSA's Complaints Director for the consideration of a formal investigation of conduct.

Best regards,

X 

Dr. Monica Wickland-Weller, MD
Senior Medical Advisor
Signed by: Monica Wickland-Weller

MWW/ml

Please see the two-page letter in figure 12 from another colleague.

Figure 12: letter regarding intimidation during the COVID-19 pandemic.

May 17, 2021

To whom it may concern –

As Professor of Immunology in the province of Ontario for the last 30 years I can tell you with confidence that this last year in Canada has been nothing more than a political pandemic where intimidation, misinformation and shaming have been prominent.

My area of expertise lies at the interface of immunology and genetics. I have won numerous awards for my research in this area including the Governor General's Award for Innovation in 2017, and a prestigious NSERC prize that will be announced later this year. I will be the first Canadian ever to be given both of these awards.

I hold numerous patents, including one early in my career for a vaccine against pleuropneumonia in swine. I clearly see the value of vaccination and am a strong supporter of safe vaccination programs once all clinical trials are completed and independently reviewed. My research over the years has focused on various animal species which is highly relevant to this pandemic and others which generally arise from animal reservoirs.

Additionally, I have been teaching immunology at the graduate and undergraduate level for the past 30 years, and am fully aware of all angles of this discipline, including the human immune system. One of the topics that I cover each year is immunity to infectious disease which is highly pertinent to covid-19.

The published peer-reviewed data are clear that the vast majority of Canadians recover from covid-19 with immunity. Very rarely do individuals get covid-19 twice. It is a small group of elderly and those with co-morbidities that are at the highest risk, and unfortunately their situation has been poorly handled. There have been fewer than 10 deaths of anyone under 20 in the country since the beginning of the pandemic yet schools and universities have been essentially shut down. This has resulted in undue mental stress and abuse. When the enacted solutions are worse than the pandemic problem the country is headed in the wrong direction.

Covid-19 cases have been reported based on PCR tests run at high thresholds without any clinical data to support the diagnosis. While caseloads appeared to be increasing (largely due to increased testing) the death rates have decreased with each successive wave. In fact, peer reviewed literature has shown that 90% of those living in the Vancouver area have antibody to SARS-CoV-2 suggesting herd immunity is much higher than expected or is being communicated to the Canadian public. Unfortunately, since antibody has not been monitored across Canada these data are not available in other regions but are likely to be similar. Recommendations to back up the PCR with clinical observations, and to test antibody as an indicator of immunity were recommended to the government and the health authorities. These recommendations were ignored.

Several colleagues and I also recommended that the use of the AZ vaccine be suspended many months ago. This too was strangely ignored. We now feel the impact of that on Canadians. This recommendation should have been made known to the public.

It is now clear that outdoor transmission estimates were also erroneous with current estimate at between 0.1-1 percent and not 10% as first reported by the CDC. Asymptomatic transmission is also known to be rare.

1 | Page

These kind of mistakes and misinformation have caused Canadians to be locked in their homes and restricted in their movements for the last 15 months.

When physicians and credible scientists, including myself, have written to the Premiers and their CMOH, our words were ignored. Often times we received no response whatsoever, but we know they received the information since I was informed of that from my local MPs. When we tried to get the mainstream press, including CBC and CTV to let the Canadian public know that a team of doctors and professors had invited the Premier of Ontario, to an open forum discussion to help move Canada safely and effectively out of the pandemic that too was ignored. The same occurred in the provinces of Alberta and Saskatchewan.

I personally have a mask exemption and yet my picture appeared on the front of a local newspaper (Guelph Today), saying that "anti-maskers dare to show their face" at a council meeting. Since when are citizens to be shamed and humiliated for attending a local council meeting, to which they were invited? I even showed my mask exemption before being admitted into the meeting. To further add to the problem, the photo in Guelph Today, was picked up on the university Facebook page where I was again criticised for not wearing a mask. Yet, not one person asked me if I had a mask exemption. I rarely go out now because without a mask a person is frowned upon, pointed at and ridiculed, even though there is no definitive proof that masks significantly prevent the spread of the virus, particularly not the various kinds of facemasks worn by the public. This is intimidation and prejudice against the group unable to wear masks.

Following this incidence, I was then contacted by a certain corporation (which shall remain anonymous) telling me not to let my picture appear without a mask again in public since it might negatively impact their business to have a university professor without a mask. This was clear intimidation.

I have also been told by certain other faculty members to only speak the government/public health narrative, and that it would only cause chaos to let the public know about my concerns about the information provided to the public on covid-19. I think Canadians are smart enough to judge the information for themselves and have a right to hear all points of view that can be backed up by facts.

I think the Canadian public will be dismayed when it comes to light that there were safe and effective treatments, including ivermectin, which should have been used to treat and prevent covid-19. What happened to the old adage, "Do no harm".

These ongoing issues have created an extremely oppressive environment where open debate about critical issues relating to SARS-Cov-2 have been stifled.

Sincerely,



Dr. Bonnie Mallard
Professor of Immunogenetics

20. A Letter That Highlights the Absurdities of Mandating COVID-19 Vaccines

Dr. Bridle wrote an open letter to the President of his University. It contains a lot of pertinent information and is included in Appendix 4.

21. The Problems with Rapid Antigen Testing

Note that Ontario is now recommending widespread use of rapid antigen tests, especially for those who have not received two injections of a COVID-19 vaccine in their shoulder. These are tests that, like the RT-PCR test, detect the presence of SARS-CoV-2. Specifically, they detect a protein from the virus, unlike the RT-PCR test that detects pieces of the genetic material from the virus. One of the most commonly used test kits is manufactured by Abbott Panbio. As indicated by the government of Ontario, this test is only to be used in asymptomatic (*i.e.*, apparently healthy) individuals. Remarkably, however, as indicated in the printed material provided by the government of Ontario, the kits have only been tested on and approved for use in symptomatic individuals! They go on to state that there is no evidence that screening with the kit is effective in asymptomatic individuals! Finally, they state that a negative test result, which is all that can be expected from a test that is ineffective in asymptomatic people, does not necessarily mean that a person does not have COVID-19! But, by definition, an asymptomatic person cannot have COVID-19 because COVID-19 is a disease and a disease can only be declared as such if signs and/or symptoms of illness are present. Indeed, these conflicting statements can be found in Figures 13a and 13b.

COVID-19 Abbott Panbio™ Rapid Test Result

Negative Rapid Antigen Screening Result

If the result of your COVID-19 screening indicates that you have a negative result, no further action is required.

i IMPORTANT

- By receiving the screening service, you agree and acknowledge that the screening service is being provided to asymptomatic individuals only despite the following limitations. The screening kit used for the screening service is the Panbio™ COVID-19 Ag Rapid Test Device (the "Screening Kit"). You further agree and acknowledge that: (i) the Screening Kits have only been tested on and approved for symptomatic individuals; (ii) there is no evidence to suggest that the Screening Kits are effective on asymptomatic individuals; and (iii) the absence of a preliminary positive screening result does not signify the absence of COVID-19. Therefore, the Screening Kits contain certain limitations and may not be accurate, effective or appropriate in all circumstances. Shoppers Drug Mart Inc. and/or Loblaw Inc. does not warrant or represent the accuracy, effectiveness or appropriateness of the screening service or the Screening Kits.
- Rapid antigen screening is used for screening purposes only and is not used to diagnose COVID-19
- Antigen screening does NOT prevent someone from getting COVID-19, does NOT completely rule out an active COVID-19 infection and should NOT be used as a diagnostic tool
- Screening is an extra health and safety step, to be used along with existing measures like social distancing, hand washing, personal protective equipment and enhanced cleaning. Individuals should complete a health screening of COVID symptoms on a daily basis and staying home when symptoms are present.
- Rapid antigen screening does NOT replace any of above health and safety measures

You should stay at home from work or school if you develop signs and symptoms of COVID-19, contact your Primary Healthcare Provider, contact your local Public Health Unit, go to a COVID-19 Assessment Centre, or call Telehealth (1-866-797-0000).

For more information, visit: <https://covid-19.ontario.ca/>

Figure 13a

COVID-19 Abbott Panbio™ Rapid Test Result

Understanding Your Results:

If you develop symptoms for COVID-19, contact your Primary Healthcare Provider, contact your local Public Health Unit, go to a COVID-19 Assessment Centre, or call Telehealth (1-866-797-0000).

Call 911 if you are seriously ill and need urgent medical attention.

Preliminary Positive Rapid Antigen Screen Result

Important: A positive rapid COVID-19 antigen screening is considered a "preliminary positive", you must arrange for a follow-up polymerase chain reaction (PCR) test **within 24 hours** by contacting your local Public Health Unit and/or booking an appointment at a local COVID-19 Assessment Centre. This test is needed to confirm a diagnosis.

You can find a full list of Ontario's COVID-19 testing locations at <https://covid-19.ontario.ca/assessment-centre-locations>.

In the meantime, self-isolate at home (except for a medical emergency) and do not come into contact with others until the PCR test results are available and you are instructed to return to school or work.

- Please note that the Pharmacist is also required to report the preliminary positive antigen screening result to the local public health unit, in addition to the actions you must take as outlined above

While the results from COVID-19 antigen screening are available faster than COVID-19 PCR tests, they may be less sensitive. Someone who does not have an active COVID-19 infection could get a positive result. For this reason, a confirmatory PCR test is required within 24 hours.

Continue to take precautionary measures as outlined by current Public Health guidelines and practice physical distancing, frequent hand hygiene and use face coverings/masks. Do not come into contact with other individuals and self-isolate.

If the result of your confirmatory PCR test is positive, your local public health unit will contact you. You will be asked for information to help determine who you were in contact with while you may have been contagious or where you may have acquired COVID-19.

For information about how to self-isolate, physical distancing and self-monitoring, visit Public Health Ontario's COVID-19 public resources webpage: <https://www.publichealthontario.ca/en/diseases-andconditions/infectious-diseases/respiratory-diseases/novel-coronavirus/public-resources>

If you have green and white health card, please go to <https://covid-19.ontario.ca> under "check your results" so that you can:

- Enter the names of anyone you have been in contact with and places you have visited. Look for the CONTACT + tab on the results webpage and follow the instructions
- If you have downloaded the COVID Alert app, you can also anonymously notify other app users that they've been near someone who has tested positive for COVID-19.

Figure 13b

Interestingly, the booklet that accompanies the rapid antigen test kit that was approved by the government of Ontario contradicts Ontario’s messaging regarding RT-PCR testing for SARS-CoV-2. Whereas Ontario claims 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 states that people who test positive at cycle thresholds above 33 are not contagious (see Figure 14). This confirms what was opined upon earlier in this report with respect to PCR tests and the misnomer of asymptomatic spreaders of SARS-CoV-2.

and specificity are based also had a nasopharyngeal swab taken, which was tested in the FDA EUA approved RT-PCR.

Panbio™ COVID-19 Ag Rapid Test Device Results

		Nasal PCR Test Result		
		Positive	Negative	Total
Panbio™ COVID-19 Ag Rapid Test Device Result (nasal swab specimens)	Positive	102	1	103
	Negative	2	403	405
	Total	104	404	508
		Sensitivity	Specificity	Overall Percent Agreement
		98.1% [93.2%; 99.8%]	99.8% [98.6%; 100.0%]	99.4% [98.3%; 99.9%]

- Performance data was calculated from a study of individuals suspected of exposure to COVID-19 or who have presented with symptoms in the last 7 days.
 - Stratification of the positive specimens post onset of symptoms or suspected exposure between 0-3 days has a sensitivity of 100.0% (95% CI: 92.3-100.0%; n=46) and 4-7 days has a sensitivity of 96.6% (95% CI: 88.1-99.6%; n=58).
 - Positive agreement of the Panbio™ COVID-19 Ag Rapid Test Device is higher with samples of Ct values ≤30 with a sensitivity of 100.0% (95% CI: 96.0-100.0%) and Ct values ≤33 with a sensitivity of 99.0% (95% CI: 94.5-100.0%). As indicated in References 8-10, patients with Ct value >30 are no longer contagious.^{8,9,10}
 - The clinical performance data was also calculated vs nasopharyngeal swab specimens using an FDA EUA RT-PCR reference and has a sensitivity of 91.1% (95% CI: 84.2-95.6%) and specificity of 99.7% (95% CI: 98.6-100.0%).
2. **External evaluation of Panbio™ COVID-19 Ag Rapid Test Device (Asymptomatic)**
- Clinical performance of Panbio™ COVID-19 Ag Rapid Test Device was determined by testing 483 asymptomatic subjects for SARS-CoV-2 antigen (Ag). Clinical specimens were determined to be positive or negative using an FDA EUA RT-PCR reference method.
- The positive results (n=50) were stratified by the comparator method cycle threshold (Ct) counts and assessed to better understand the correlation of product performance, as a surrogate for the amount of virus present in the clinical sample. A lower Ct value corresponds to a higher virus concentration. As presented in the table below, the positive agreement increases with lower Ct values.

Figure 14

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 (See their “Table 1” below)²²¹. 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). Many Canadians, especially those who have not received a COVID-19 vaccine, are being forced to use these kits between two to five times per week to maintain their jobs, volunteer positions, etc. Each kit costs ~\$16 from the manufacturer. Pharmacies are charging ~\$40 (and up to ~\$99) per test. This can amount to substantial costs for people trying to work; and substantial profits for those in the testing business. To reiterate, these rapid antigen tests could only be positive if someone had such a high viral load that they would clearly be symptomatic.

Conclusion: The rapid antigen test will never provide a true positive result for asymptomatic people who are using them; and they are the only ones allowed to use them. As such rapid antigen testing of asymptomatic/healthy people appears to be a facade to suggest that due diligence is being practiced with respect to public health. In reality, people are wasting a lot of money and trips to pharmacies for something that can never reveal the information they are being promoted for (*i.e.*, early detection of infection). It would also mean that companies are making massive profits for something that has zero public health value. People who have not received a COVID-19 vaccine should not be forced to conduct rapid antigen testing as a requirement to work.

Table 1: Performance comparison between the Abbott ID NOW™ and Abbott Panbio™ Rapid tests for SARS-CoV-2^a

Patient identification ^b	qPCR test location	E-gene Ct	Adjusted Ct for input ^c	Approximate number of input copies ^{d,e}	ID NOW result	Panbio result
Patient 1	CPL	16	22.6	1,294,497	Positive	Positive
Patient 2	CPL	19	25.6	271,908	Positive	Positive
Patient 3	CPL	19	25.6	383,421	Positive	Positive
Patient 4	CPL	20	26.6	586,124	Positive	Positive
Patient 5	NML	20.4	27	ND	Positive	Positive
Patient 6	NML	22.2	28.8	ND	Positive	Positive
Patient 7	NML	22.3	28.9	ND	Positive	Positive
Patient 8	NML	24.6	31.2	ND	Positive	Negative
Patient 9	CPL	25	31.6	16,116	Positive	Negative
Patient 10	NML	25.2	31.8	ND	Positive	Negative
Patient 11	CPL	26	32.6	1,547	Positive	Negative
Patient 12	CPL	26	32.6	2,428	Positive	Negative
Patient 13	NML	27.9	34.5	3,681	Positive	Negative
Patient 14	CPL	30	36.6	164	Positive	Negative
Patient 15	NML	30	36.6	ND	Positive	Negative
Patient 16	NML	31.6	38.2	272	Positive	Negative
Patient 17	CPL	Negative	0	0	Negative	Negative
Patient 18	CPL	Negative	0	0	Negative	Negative
Patient 19	CPL	Negative	0	0	Negative	Negative
Pooled	NML	Negative	0	0	Negative	Negative

Abbreviations: CPL, Cadham Provincial Laboratory; NML, National Microbiology Laboratory; qPCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

^a Patient samples in transport media were spiked into the ID Now or Panbio rapid tests, along with a healthy donor nasopharyngeal swab

^b 19 clinical samples were used as the study panel (16 positive and 4 negative)

^c Adjusted Ct is the theoretical Ct adjusted for differences in input volume

^d ND = viral load not determined on GeneXpert

^e Viral concentration was determined for some patient samples used in this panel with the GeneXpert and an in-house standard curve

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

As a researcher with funding to develop COVID-19 vaccines, I have been monitoring developments with respect to early treatment options very closely. These include the use of hydroxychloroquine, vitamin D3, and ivermectin. Although each of these appear to be valid, safe, and effective treatment options, due to time constraints, I have focused over the past year on careful examinations of the growing body of literature but using ivermectin as an effective early treatment for COVID-19. I was originally somewhat concerned that my vaccine research could be impacted in the absence of their emergency use authorization. Indeed, I have been very surprised that emergency use authorization of experimental vaccines has remained in place despite an avalanche of data that strongly supports the safe and effective use of ivermectin to treat COVID-19 when the drug is administered early in the disease presentation and is supervised by a physician. To demonstrate how much evidence there is in support of ivermectin for the treatment of COVID-19, I have attached an exhaustive list and summary of relevant references in Appendix 3.

Executive Summary

- Whereas vaccines are effective at preventing disease in an otherwise healthy individual, alternative treatments are urgently required for patients already infected with SARS-CoV-2 virus. To date, this has consisted of keeping patients alive while they build up their own immunity to fight the disease.
- In a proof-of-concept in vitro study, it was shown that the drug ivermectin inhibits the replication of SARS-CoV-2.
- Subsequent clinical studies in over 22 countries had demonstrated using TaqMan RT-PCR that the replication of the virus was indeed reduced, collating with improvements in the patient's medical condition.
- Shorter hospitalization and lower mortality rates were observed in patients treated with ivermectin when compared to the placebo group.
- Ivermectin was shown in clinical studies to be effective when administered prophylactically to human subjects.
- Ivermectin has been used for treating patients for around 40 years, with a proven safety record.

Introduction

Whereas vaccines are effective at preventing disease in an otherwise healthy individual²²², nothing is better at fighting disease than utilizing a person's own immune system. However, once someone is already infected with the disease, a vaccine would be of no use. Therefore, alternative treatments are urgently required for patients already infected with SARS-CoV-2. To date, this has consisted of keeping patients alive while they build up their own immunity to the disease. Health Canada has not authorized any drugs to prevent, treat or cure COVID-19 in patients, except for Veklury (remdesivir) from Gilead Sciences Canada Inc., to treat COVID-19 in patients with pneumonia requiring supplemental oxygen²²³. However, there is still a gap that needs to be filled to effectively treat patients infected with SARS-CoV-2. It is recommended that ivermectin should be considered as a suitable candidate to fill the treatment gap for early out-patient treatment for COVID-19, and as a prophylactic, during the vaccine rollout period.

Ivermectin – Proof-of-Concept

Using TaqMan RT-PCR, Caly et. al. (2020) demonstrated that ivermectin effectively inhibited replication of SARS-CoV-2 in-vitro by blocking the ability of IMP α / β 1 to bind to the coronavirus cargo protein in the cytoplasm, therefore, preventing it from going through the nuclear pore complex (NPC) and entering the nucleus (figure 8).

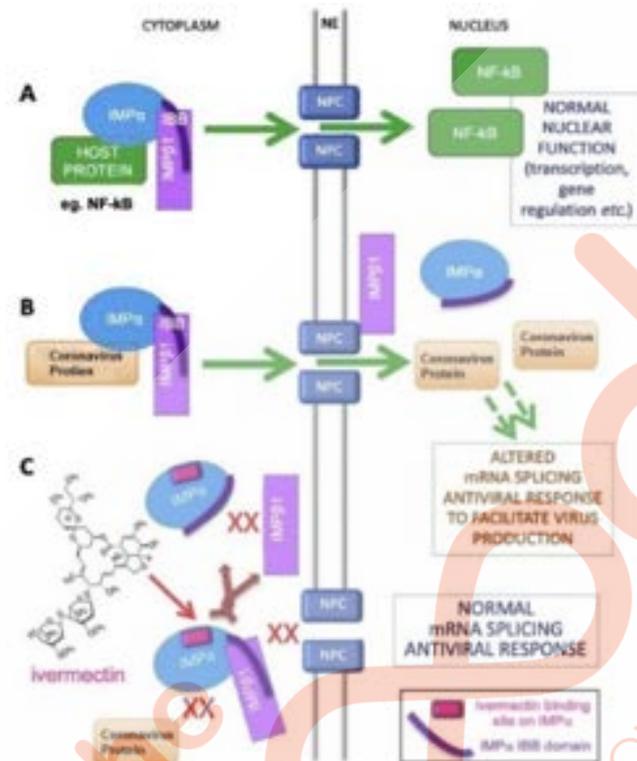


Figure 8. Schematic of ivermectin's proposed antiviral action on Covid-19

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

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

The authors noted a 93–99.8% decrease in viral RNA for ivermectin versus control at 24 hours both in the released and cell-associated viral RNA, respectively. Likewise, they reported that by 48 hours there was a >5000-fold decrease of viral RNA, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 hours. Consistent with this, no further reduction in viral RNA was observed at 72 hours. Under the conditions tested, the IC₅₀ of ivermectin treatment was determined to be approximately 2 μ M. Ivermectin has an established safety profile for human use and is approved both by the US FDA and Health Canada. It's been used for a number of treatments since the 1980s, including treatments for intestinal infections, lice, scabies, and river blindness. Now that this drug has been found to inhibit replication of SARS-CoV-2 in vitro, it was not surprising that clinical studies were subsequently initiated throughout the world.

Ivermectin – Clinical Trial Data

Currently, there are approximately 70 clinical trials worldwide evaluating the clinical benefit of ivermectin to treat or prevent Covid-19. However, these trials include variations on dosing regimens, combination

therapies, and prophylactic protocols²²⁴. To illustrate these differences, the results of two clinical trials using different dosing regimens will be described, focusing specifically on the dosing regimen, prior to summarising the results from a meta-analysis of clinical trials of ivermectin to treat infection with SARS-CoV-2.

Clinical trial in Bangladesh²²⁵

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

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

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

Group 3: Placebo control group.

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

Clinical trial in Egypt²²⁶

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The main difference between both studies i.e. ²²⁵and ²²⁶ was the dosage of ivermectin administered to patients infected with SARS-CoV-2, 0.2mg/kg/day versus 0.4mg/kg/day with food, respectively. When comparing both studies, the difference as to whether treatment was effective or not was dependent upon the dosage given. Although in the Ahmed et. al. study, the rate of viral clearance was in favour of ivermectin, it was not to the same extent as that observed in the Elgazzar et. al. study (Figure 8).

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

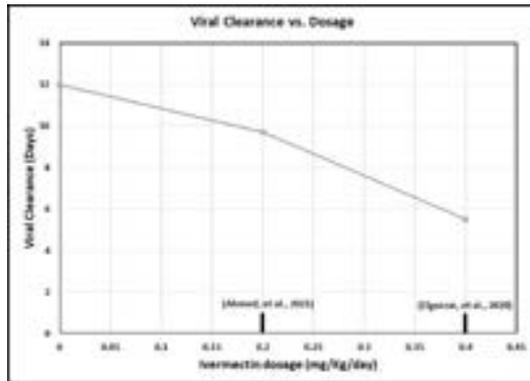


Figure 8 also shows that the rate of viral clearance is proportional to dose, further validating the in vitro model, that ivermectin inhibits viral replication.

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

Ivermectin, a widely available generic drug, is currently re-purposed for the treatment of patients with the COVID-19 virus, being evaluated in clinical trials throughout the world. So, the first question one must ask is: Do we have enough clinical evidence to support the worldwide approval of ivermectin to treat COVID-19? Although data from a single clinical trial may be considered unsuitable by Health Canada, the combined data from all the available clinical trials to date should be large enough to reliably assess the clinical efficacy of ivermectin, and that is where the meta-analysis of the available clinical trials comes in. The second question is: What are going to be our endpoints?

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

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

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

Meta-analysis was performed by Front Line Covid-19 Critical Care Alliance (FLCCC) using data from multiple clinical trials to determine the effectiveness of ivermectin to treat patients infected with SARS-CoV-2.²²⁷

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

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

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

- 2) Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue via several observed and proposed mechanisms (Caly et al., 2020a).
- 3) Ivermectin has potent anti-inflammatory properties with in vitro data demonstrating profound inhibition of both cytokine production and transcription of nuclear factor- κ B (NF- κ B), the most potent mediator of inflammation (Zhang et al., 2008; Ci et al., 2009; Zhang et al., 2009).
- 4) Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses (Arevalo et al., 2020; de Melo et al., 2020).
- 5) Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients (Behera et al., 2020; Bernigaud et al., 2020; Carvallo et al., 2020b; Elgazzar et al., 2020; Hellwig and Maia, 2020; Shouman, 2020).
- 6) Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms (Carvallo et al., 2020a; Elgazzar et al., 2020; Gorial et al., 2020; Khan et al., 2020; Mahmud, 2020; Morgenstern et al., 2020; Robin et al., 2020).
- 7) Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients (Elgazzar et al., 2020; Hashim et al., 2020; Khan et al., 2020; Niaee et al., 2020; Portmann-Baracco et al., 2020; Rajter et al., 2020; Spoorthi V, 2020).
- 8) Ivermectin reduces mortality in critically ill patients with COVID-19 (Elgazzar et al., 2020; Hashim et al., 2020; Rajter et al., 2020).
- 9) Ivermectin leads to striking reductions in case-fatality rates in regions with widespread use (Chamie, 2020).⁵
- 10) The safety, availability, and cost of ivermectin is nearly unparalleled given its near nil drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered (Kircik et al., 2016).
- 11) The World Health Organization has long included ivermectin on its “List of Essential Medicines.” (<https://trialsitenews.com/an-old-drug-tackles-new-tricks-ivermectin-treatment-in-three-brazilian-towns/>; <https://www.who.int/publications/i/item/WHOMVPEMPIAU201907>)

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

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

As stated above, the only drug that Health Canada has authorized with conditions is remdesivir for the treatment of patients with COVID-19. On November 20, 2020 the WHO issued a statement recommending against the use of remdesivir in patients with COVID-19 due to the observed lack of efficacy²²⁸. Despite this, Canada is continuing to use remdesivir as a treatment for those with severe late-stage COVID-19.

Conclusion: Having reviewed the scientific literature, the conclusion can be drawn that the data is such that Canada should include ivermectin for early out-patient treatment for COVID-19, and as a prophylactic, while people are being vaccinated. As far as integrity goes, multiple clinical trials from different countries saying the same thing, that the treatment works, both in the early and late stages of the disease. Principal Investigators on these studies were acting in good faith with no financial interests by the institutions carrying them out. The data from these trials are available for consideration²²⁷, and there are clinical trials worldwide still ongoing. Ivermectin has been used to treat patients for around 40 years, has a proven safety record, off-patent, cheap, and available. Safety is not an issue since ivermectin has been approved for human use both in the USA and Canada. Ivermectin has never been withdrawn off the market for safety reasons. The dosages proposed for the treatment of COVID-19 for prophylaxes and out-patients is more than covered based upon the data from the Phase 1 ascending dose study in the NDA submission²²⁹, subsequently published in a peer reviewed publication²³⁰. The availability of effective early treatment strategies for COVID-19 negates the need for COVID-19 vaccine mandates.

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TODAY + TOMORROW + ALWAYS

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Appendix 1

Pfizer's Report to the Japanese Government



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SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048)

2.6.4 薬物動態試験の概要文

本項で使用する用語・略語

用語・略号	省略していない表現または定義
ALC-0159	本剤に添加される PEG 脂質
ALC-0315	本剤に添加されるアミノ脂質
[³ H]-CHE	Radiolabeled [Cholesteryl-1,2- ³ H(N)]-Cholesteryl Hexadecyl Ether : 放射性標識 [コレステリル-1,2- ³ H(N)] ヘキサデシルエーテル
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine : 1,2-ジステアロイル-sn-グリセロ-3-ホスホコリン
GLP	Good Laboratory Practice : 医薬品の安全性に関する非臨床試験の実施の基準
LNP	Lipid-nanoparticle : 脂質ナノ粒子
modRNA	Nucleoside-modified mRNA : 修飾ヌクレオシド mRNA
mRNA	Messenger RNA : メッセンジャーRNA
m/z	m/z (m・オーバー・z) : イオンの質量を統一原子質量単位 (=ダルトン) で割って得られた無次元量をさらにイオンの電荷数の絶対値で割って得られる無次元量
PEG	Polyethylene glycol : ポリエチレングリコール
PK	Pharmacokinetics : 薬物動態
RNA	Ribonucleic acid : リボ核酸
S9	Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g : 肝ホモジネートを 9000 g で遠心分離した上清画分
WHO	World Health Organization : 世界保健機関

1. まとめ

BNT162b2 (BioNTech コード番号 : BNT162, Pfizer コード番号 : PF-07302048) は、重症急性呼吸器症候群コロナウイルス 2 (SARS-CoV-2) のスパイク糖タンパク質 (S タンパク質) 全長体をコードする修飾ヌクレオシド mRNA (modRNA) であり、SARS-CoV-2 による感染症に対する mRNA ワクチンの本質として開発が進められている。BNT162b2 の製剤化にあたっては、2つの機能脂質である ALC-0315 (アミノ脂質) および ALC-0159 (PEG 脂質) ならびに 2つの構造脂質として DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) およびコレステロールと混合することで BNT162b2 を封入する脂質ナノ粒子 (LNP) が形成される (以降、「BNT162b2 封入 LNP」)。

BNT162b2 封入 LNP の非臨床薬物動態を評価するために、LNP に含まれる ALC-0315 および ALC-0159 の吸収 (PK)、代謝および排泄を評価する *in vivo* および *in vitro* 試験ならびに BNT162b2 の代替レポーターとしてルシフェラーゼまたは放射能標識した脂質を利用した生体内分布試験を実施した。

感染症予防を目的としたワクチンの開発では全身曝露量の評価を必要としないことを踏まえ (WHO, 2005 ; 感染症予防ワクチンの非臨床試験ガイドライン)^{1,2}, BNT162b2 封入 LNP の筋肉内投与による PK 試験は実施しなかった。また、本剤に含有される他の 2種類の脂質 (コレステロールおよび DSPC) は天然に存在する脂質であり、内在性脂質と同様に代謝、排泄されると考えられる。加えて、BNT162b2 は取り込んだ細胞中のリボヌクレアーゼにより分解されて核酸代謝され、BNT162b2 由来の S タンパク質はタンパク分解を受けると予想される。以上のことから、あらためてこれらの成分の代謝および排泄を評価する必要はないと考えられた。

BNT162b2 の代替レポーターとしてルシフェラーゼをコードする RNA を封入した LNP (ルシフェラーゼ RNA を BNT162b2 封入 LNP と同一の脂質構成を持つ LNP に封入 : 以降、「ルシフェラーゼ RNA 封入 LNP」) を Wistar Han ラットに静脈内投与した PK 試験では、血漿、尿、糞および肝臓試料を経時的に採取して、各試料中の ALC-0315 および ALC-0159 濃度を測定した。その結果、ALC-0315 および ALC-0159 は血中から肝臓にすみやかに分布することが示された。また、ALC-0315 および ALC-0159 はそれぞれ投与量の約 1% および約 50% が未変化体として糞中に排泄され、尿中においてはいずれも検出限界未満であった。

生体内分布試験では、ルシフェラーゼ RNA 封入 LNP を BALB/c マウスに筋肉内投与した。その結果、ルシフェラーゼの発現が投与部位でみられ、それより発現量は低値であったものの肝臓でも認められた。ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ、投与後 9 日には消失した。肝臓での発現も投与後 6 時間に認められ、投与後 48 時間までに消失した。また、ルシフェラーゼ RNA 封入 LNP の放射能標識体をラットに筋肉内投与して生体内分布を定量的に評価したところ、放射能濃度は投与部位で最も高値であった。投与部位以外では肝臓が最も高かった (投与量の最大 18%)。

ALC-0315 および ALC-0159 の代謝を CD-1/ICR マウス、Wistar Han または Sprague Dawley ラット、カニクイザルもしくはヒトの血液、肝ミクロソーム、肝 S9 画分および肝細胞を用いて *in vitro* で評価した。また、上記のラット静脈内投与 PK 試験で採取した血漿、尿、糞および肝臓試料を用いて *in vivo* 代謝についても検討した。これら *in vitro* および *in vivo* 試験から、ALC-0315 および ALC-0159 は、試験したいずれの動物種でも、それぞれエステル結合およびアミド結合の加水分解により徐々に代謝されることが示された。

2.6.4 薬物動態試験の概要文

以上の非臨床薬物動態評価より、循環血中に到達した LNP は肝臓に分布することが示された。また、ALC-0315 および ALC-0159 の消失には、それぞれ代謝および糞中排泄が関与することが示唆された。

2. 分析法

報告書番号：PF-07302048_06[REDACTED]_072424

GLP 非適用のラット静脈内投与 PK 試験 (M2.6.4.3 項) で LNP の構成脂質である ALC-0315 よび ALC-0159 濃度を定量するために適切な性能を有する LC/MS 法を開発した。すなわち、20 µL の血漿、肝ホモジネート (肝臓の 3 箇所から採取した切片を用いてホモジネートを調製し、それらをプールしたものを適宜、ブランクマトリクスで希釈)、尿および糞ホモジネート (適宜、ブランクマトリクスで希釈) 試料をそれぞれ内部標準物質 (PEG-2000) を含有するアセトニトリルで除タンパクした後、遠心分離し、その上清を LC-MS/MS 測定に供した。

3. 吸収

報告書番号：PF-07302048_06[REDACTED]_072424, 概要表：2.6.5.3

ALC-0315 および ALC-0159 の体内動態を検討するため、ルシフェラーゼ RNA 封入 LNP を雄性 Wistar Han ラットに 1 mg RNA/kg の用量で単回静脈内投与し、経時的 (投与前、投与後 0.1, 0.25, 0.5, 1, 3, 6 および 24 時間ならびに投与後 2, 4, 8 および 14 日) に血漿および肝臓をスパースサンプリングにより採取 (3 匹/時点) した。血漿中および肝臓中の ALC-0315 および ALC-0159 濃度を測定し、PK パラメータを算出した (Table 1)。血中の ALC-0315 および ALC-0159 は、投与後 24 時間までにすみやかに肝臓へ分布した。また、投与後 24 時間の血漿中濃度は最高血漿中濃度の 1%未満であった (Figure 1)。見かけの終末相消失半減期 ($t_{1/2}$) は血漿中および肝臓中で同程度で、ALC-0315 は 6~8 日、ALC-0159 は 2~3 日であった。本試験の結果から、肝臓が血中からの ALC-0315 および ALC-0159 を取り込む主要組織の 1 つであることが示唆された。

本試験において実施した ALC-0315 および ALC-0159 の尿中および糞中濃度の検討結果については M2.6.4.6 項で述べる。

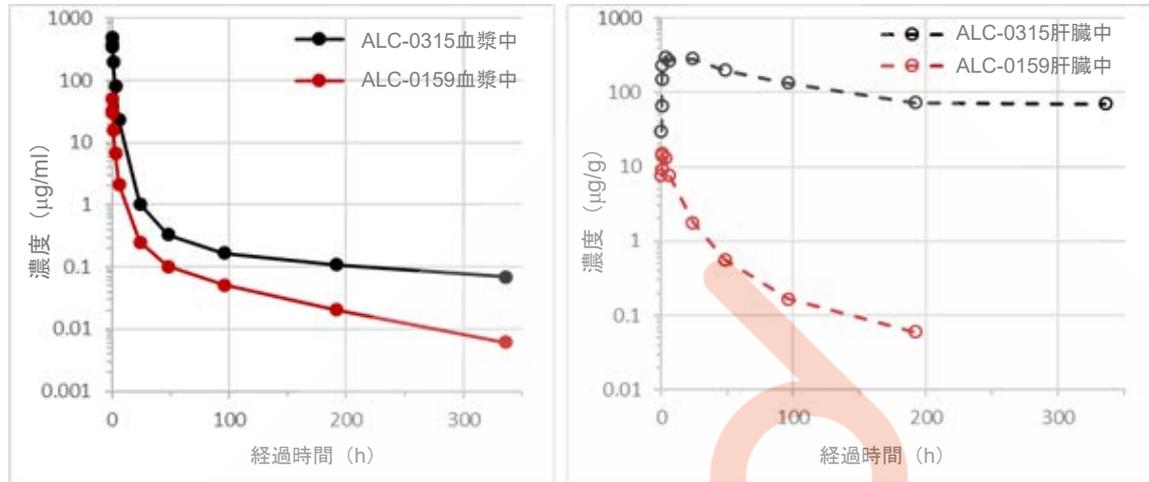
Table 1 ルシフェラーゼ RNA 封入 LNP を Wistar Han ラットに 1 mg RNA/kg の用量で静脈内投与したときの ALC-0315 および ALC-0159 の薬物動態

分析物	分析物の投与量 (mg/kg)	性/N	$t_{1/2}$ (h)	AUC _{inf} (µg·h/mL)	AUC _{last} (µg·h/mL)	肝臓への分布割合 (%) ^a
ALC-0315	15.3	雄/3 ^b	139	1030	1020	60
ALC-0159	1.96	雄/3 ^b	72.7	99.2	98.6	20

a. [最高肝臓分布量 (µg)] / [投与量 (µg)] として算出。

b. 各時点 3 匹。スパースサンプリング。

Figure 1 ルシフェラーゼ RNA 封入 LNP を Wistar Han ラットに 1 mg RNA/kg の用量で静脈内投与したときの ALC-0315 および ALC-0159 の血漿および肝臓中濃度

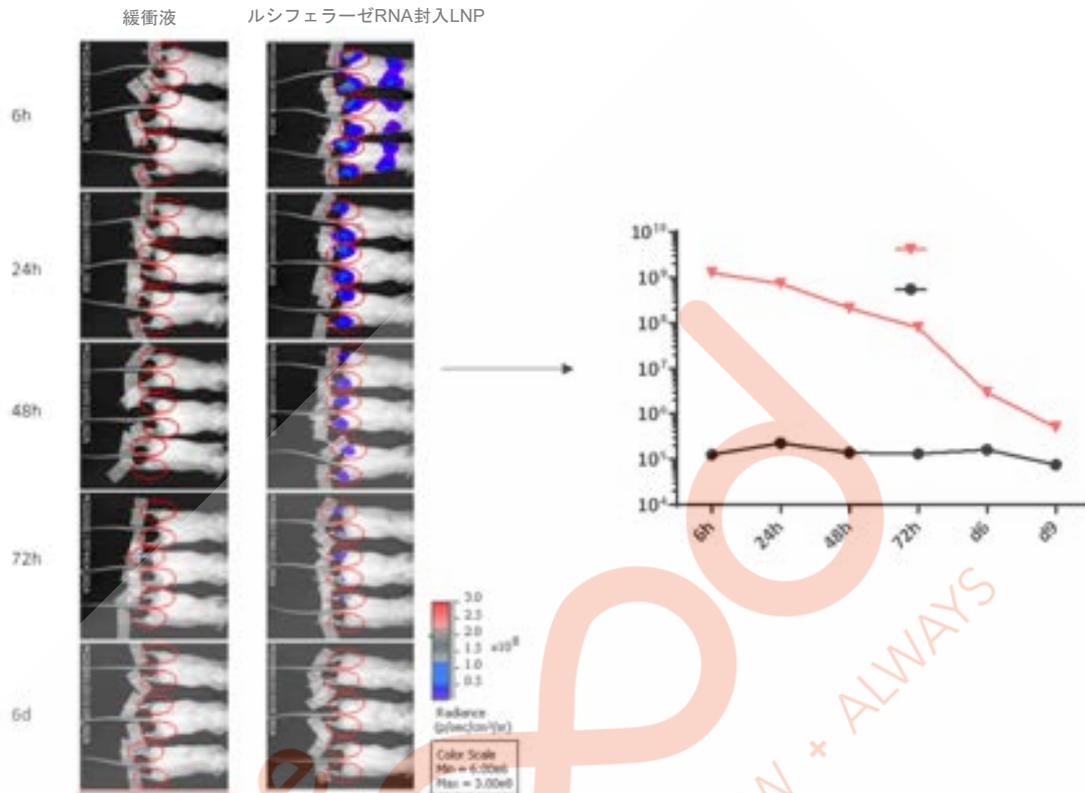


4. 分布

報告書番号：R-0072, 185350, 概要表：2.6.5.5A, 2.6.5.5B

雌性 BALB/c マウス (3 匹) にルシフェラーゼ RNA 封入 LNP を投与し、ルシフェラーゼ発光を代替マーカーとして BNT162b2 の生体内分布を検討した。すなわち、ルシフェラーゼ RNA 封入 LNP をマウスの左右の後肢に各 1 µg RNA (計 2 µg RNA) の用量で筋肉内投与した。その後、ルシフェラーゼ発光検出の 5 分前に発光基質であるルシフェリンを腹腔内投与し、イソフルラン麻酔下、in vivo における発光を Xenogen IVIS Spectrum を用いて投与後 6 および 24 時間ならびに 2, 3, 6 および 9 日に測定することにより、ルシフェラーゼタンパクの同一個体での経時的な発現推移を評価した。その結果、ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ、投与後 9 日には消失した。肝臓での発現も投与後 6 時間からみられ、投与後 48 時間までに消失した。肝臓への分布は局所投与したルシフェラーゼ RNA 封入 LNP の一部が循環血中に到達し、肝臓で取り込まれたことを示すものと考えられた。M2.6.4.3 項で詳述したように、ラットにルシフェラーゼ RNA 封入 LNP を静脈内投与した場合には、肝臓が ALC-0315 および ALC-0159 の主要な分布臓器であることが示唆されており、このことはマウスに筋肉内投与した本試験結果の所見と符合するものであった。なお、ラット反復投与毒性試験で肝障害を示す毒性所見は認められていない (M2.6.6.3 項)。

Figure 2 ルシフェラーゼ RNA 封入 LNP を筋肉内投与した BALB/c マウスにおける生体内発光



雌雄 Wistar Han ラットに、³H]-コレステリルヘキサデシルエーテル (³H]-CHE) で標識した LNP を用いたルシフェラーゼ RNA 封入 LNP を 50 µg RNA の用量で筋肉内投与し、投与後 15 分ならびに 1, 2, 4, 8, 24 および 48 時間の各時点において雌雄各 3 匹から血液、血漿および組織を採取し、液体シンチレーション計数法により放射能濃度を測定することで LNP の生体内分布を評価した。雌雄ともに、放射能濃度はいずれの測定時点においても投与部位が最も高値であった。血漿中の放射能濃度は投与後 1~4 時間で最も高値を示した。また、主に肝臓、脾臓、副腎および卵巣への分布がみられ、これらの組織において放射能濃度が最も高くなったのは投与後 8~48 時間であった。投与部位以外での投与量に対する総放射能回収率は肝臓で最も高く（最大 18%）、脾臓（1.0%以下）、副腎（0.11%以下）および卵巣（0.095%以下）では肝臓と比較して著しく低かった。また、放射能の平均濃度および組織分布パターンは雌雄でおおむね類似していた。

BNT162b2 がコードする抗原の生体内発現分布は LNP 分布に依存すると考えられる。本試験で用いたルシフェラーゼ RNA 封入 LNP の脂質の構成は、BNT162b2 の申請製剤と同一であることから、本試験結果は BNT162b2 封入 LNP の分布を示すと考えられる。

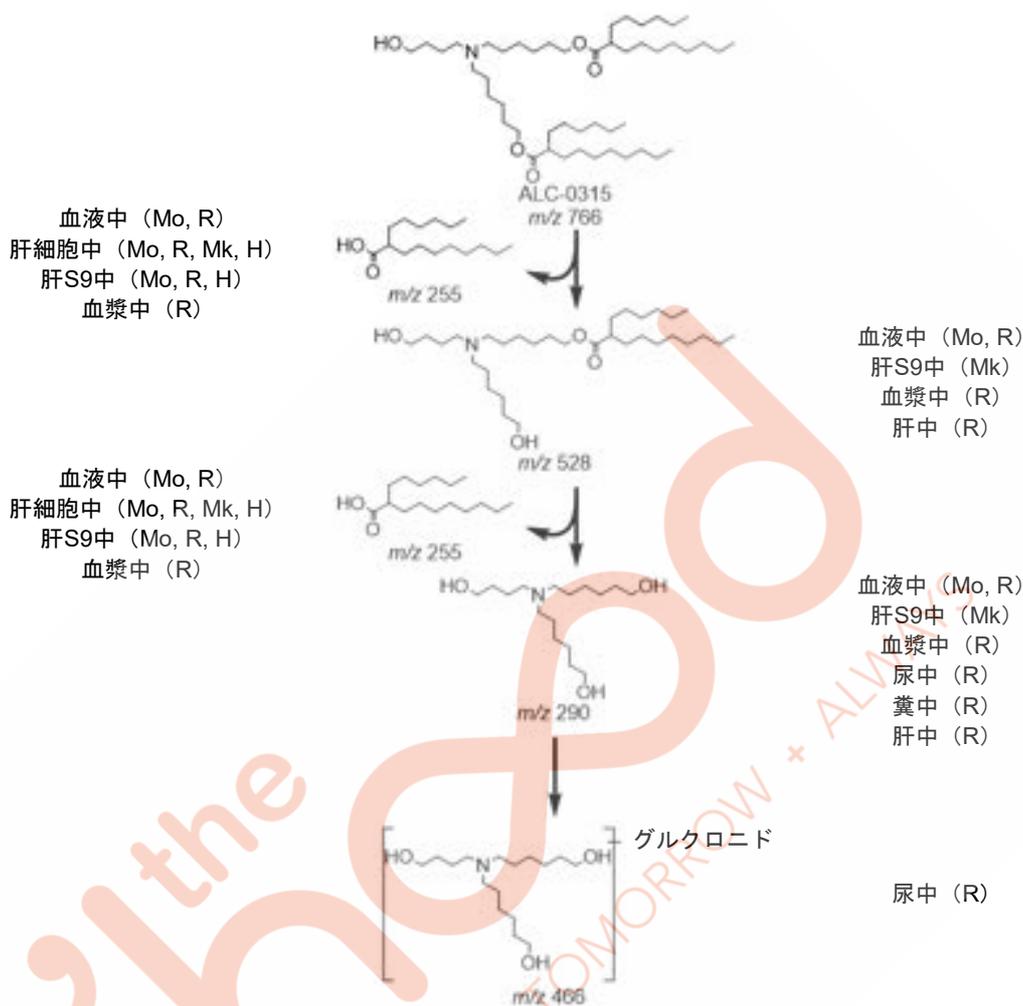
5. 代謝

報告書番号：01049-008, 01049-009, 01049-010, 01049-020, 01049-021, 01049-022, PF-07302048_05-043725, 概要表：2.6.5.10A, 2.6.5.10B, 2.6.5.10C, 2.6.5.10D

CD-1/ICR マウス, Wistar Han または Sprague Dawley ラット, カニクイザルならびにヒトの肝ミクロソーム, 肝 S9 画分および肝細胞を用いて, ALC-0315 および ALC-0159 の *in vitro* 代謝安定性を評価した。ALC-0315 または ALC-0159 を各動物種の肝ミクロソームまたは肝 S9 画分 (120 分間インキュベーション) もしくは肝細胞 (240 分間インキュベーション) に添加して, インキュベーション後の未変化体の割合を測定した。その結果, ALC-0315 および ALC-0159 はいずれの動物種・試験系でも代謝的に安定であり, 未変化体の最終的な割合は 82%超であった。

さらに ALC-0315 および ALC-0159 の代謝経路について *in vitro* および *in vivo* で評価した。これらの試験では, CD-1 マウス, Wistar Han ラット, カニクイザルおよびヒトの血液, 肝 S9 画分および肝細胞を用いて *in vitro* での代謝を評価した。また, ラット PK 試験で採取した血漿, 尿, 糞および肝臓試料を用い, *in vivo* での代謝を評価した (M2.6.4.3 項)。試験結果から, ALC-0315 と ALC-0159 の代謝はいずれも緩徐であり, それぞれエステル結合およびアミド結合の加水分解により代謝されることが明らかになった。Figure 3 および Figure 4 に示した加水分解による代謝は, 評価したすべての動物種でみられた。

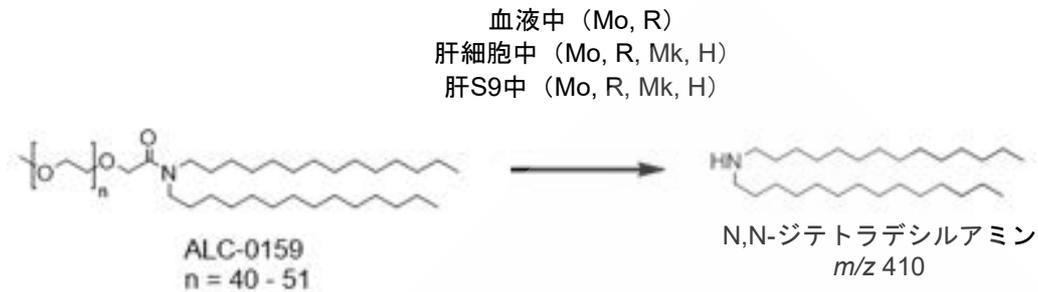
Figure 3 種々の動物種での ALC-0315 の推定生体内代謝経路



H: ヒト, Mk: サル, Mo: マウス, R: ラット

ALC-0315 はエステル加水分解を2回連続で受けることにより代謝される。この2回の加水分解により、最初、モノエステル代謝物 (m/z 528)、次に二重脱エステル化代謝物 (m/z 290) が生成される。この二重脱エステル化代謝物はさらに代謝され、グルクロン酸抱合体 (m/z 466) となるが、このグルクロン酸抱合体はラット PK 試験で尿中のみ検出された。また、2回の加水分解の酸性生成物がいずれも 6-ヘキシルデカン酸 (m/z 255) であることも確認された。

Figure 4 種々の動物種での ALC-0159 の推定生体内代謝経路



H: ヒト, Mk: サル, Mo: マウス, R: ラット

ALC-0159 は、アミド結合の加水分解により *N,N*-ジテトラデシルアミン (*m/z* 410) が生成される経路が主要な代謝経路であった。この代謝物は、マウス・ラットの血液ならびにマウス・ラット・サル・ヒトの肝細胞および肝 S9 画分中に検出された。In vivo 試料からは ALC-0159 の代謝物は確認されなかった。

6. 排泄

リシフェラーゼ RNA 封入 LNP を 1 mg RNA/kg の用量でラットに静脈内投与した PK 試験 (M2.6.4.3 項) で経時的に採取した尿および糞中の ALC-0315 および ALC-0159 濃度を測定した。ALC-0315 および ALC-0159 の未変化体はいずれも尿中に検出されなかった。一方、糞中には ALC-0315 および ALC-0159 の未変化体が検出され、投与量当たりの割合はそれぞれ約 1% および約 50% であった。また、Figure 3 に示したように、ALC-0315 の代謝物が尿中で検出された。

7. 薬物動態学的薬物相互作用

本ワクチンの薬物動態学的薬物相互作用試験は実施していない。

8. その他の薬物動態試験

本ワクチンのその他の薬物動態試験は実施していない。

9. 考察および結論

ラット PK 試験において、血漿および肝臓中 ALC-0315 濃度は、投与後 2 週間までに最高濃度のそれぞれ約 7000 分の 1 および約 4 分の 1 に減少し、ALC-0159 濃度はそれぞれ約 8000 分の 1 および約 250 分の 1 に減少した。t_{1/2} は血漿中および肝臓中で同程度で、ALC-0315 は 6~8 日、ALC-0159 は 2~3 日であった。血漿中 t_{1/2} 値は、それぞれの脂質が LNP として組織中に分布し、その後、消失過程で血漿中に再分布したことを表すと考えられる。

ALC-0315 の未変化体は尿中と糞中のいずれにもほとんど検出されなかったが、ラット PK 試験で採取した糞および血漿試料からモノエステル代謝物、二重脱エステル化代謝物および 6-ヘキシルデカン酸が、尿からは二重脱エステル化代謝物のグルクロン酸抱合体が検出された。この代謝過程が ALC-0315 の主要消失機序と考えられるが、この仮説を検証する定量データは得られていない。一方、ALC-0159 は投与量の約 50% が未変化体として糞中に排泄された。In vitro 代謝実験において、アミド結合の加水分解により緩徐に代謝された。

BNT162b2 がコードする抗原の生体内発現分布は LNP 分布に依存すると考えられることから、BALB/c マウスにルシフェラーゼ RNA 封入 LNP を筋肉内投与し、代替レポータータンパク質の生体内分布を検討した。その結果、ルシフェラーゼの発現が投与部位においてみられ、それより発現量は低値であったものの肝臓でも認められた。ルシフェラーゼの投与部位での発現は投与後 6 時間から認められ、投与後 9 日には消失した。肝臓での発現は投与後 6 時間から認められ、投与後 48 時間までに消失した。肝臓への分布は局所投与したルシフェラーゼ RNA 封入 LNP が循環血中に到達し、肝臓で取り込まれたことを示すものと考えられた。また、ラットにルシフェラーゼ RNA 封入 LNP の放射能標識体を筋肉内投与したところ、放射能濃度は投与部位で最も高値を示した。投与部位以外では、肝臓で最も高く、次いで脾臓、副腎および卵巣でも検出されたが、これらの組織における投与量に対する総放射能回収率は肝臓より著しく低かった。この結果は、マウス生体内分布試験において肝臓でルシフェラーゼ発現がみられたことと符合した。なお、ラット反復投与毒性試験で肝障害を示す毒性所見は認められなかった (M2.6.6.3 項)。

以上の非臨床薬物動態評価より、循環血中に到達した LNP は肝臓に分布することが示された。また、ALC-0315 および ALC-0159 の消失には、それぞれ代謝および糞中排泄が関与することが示唆された。

10. 図表

図表は本文中および概要表に示した。

参考文献

- ¹ World Health Organization. Annex 1. Guidelines on the nonclinical evaluation of vaccines. In: WHO Technical Report Series No. 927, Geneva, Switzerland. World Health Organization; 2005:31-63.
- ² 感染症予防ワクチンの非臨床試験ガイドラインについて(薬食審査発 0527 第 1 号, 平成 22 年 5 月 27 日)

2.6.5.1 PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test Item	Method of Administration	Testing Facility	Report Number
Single Dose Pharmacokinetics					
Single Dose Pharmacokinetics and Excretion in Urine and Feces of ALC-0159 and ALC-0315	Rat (Wistar Han)	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	IV bolus	Pfizer Inc ^a	PF-07302048_06-072424
Distribution					
In Vivo Distribution	Mice BALB/c	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	IM Injection	██████████ ^b	R-██████-0072
In Vivo Distribution	Rat (Wistar Han)	modRNA encoding luciferase formulated in LNP comparable to BNT162b2 with trace amounts of [³ H]-CHE as non-diffusible label	IM Injection	██████████ ^c	185350
Metabolism					
In Vitro and In Vivo Metabolism					
In Vitro Metabolic Stability of ALC-0315 in Liver Microsomes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver microsomes	ALC-0315	In vitro	██████████ ^d	01049-██████008
In Vitro Metabolic Stability of ALC-0315 in Liver S9	human liver microsomes Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 liver fractions	ALC-0315	In vitro	██████████ ^d	01049-██████009

SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048)

2.6.5 薬物動態試験の概要表

2.6.5.1 PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test Item	Method of Administration	Testing Facility	Report Number
In Vitro Metabolic Stability of ALC-0315 in Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	ALC-0315	In vitro		01049-010
In Vitro Metabolic Stability of ALC-0159 in Liver Mitochondria	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human liver mitochondria	ALC-0159	In vitro		01049-020
In Vitro Metabolic Stability of ALC-0159 in Liver S9	Mouse (CD-1/ICR), rat (Sprague Dawley), monkey (Cynomolgus), and human S9 fractions	ALC-0159	In vitro		01049-021
In Vitro Metabolic Stability of ALC-0159 in Hepatocytes	Mouse (CD-1/ICR), rat (Sprague Dawley and Wistar Han), monkey (Cynomolgus), and human hepatocytes	ALC-0159	In vitro		01049-022
Biotransformation of ALC-0159 and ALC-0315 In Vitro and In Vivo in Rats	CD-1 mouse, Wistar Han rat, cynomolgus monkey, and human blood, liver S9 fractions and hepatocytes	ALC-0315 and ALC-0159	In vitro or IV (in vivo in rats)	Pfizer Inc ^e	PF-07302048_05-043725

2.6.5 薬物動態試験の概要表

2.6.5.1 PHARMACOKINETICS OVERVIEW

Test Article: BNT162b2

Type of Study	Test System	Test Item	Method of Administration	Testing Facility	Report Number
<p>ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4-hydroxybutyl)azanediy]bis(hexane-6,1-diyl]bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; IM = Intramuscular; IV = Intravenous; LNP = lipid nanoparticles; S9 = Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g.</p> <p>a. La Jolla, California. b. , Germany. c. , UK. d. , China. e. Groton, Connecticut.</p>					

2.6.5 薬物動態試験の概要表

2.6.5.3. PHARMACOKINETICS AFTER A SINGLE DOSE

Test Article: modRNA encoding luciferase in LNP
Report Number: PF-07302048_06 [REDACTED]_072424

Species (Strain)	Rat (Wistar Han)
Sex/Number of Animals	Male/ 3 animals per timepoint ^a
Feeding Condition	Fasted
Method of Administration	IV
Dose modRNA (mg/kg)	1
Dose ALC-0159 (mg/kg)	1.96
Dose ALC-0315 (mg/kg)	15.3
Sample Matrix	Plasma, liver, urine and feces
Sampling Time Points (h post dose):	Pre-dose, 0.1, 0.25, 0.5, 1, 3, 6, 24, 48, 96, 192, 336
Analyte	ALC-0315 ALC-0159
PK Parameters:	Mean ^b
AUC _{inf} (µg•h/mL) ^c	1030
AUC _{last} (µg•h/mL)	1020
Initial t _½ (h) ^d	1.62
Terminal elimination t _½ (h) ^e	139
Estimated fraction of dose distributed to liver (%) ^f	59.5
Dose in Urine (%)	NC ^g
Dose in Feces (%) ^h	1.05
	Mean ^b
	99.2
	98.6
	1.74
	72.7
	20.3
	NC ^g
	47.2

ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4-hydroxybutyl)azanediy]bis(hexane-6,1-diyl)bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; AUC_{inf} = Area under the plasma drug concentration-time curve from 0 to infinite time; AUC_{last} = Area under the plasma drug concentration-time curve from 0 to the last quantifiable time point; BLQ = Below the limit of quantitation; LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA; PK = Pharmacokinetics; t_½ = Half-life.

- Non-serial sampling, 36 animals total.
- Only mean PK parameters are reported due to non-serial sampling.
- Calculated using the terminal log-linear phase (determined using 48, 96, 192, and 336 h for regression calculation).
- ln(2)/initial elimination rate constant (determined using 1, 3, and 6 h for regression calculation).
- ln(2)/terminal elimination rate constant (determined using 48, 96, 192, and 336 h for regression calculation).
- Calculated as follows: highest mean amount in the liver (µg)/total mean dose (µg) of ALC-0315 or ALC-0159.
- Not calculated due to BLQ data.
- Fecal excretion, calculated as: (mean µg of analyte in feces/ mean µg of analyte administered) × 100

SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048)

2.6.5 薬物動態試験の概要表

2.6.5.A. PHARMACOKINETICS: ORGAN DISTRIBUTION

Test Article: modRNA encoding luciferase in LNP
Report Number: R-0072

Species (Strain):	Mice (BALB/c)
Sex/Number of Animals:	Female/3 per group
Feeding Condition:	Fed ad libitum
Vehicle/Formulation:	Phosphate-buffered saline Intramuscular injection
Method of Administration:	Intramuscular injection
Dose (mg/kg):	1 µg/hind leg in gastrocnemius muscle (2 µg total)
Number of Doses:	1
Detection:	Bioluminescence measurement
Sampling Time (hour):	6, 24, 48, 72 hours; 6 and 9 days post-injection

Time point	Total Mean Bioluminescence signal (photons/second)		Mean Bioluminescence signal in the liver (photons/second)
	Buffer control	modRNALuciferase in LNP	
6 hours	1.28×10 ⁵	1.26×10 ⁹	4.94×10 ⁷
24 hours	2.28×10 ⁵	7.31×10 ⁸	2.4×10 ⁶
48 hours	1.40×10 ⁵	2.10×10 ⁸	Below detection ^a
72 hours	1.33×10 ⁵	7.87×10 ⁷	Below detection ^a
6 days	1.62×10 ⁵	2.92×10 ⁶	Below detection ^a
9 days	7.66×10 ⁴	5.09×10 ⁵	Below detection ^a

LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA.
 a. At or below the background level of the buffer control.

2.6.5 薬物動態試験の概要表

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [³H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Species (Strain):	Rat (Wistar Han)	
Sex/Number of Animals:	Male and female/3 animals/sex/timepoint (21 animals/sex total for the 50 µg dose)	
Feeding Condition:	Fed ad libitum	
Method of Administration:	Intramuscular injection	
Dose:	50 µg [³ H]-08-A01-C0 (lot # NC-0552-1)	
Number of Doses:	1	
Detection:	Radioactivity quantitation using liquid scintillation counting	
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, and 48 hours post-injection	

Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL)) (males and females combined)								% of administered dose (males and females combined)							
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h		
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	--	--	--	--	--	--	--		
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2	0.001	0.007	0.010	0.015	0.035	0.066	0.106		
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002		
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	--	--	--	--	--	--	--		
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77	--	--	--	--	--	--	--		
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009		
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003		
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030		
Injection site	128	394	311	338	213	195	165	19.9	52.6	31.6	28.4	21.9	29.1	24.6		
Kidneys	0.391	1.16	2.05	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057		
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34	0.008	0.025	0.065	0.192	0.405	0.692	0.762		
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3	0.602	2.87	7.33	11.9	18.1	15.4	16.2		
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09	0.052	0.101	0.178	0.169	0.122	0.101	0.101		

2.6.5 薬物動態試験の概要表

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [³H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Sample	Total Lipid concentration (µg lipid equivalent/g [or mL]) (males and females combined)						% of Administered Dose (males and females combined)							
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	--	--	--	--	--	--	--
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37	--	--	--	--	--	--	--
Muscle (females)	0.021	0.061	0.084	0.103	0.096	0.095	0.192	--	--	--	--	--	--	--
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	--	--	--	--	--	--	--
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4	0.013	0.093	0.325	0.385	0.982	0.821	1.03
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420	--	--	--	--	--	--	--
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805	--	--	--	--	--	--	--
Blood:Plasma ratio ^a	0.815	0.515	0.550	0.510	0.555	0.530	0.540	--	--	--	--	--	--	--

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [³H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

-- = Not applicable, partial tissue taken; [³H]-08-A01-C0 = An aqueous dispersion of LNPs, including ALC-0315, ALC-0159, distearoylphosphatidylcholine, cholesterol, mRNA encoding luciferase and trace amounts of radiolabeled [Cholesteryl-1-2-3H(N)]-Cholesteryl Hexadecyl Ether, a nonexchangeable, non-metabolizable lipid marker used to monitor the disposition of the LNPs; ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N'-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the LNP formulation used in BNT162b2; ALC-0315 = (4--hydroxybutyl)azanediy]bis(hexane-6,1-diy])bis(2-hexyldecanoate), a proprietary aminolipid included as an excipient in the LNP formulation used in BNT162b2; LNP = Lipid nanoparticle; mRNA = messenger RNA.

a. The mean male and female blood:plasma values were first calculated separately and this value represents the mean of the two values.

2.6.5.9. PHARMACOKINETICS: METABOLISM IN VIVO, RAT

Test Article: **modRNA encoding luciferase in LNP**
 Report Number: **PF-07302048_05** XXXXXXXXXX **_043725**

Species (Strain):

Rat (Wistar Han)

Sex/ Number of animals

Male/ 36 animals total for plasma and liver, 3 animals for urine and feces

Method of Administration:

Intravenous

Dose (mg/kg):

1

Test System:

Plasma, Urine, Feces, Liver

Analysis Method:

Ultrahigh performance liquid chromatography/ mass spectrometry

Biotransformation	m/z	Metabolites of ALC-0315 Detected			
		Plasma	Urine	Feces	Liver
N-dealkylation, oxidation	102.0561 ^a	ND	ND	ND	ND
N-Dealkylation, oxidation	104.0706 ^b	ND	ND	ND	ND
N-dealkylation, oxidation	130.0874 ^a	ND	ND	ND	ND
N-Dealkylation, oxidation	132.1019 ^b	ND	ND	ND	ND
N-dealkylation, hydrolysis, oxidation	145.0506 ^a	ND	ND	ND	ND
Hydrolysis (acid)	255.2330 ^a	+	ND	ND	ND
Hydrolysis, hydroxylation	271.2279 ^a	ND	ND	ND	ND
Bis-hydrolysis (amine)	290.2690 ^b	+	+	+	+
Hydrolysis, glucuronidation	431.2650 ^a	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	464.2865 ^a	ND	ND	ND	ND
Bis-hydrolysis (amine), glucuronidation	466.3011 ^b	ND	+	ND	ND
Hydrolysis (amine)	528.4986 ^b	+	ND	ND	+
Hydrolysis (amine), Glucuronidation	704.5307 ^b	ND	ND	ND	ND
Oxidation to acid	778.6930 ^a	ND	ND	ND	ND
Oxidation to acid	780.7076 ^b	ND	ND	ND	ND
Hydroxylation	782.7232 ^b	ND	ND	ND	ND
Sulfation	844.6706 ^a	ND	ND	ND	ND
Sulfation	846.6851 ^b	ND	ND	ND	ND
Glucuronidation	940.7458 ^a	ND	ND	ND	ND
Glucuronidation	942.7604 ^b	ND	ND	ND	ND

Note: Both theoretical and observed metabolites are included.

m/z = mass to charge ratio; ND = Not detected; + = minor metabolite as assessed by ultraviolet detection.

a. Negative ion mode.

b. Positive ion mode.

2.6.5.10B. PHARMACOKINETICS: METABOLISM IN VITRO CONTINUED

Test Article: ALC-0159
 Report Numbers: 01049-020
 01049-021
 01049-022

Type of Study:	Liver Microsomes + NADPH	Stability of ALC-0159 In Vitro	Hepatocytes
Study System:		S9 Fraction + NADPH, UDPGA, and alamethicin	
ALC-0159 Concentration:	1 μM	1 μM	1 μM
Duration of Incubation (min):	120 min	120 min	240 min
Analysis Method:	Ultra-high performance liquid chromatography-tandem mass spectrometry		

Incubation time (min)	Liver Microsomes					Percent ALC-0159 remaining					Hepatocytes				
	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Monkey (Cyno)	Human	Mouse (CD-1/ICR)	Rat (SD)	Rat (WH)	Monkey (Cyno)	Human	
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	
15	82.27	101.24	112.11	100.83	99.59	98.93	84.38	91.30	106.73	--	--	--	--	--	
30	86.40	93.78	102.69	85.12	92.28	91.10	90.87	97.96	107.60	100.85	93.37	113.04	90.23	106.34	
60	85.54	98.34	105.38	86.36	95.53	102.85	97.97	105.56	104.97	94.92	91.81	105.07	92.93	101.58	
90	85.41	95.44	100.90	94.63	97.97	90.75	93.51	108.33	109.36	94.28	90.25	112.80	94.59	92.67	
120	95.87	97.10	108.97	93.39	93.09	106.76	92.70	105.74	119.59	87.08	89.47	104.11	97.51	96.04	
180	--	--	--	--	--	--	--	--	--	94.92	93.96	102.90	89.81	93.66	
240	--	--	--	--	--	--	--	--	--	102.75	94.93	98.79	92.93	102.57	

-- = Data not available; ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), a proprietary polyethylene glycol-lipid included as an excipient in the lipid nanoparticle formulation used in BNT162b2; Cyno = Cynomolgus; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; NC = not calculated; SD = Sprague Dawley; WH = Wistar-Han; UDPGA = uridine-diphosphate-glucuronic acid trisodium salt.

**2.6.5.10C. PHARMACOKINETICS: METABOLISM
IN VITRO CONTINUED**

Test Article: ALC-0315
Report Number: PF-07302048_05_043725

Type of study	Study system	ALC-0315 concentration	Duration of incubation	Metabolism of ALC-0315 In Vitro		Ultrahigh performance liquid chromatography/ mass spectrometry													
				Blood	Hepatocytes	Blood		Hepatocytes			Liver S9 Fraction								
Analysis Method:				10 µM 24 h	10 µM 4 h	Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human	Mouse	Rat	Monkey	Human		
Biotransformation	N-dealkylation, oxidation					ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
	N-Dealkylation, oxidation	102.0561 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
	N-Dealkylation, oxidation	104.0706 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
	N-dealkylation, oxidation	130.0874 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
	N-Dealkylation, oxidation	132.1019 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
	N-dealkylation, hydrolysis, oxidation	145.0506 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Hydrolysis (acid)	255.2330 ^a	+	+	ND	ND	+	+	+	+	+	+	+	+	+	+	+	+	+
	Hydrolysis, hydroxylation	271.2279 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Bis-hydrolysis (amine)	290.2690 ^b	+	+	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Hydrolysis, glucuronidation	431.2650 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Bis-hydrolysis (amine), glucuronidation	464.2865 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Bis-hydrolysis (amine), glucuronidation	466.3011 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Hydrolysis (amine)	528.4986 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Hydrolysis (amine), glucuronidation	704.5307 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Oxidation to acid	778.6930 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Oxidation to acid	780.7076 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Hydroxylation	782.7232 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sulfation	844.6706 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
Sulfation	846.6851 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
Glucuronidation	940.7458 ^a	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
Glucuronidation	942.7604 ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	

Note: Both theoretical and observed metabolites are included.
m/z = mass to charge ratio; ND = Not detected; + = metabolite present.
a. Negative ion mode.
b. Positive ion mode.

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Appendix 2

Pfizer's Report to the European Medicines Agency





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2021
EMA/707383/2020 Corr.1*¹
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Comirnaty

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005735/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

¹ * Correction dated 19 February 2021 to clarify ERA statement



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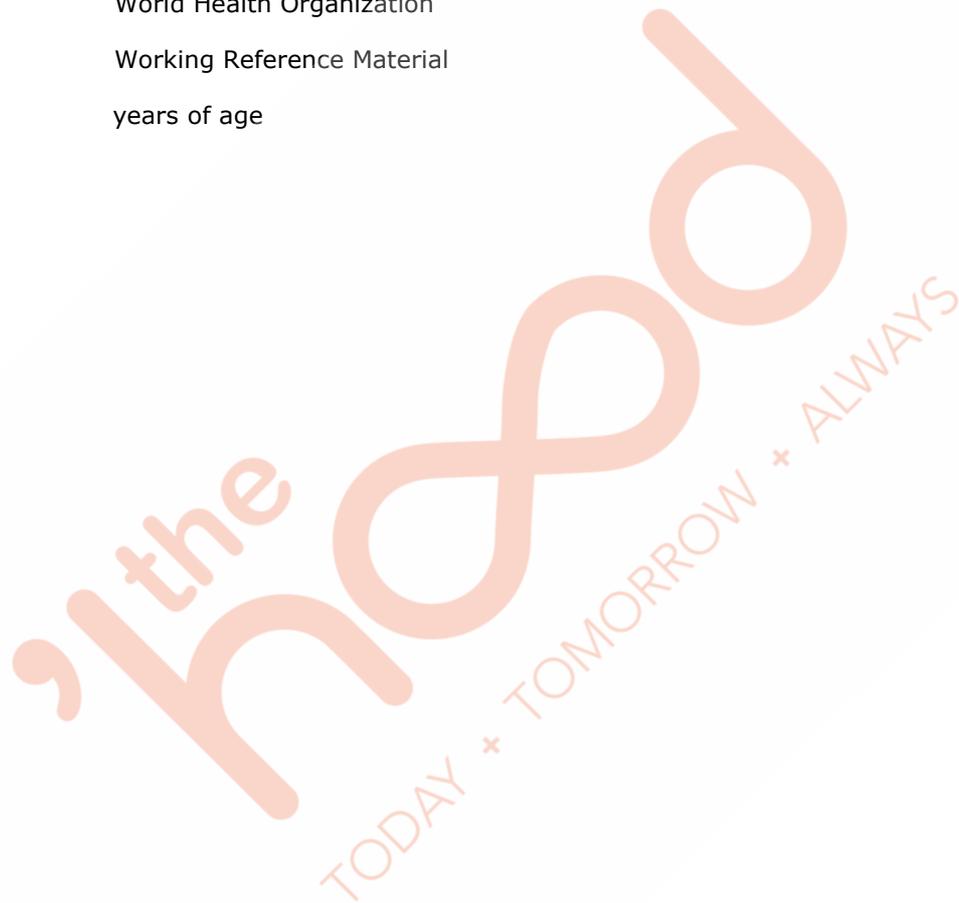
List of abbreviations

AE	adverse event
AESI	adverse event of special interest
BDR	blinded data review
BLQ	below the level of quantitation
BMI	body mass index
CD	Circular dichroism
CDC	Centers for Disease Control and Prevention (United States)
CGE	Capillary gel electrophoresis
COVID-19	coronavirus disease 2019
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRF	case report form
CRM	Clinical Reference Material
CRO	contract research organization
CSR	clinical study report
CV	curriculum vitae
C&E	Cause and Effect Matrices
DCT	data collection tool
DLS	Dynamic Light Scattering
DMC	data monitoring committee
DOE	Design of experiments
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
e-diary	electronic diary
EU	European Union
FIH	first-in-human
FSFV	first subject first visit
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCS	human convalescent serum
HCV	hepatitis C virus
HCV	Ab hepatitis C virus antibody
HIV	human immunodeficiency virus
HPLC-CAD	High-Performance Liquid Chromatography - Charged Aerosol Detector
IA	interim analysis
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	Investigational New Drug
IPT-C	In-process testing control
IPT-M	In-process testing monitoring
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
IVT	in vitro transcription
IWR	interactive web response
LAL	Limulus Amebocyte Lysate
LC-UV/MS	Liquid Chromatography – Ultraviolet / Mass Spectrometry
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mRNA	Messenger ribonucleic acid
modRNA	nucleoside-modified messenger ribonucleic acid

NAAT	nucleic acid amplification test
N-binding	SARS-CoV-2 nucleoprotein binding
NMT	Not more than
NOR	Normal Operating Range
NT50	neutralizing titer 50
NT90	neutralizing titer 90
NVA	nonvaccine antigen
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PAR	Proven Acceptable Range
(q)PCR	(quantitative) Polymerase Chain Reaction
PD	protocol deviation
Ph.Eur.	European Pharmacopoeia
PPQ	Process Performance Qualification
PRM	Primary Reference Material
Prevax	prevaccination
PT	preferred term
QA	quality assurance
QA	Quality Attribute
QTL	quality tolerance limit
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RDC	remote data capture
RNA	ribonucleic acid
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
RT-PCR	Real Time Polymerase Chain Reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRVA	shoulder injury related to vaccine administration
SMQ	standardized MedDRA queries
SOC	system organ class
Tdap	diphtheria vaccine toxoid; pertussis vaccine acellular 3 component; tetanus vaccine toxoid

TME	targeted medical event
TSE	Transmissible Spongiform Encephalopathy
UFDF	Ultrafiltration/diafiltration
US	United States
Vax	vaccination
VE	vaccine efficacy
WBC	white blood cell count
WCB	Working Cell Bank
WHO	World Health Organization
WRM	Working Reference Material
YOA	years of age



1. Background information on the procedure

1.1. Submission of the dossier

The applicant BioNTech Manufacturing GmbH submitted on 30 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Comirnaty, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 July 2020.

The applicant applied for the following indication:

"Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older. The use of Comirnaty vaccine should be in accordance with official guidance."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0480/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0480/2020 was not yet completed as some measures were deferred.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, as it is intended for the prophylaxis of a life-threatening disease. In addition, the above-mentioned medicinal product is intended for use in an emergency situation, in response to public health threats duly recognised by the World Health Organisation and by the Union.

New active Substance status

The applicant requested the active substance Single-stranded, 5'-capped messenger RNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike

(S) protein of SARS-CoV-2 contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2. Steps taken for the assessment of the product²

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

The CHMP confirmed eligibility to the centralised procedure on	23 July 2020
Confirmation by ETF on the eligibility to the rolling review procedure on	24 July 2020
Agreement by ETF to start the rolling review procedure on	25 September 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	05 October 2020
The procedure (Rolling Review 1) started on	06 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	22 October 2020
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	28 October 2020
ETF discussions took place on	29 October 2020
Adoption of first Interim Opinion on the RR via 24 hour written procedure on	06 November 2020
The applicant submitted documentation as part of a rolling review on quality data to support the marketing authorisation application	06 November 2020

² These steps do not reflect the additional submissions made by the applicant during the active assessment phases.

The procedure (Rolling Review 2) started on	07 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, Peer Reviewer and ETF on	19 November 2020
BWP extraordinary adobe meeting was held on	24 November 2020
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF on	25 November 2020
ETF discussions took place on	26 November 2020
Adoption of the 2nd interim opinion for this rolling review on	30 November 2020
The application for the marketing authorisation was formally received by the EMA on	30 November 2020
The procedure started on	1 December 2020
BWP extraordinary adobe meeting was held on	15 December 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, peer reviewer and ETF on	16 December 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	16 December 2020
BWP extraordinary adobe meeting with an Oral Explanation by the applicant was held on	16 December 2020
ETF discussions took place on	17 December 2020
The Rapporteurs circulated the Joint Assessment Report to all CHMP members on	17 December 2020
BWP extraordinary adobe meeting was held on	18 December 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary meeting on	18 December 2020
CHMP extraordinary adobe meeting was held on	18 December 2020
The following GMP and GLP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
<ul style="list-style-type: none"> – GMP inspections (distant assessments) of the sites Wyeth BioPharma, Andover (manufacturer DS, QC DS, QC DP) and Pfizer Inc., Chesterfield (QC DP, QC DP), both located in the USA, were carried out between 20 November 2020 and 02 December 2020. The outcome of the inspections carried out were issued on 15 December 2020. 	15 December 2020
<ul style="list-style-type: none"> – A GLP inspection at a CRO in Germany between 3 to 6 November 2020. The outcome of the inspection carried out was issued on 6 November 2020. 	6 November 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Comirnaty on	21 December 2020
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2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

COVID-19 is caused by SARS-CoV-2, a zoonotic virus that first emerged as a human pathogen in China and has rapidly spread around the world by human to human transmission. In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel Coronavirus (2019-nCoV) was the underlying cause. In early January 2020, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public, and the virus was categorized in the Betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to other coronaviruses that infect humans, including the Middle East respiratory syndrome (MERS) coronavirus. SARS-CoV-2 infections and the resulting disease COVID-19 have spread globally, affecting a growing number of countries. On 11 March 2020 the WHO characterized the COVID-19 outbreak as a pandemic. As of 01 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

2.1.2. Epidemiology and risk factors

Every individual is at risk of infection as there is no pre-existing immunity to the SARS-CoV-2. Following infection some but not all individuals develop protective immunity in terms of neutralising antibody responses and cell mediated immunity. However, it is currently unknown to what extent and for how long this protection lasts.

According to WHO 80% of infected individuals recover without need for hospital care, while 15% develop more severe disease and 5% need intensive care.

Increasing age and underlying medical conditions are considered risk factors for developing severe disease.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is an RNA virus with four structural proteins. One of them, the Spike protein is a surface protein which binds the angiotensin-converting enzyme 2 (ACE-2) present on host cells. Therefore, the Spike protein is considered a relevant antigen for vaccine development. It has been shown that antibodies against the Spike protein neutralise the virus and prevent infection.

2.1.4. Clinical presentation and diagnosis

The presentation of COVID-19 is generally with cough and fever, with chest radiography showing ground-glass opacities or patchy shadowing. However, many patients present without fever or radiographic changes, and infections may be asymptomatic which is relevant to controlling transmission. For symptomatic subjects, progression of disease may lead to acute respiratory distress syndrome requiring ventilation and subsequent multi-organ failure and death.

Common symptoms in hospitalized patients (in order of highest to lowest frequency) include fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhoea, headache, weakness, and rhinorrhoea. Anosmia (loss of smell) or ageusia (loss of taste) may be the sole presenting symptom in approximately 3% of individuals who have COVID-19.

The US Centres for Disease Control and Prevention (CDC) defined COVID-19 symptoms as including 1 or more of the following:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrheal
- Vomiting
- Fatigue
- Headache
- Nasal congestion or runny nose
- Nausea

All ages may present with the disease, but notably case fatality rates (CFR) are elevated in persons >60 years of age. For example, in Italy the CFR was 0.3% in adults <40 years of age but 12.8% in adults 70 to 79 years of age and 20.2% in patients ≥80 years of age. Comorbidities are also associated with increased CFR, including cardiovascular disease, diabetes, hypertension, and chronic respiratory disease. Healthcare workers are overrepresented among COVID-19 patients due to occupational exposure to infected patients.

In most situations, a molecular test is used to detect SARS-CoV-2 and confirm infection. The reverse transcription polymerase chain reaction (RT-PCR) test methods targeting SARS-CoV-2 viral RNA are the gold standard in vitro methods for diagnosing suspected cases of COVID-19. Samples to be tested are collected from the nose and/or throat with a swab. Molecular methods used to confirm an active infection are usually performed within a few days of exposure and around the time that symptoms may begin.

2.1.5. Management

The management of COVID-19 has developed during 2020, and now includes antiviral therapy (e.g. remdesivir), antibodies administered from convalescent plasma and hyperimmune immunoglobulins, anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants. These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals who have COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for a prophylactic vaccine during the ongoing pandemic, both for protection of particularly vulnerable groups as well as mitigating the effects of the pandemic at a population level, e.g. to maintain a functioning health care system, and to avoid the social and economic consequences of the stringent measures needed to diminish virus spread. There is currently no approved vaccine in EU for prevention of COVID-19.

About the product

BNT162b is a mRNA vaccine for prevention of COVID-19. The vaccine is made of a mRNA encoding for the full-length SARS-CoV-2 spike glycoprotein (S) encapsulated in lipid nanoparticles (LNPs). The sequence of the S protein was chosen based on the sequence for the "SARS-CoV-2 isolate Wuhan-Hu-1", which was available when the program was initiated: GenBank: MN908947.3 (complete genome) and GenBank: QHD43416.1 (spike surface glycoprotein).

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimized sequence encoding the spike antigen of SARS-CoV-2. The RNA contains common structural elements optimized for mediating high RNA stability and translational efficiency (see section 2.2). The LNPs protect the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (IM) delivery.

The mRNA is translated into the SARS-CoV-2 S protein in the host cell cytosol. The S protein is then expressed on the cell surface where it induces an adaptive immune response. The S protein is identified as a target for neutralising antibodies against the virus and is therefore considered a relevant vaccine component.

The vaccine, BNT162b2 (30 µg), is administered intramuscularly (IM) in two 30 µg doses of the diluted vaccine solution given 21 days apart.

Intended indication: *'Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older'*.

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive:

According to the Applicant, there is a positive benefit-risk balance for Comirnaty in the active immunisation to prevent COVID-19 disease caused by SARS-CoV-2, in individuals 16 years of age and older. This is based on evidence from the pivotal study C4591001 (also referred to as BNT162-02), a Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding Study investigating the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in healthy individuals.

The Applicant stated that the available data to date indicate that its vaccine was 95 percent effective and had no serious side effects, showing that the vaccine prevented mild and severe forms of COVID-19.

- It is likely that the applicant will be able to provide comprehensive data.

The Applicant intends to continue the ongoing pivotal Phase 3 study with participants as originally allocated for as long as possible, to obtain long-term data and to ensure sufficient follow-up to support a standard marketing authorisation. In case of availability of any COVID-19 vaccine, the sponsor will appeal to participants to remain in the ongoing study as originally randomized for as long as possible, ideally until a COVID-19 vaccine has full regulatory approval. In all cases, it is intended to follow participants up to the original planned 24 months post-vaccination, regardless of any participants opting to crossover from placebo to active vaccination. The safety and effectiveness of COMIRNATY in individuals <16 years of age have not been established for this application. Four studies in paediatric subjects are planned as laid down in the paediatric investigation plan. A study in pregnant women is also planned in the EU. A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of Comirnaty (Study C4591010) will be conducted in the EU using primary data collection that monitors a cohort of vaccinees and evaluates risk of AESIs. The Applicant will also conduct, non-interventional studies (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 in a real-world setting. These studies will allow to determine the effectiveness of vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups.

- Unmet medical needs will be addressed

According to the Applicant, as there is no approved other vaccine in the EU or successful COVID-19 therapy available in the EU, unmet medical need is existing and is likely to be addressed by this vaccine in view of the high level of protection observed in the pivotal clinical trial.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

According to the Applicant, Efficacy of COMIRNATY to prevent COVID-19 was demonstrated at the final analysis. The observed VE in each subgroup as defined by age, including elderly ≥ 65 years old, sex, race/ethnicity, country, obese subjects, and subjects at risk due to comorbidities, was overall consistent with the effectiveness of BNT162b2 to protect vaccinees against the disease. The benefit of immediate availability of Comirnaty through conditional marketing authorisation is based on the fact that there is no approved vaccine or successful COVID-19 therapy available in the European Union. An effective vaccine can impact the pandemic at this critical time and a COVID-19 vaccination program implemented soon can likely prevent further pandemic waves and thus substantially reduce mortality due to disease.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for dispersion for injection containing 225 µg/ 0.45 mL (prior to dilution) of BNT162b2 (5'capped mRNA encoding full length SARS-CoV-2 Spike protein) as active substance (AS).

Other ingredients are: ALC-0315 (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide), 1,2-

Distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose and water for injections.

The product is available in a 2 mL clear vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Pack size: 195 vials.

The multidose (5 dose) vial is stored frozen and must be thawed prior to dilution. After thawing, the vaccine should be diluted and used immediately.

After dilution with 1.8 mL sodium chloride (0.9%) solution (not supplied), one dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

2.2.2. Active Substance

General Information

The active substance consists of a single-stranded, 5'-capped mRNA that is translated into a codon-optimised sequence encoding the spike antigen of SARS-CoV-2. The vaccine is based on the spike glycoprotein (S) of SARS-CoV-2. The sequence was chosen based on the sequence for the "Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1". The protein sequence contains two proline mutation, which ensures an antigenically optimal pre-fusion confirmation (P2 S). The RNA does not contain any uridines; instead of uridine the modified N1-methylpseudouridine is used in RNA synthesis. The applicant will provide clarification on the mechanism of action for BNT162b2.

Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured and controlled by either Wyeth BioPharma Division, Andover, United States or by BioNTech Manufacturing GmbH, Mainz, Germany, and Rentschler Biopharma SE, Laupheim, Germany.

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release. These issues were classified as a Major Objection (MO). After further information was obtained from the sites and inspectors, the MO was considered resolved.

EU GMP certificates for the manufacturing and testing sites were subsequently obtained. In conclusion, appropriate manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing sites.

Description of manufacturing process and process controls

Information on the manufacturing process and process controls for both the Andover and the BNT Mainz & Rentschler manufacturing sites were provided.

The manufacturing process of BNT162b2 active substance involves five major steps. The RNA is synthesised from linear DNA via an in vitro transcription (IVT) step. The IVT step is followed by a number of purification and filtration steps. Lastly, the RNA undergoes a final filtration before being dispensed and stored frozen.

Flow diagrams were provided, presenting the process steps, process inputs and the process controls for each step. The purpose of each step in the manufacturing process is sufficiently described. The ranges of hold times and process parameters and routine in-process controls are listed with corresponding acceptance criteria, for each step. It is noted that not all process parameters are listed, but that the lists include all critical and several non-critical process parameters. It is agreed that the key process parameters are described in the dossier. The applicant has agreed to upgrade these parameters to critical process parameters (CPPs) and to include acceptable ranges for these CPPs. Updated information has been submitted during the procedure which comprised modifications of the acceptable ranges of several process parameters and the addition of some controls. The strategy is found acceptable, and the Applicant will provide information on acceptable ranges for some parameters.

The active substance is stored between -15°C and -25°C. Transportation using an insulated shipper is qualified and shipping time to finished product manufacturing sites are defined. Shipping validation of the intermediate has been agreed as recommendation.

The batch numbering system is sufficiently described.

Control of materials

An adequate overview of the raw materials and solutions used in the active substance manufacturing process is provided.

Representative certificates of analysis have been provided. The submitted information supports the appropriate quality of raw materials. It is recommended that the applicant should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials (**REC1**) and should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases (**REC2**). The description of synthesis of 5'cap and its related impurities were requested during the procedure. Appropriate information was given. The applicant should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021 (**REC3**).

The BNT162b2 active substance is manufactured by in vitro transcription using a linear DNA template, produced via plasmid DNA from transformed *Escherichia coli* cells.

The linear DNA template is not part of the final product but defines the sequence of the mRNA product and therefore it is fundamental to ensure the adequate control of the active substance. Changes to the manufacturing process of the linear DNA template (e.g. change to plasmid host cell) may result in a different impurity profile in the active substance. Additional details on the manufacturing process and the control strategy for this starting material, initially only shortly described, have been provided and the dossier will be updated accordingly.

The cell banks involved in the plasmid manufacturing process are described. Master cell bank (MCB) and working cell bank (WCB) qualification tests are listed. Relevant specifications are set and data from the current MCB and WCB are provided. The plasmid MCBs and WCBs are enrolled in a cell bank stability program. The strategy is considered adequate, noting that the dossier will be updated as appropriate. A protocol for establishment of future WCBs is provided.

Following fermentation, the cells are harvested and chemically lysed to recover the plasmid DNA. After this lysis step, the circular plasmid DNA is purified. The circular plasmid DNA is filtered and stored frozen. The strategy for establishing the initial shelf-life is endorsed and data provided support the proposed shelf life. A list of the raw materials as well as other materials used in the manufacture of the

linear DNA template is provided. All materials used are animal origin free and sourced from approved suppliers.

Specifications for the circular plasmid DNA as well as for the DNA linear template are provided. Process- and product-related impurities including host cell genomic DNA, RNA, proteins, endotoxins, bioburden and plasmid isoforms, for the plasmid DNA, are routinely quantified. The reference material is described. Implementation of any changes in the manufacture of the linear DNA template should be applied for in a variation application.

Control of critical steps and intermediates

Process parameters and tests that are used to control the process and active substance quality are provided. The list of CPPs was provided with corresponding updated acceptable ranges.

A summary of the quality attributes with the rationale for the criticality assignment is provided. The rationale for classification into CQA or QA is presented for each attribute and appears reasonable.

The in-process test methods are defined and described in the dossier.

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The BNT162b2 active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial process validation/ process performance qualification batches at all sites. All acceptance criteria for the critical operational parameters and acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

In comparability studies, a decrease in RNA integrity was observed for the initial Process 2 batches compared to Process 1 batches. This is further discussed in the subsequent section on manufacturing process development. After adjustment of process parameters for CTP and ATP volumes, RNA integrity level is more consistent and verify that the volume adjustments made for ATP and CTP volumes consistently provide reproducible results with RNA integrity levels more similar to levels achieved in Process 1 batches. Since the target volumes for ATP and CTP have been increased, the proven acceptable ranges (PARs) ranges need to be adjusted and the dossier updated accordingly **(REC8)**. The robustness of the DNase digestion step is not considered comprehensively demonstrated although there is routine control of residual DNA impurities at the active substance level. It has been confirmed that studies to enhance the robustness of this step are ongoing and these should be reported **(REC7)**. The finalised indirect filter qualification assessment, according to the applicant, already available and should be provided for evaluation **(REC6)**.

Relevant hold times and transport times have been defined and were validated by appropriate studies.

The shipping qualification strategy is described in detail and considers both thermal and mechanical aspects of shipping. The shipping procedures and configuration for transport of frozen AS to the

finished product manufacturing sites were validated to maintain product temperature in the acceptable range for a defined duration.

A transport verification study is planned and results will be available in Q1/2021. The recommendation to provide shipping performance qualification data has been agreed (**REC6**).

Manufacturing process development

Process development changes were adequately summarised. Two active substance processes have been used during the development history; Process 1 (clinical trial material) and Process 2 (commercial process). Details about process differences, justification for making changes, and results from a comparability study are provided. The major changes between active substance process versions were described in the dossier.

Batch analysis results showing comparability between non-clinical and clinical batches are provided. Additional characterization of product-related species and their relation to final product specifications will be provided as a specific obligation.

Electropherograms were presented demonstrating similarities in the peak pattern of RNA species, but some differences between Process 1 and 2 were also noted. It can therefore not be concluded that identical species are obtained by the processes. It is likely that the fragmented species will not result in expressed proteins, due to their expected poor stability and poor translational efficiency (see below). However, the lack of experimental data on the truncated RNA and expressed proteins does not permit a definitive conclusion and needs further characterisation. Therefore, additional characterisation data remain to be provided as a specific obligation (**SO1**).

Regarding the 5' cap end of the AS, reversed phase high performance liquid chromatography-UV and mass spectrometry (LC-UV/MS) characterisation confirmed that the 5'-capped and uncapped structures are the same but that there is a slight shift towards higher 5'-capping levels in Process 2. The reported quality attribute 'capped-intact RNA' is intended to reflect the proportion of the RNA molecules in the active substance that are a fully intact molecule and have the 5'-cap. It is noted that the capped-intact RNA is not measured, but only calculated from the results of 5'-cap and %RNA integrity tests. Therefore, this argument alone cannot fully confirm the comparability of Process 2 versus Process 1, and further characterisation data and justification of specifications were requested.

According to the Applicant, the majority of fragments are expected to be comprised of truncated transcripts including the 5' region but lacking the 3' region and poly(A)tail. However, the results indicating a substantial proportion of shorter/truncated mRNA with both cap and poly(A)tail are not in agreement with this statement. Therefore, the Applicant was asked to discuss and justify the obtained results and explain the apparent discrepancy. Additional characterisation data using an orthogonal method with enriched samples for fragmented species was provided. Preliminary characterization data on isolated fragmented species suggests they predominantly include the 5'-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction. The characterisation data are requested to be completed with analysis of the main peak from ion pairing RP-HPLC and analysis of other samples from Process 1 and optimised Process 2 (**SO1**). The Applicant will continue to evaluate any potential overestimation of poly(A) tail and should characterise fragments for any future AS process changes (**SO1**).

Furthermore, the poly(A)tail of the 3' end was characterised by LC-UV/MS. While the results were demonstrated to be comparable between Process 1 and Process 2 batches, significant differences were identified. As expected, poly(A) tail heterogeneity was observed both for Process 1 and Process 2 batches. Thus, slight differences in the poly(A)tail pattern were observed when comparing Process 1

and Process 2 AS batches. The Applicant explains that the redistribution is probably due to the use of a linearised DNA plasmid template in Process 2 instead of a PCR-derived DNA template in Process 1. For both processes, the poly(A)tail is anticipated to be sufficiently long to guarantee stability of the RNA and function in translation. This explanation is considered reasonable by the CHMP.

The overall primary sequence of BNT162b2 active substance was demonstrated to be comparable by LC/MS/MS -oligonucleotide mapping. Circular dichroism (CD) spectroscopy confirmed that the higher-order structure of Process 1 and Process 2 AS batches were comparable.

To demonstrate functionality, the protein size after in-vitro expression of BNT162b2 active substance was determined. The expressed protein sizes were demonstrated to be comparable between Process 1 and Process 2 batches. However, further clarification is requested and include correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **(SO1)**.

A second comparability study was presented to assess comparability across the Process 2 manufacturing facilities, batches each from the Andover and BioNTech sites were included in the study. In addition, Process 2 batches, planned for clinical supply and for emergency supply in the US market and representative batches from Process 1 were included in the comparison.

In conclusion, the Process 2 batches manufactured at the Andover and BioNTech sites were demonstrated to be comparable with respect to identity as monitored by agarose gels and 5'Cap structure characterised by LC-UV and subsequent MS analysis. Furthermore, the primary sequence and the secondary structure was demonstrated to be comparable for all Process 1 and Process 2 batches included in the study. Poly(A) tail length and distribution was investigated by RP-HPLC and MS analysis. All process 2 batches were found comparable, while the Process 1 batches showed a somewhat different poly(A) tail pattern.

The expressed protein size after in-vitro expression of BNT162b2 active substance was determined and the results demonstrate comparability between batches. However, the identity of the bands identified by WB are not sufficiently justified and further clarification is requested **(SO1)**.

Overall, the submitted data confirm consistent and comparable quality of Process 2 batches manufactured at the Andover and BioNTech sites.

Process characterisation studies using scale-down models of individual unit operations, were performed.

It should be noted that future changes to any of the process parameters, regardless of the classification of CPP or non-CPP, should be applied for as variation to the terms of the MA.

Initially, addition volumes for ATP and CTP were identified as non-CPPs as both were supplied in theoretical excess. Following additional manufacturing campaigns and additional small-scale studies it was shown that these volumes could be limiting, and the ranges were widened at the higher end. It is noted that after the adjustment of these volumes, the percentage of RNA integrity has increased to levels more consistent with Process 1 batches. Nevertheless, since the target volumes for ATP and CTP have been increased to avoid that these nucleotides are rate-limiting in order to increase the percentage of RNA integrity, the PAR ranges need to be adjusted and the dossier updated accordingly **(RECS)**.

The acceptable ranges for CPPs will be updated in the dossier.

A safety risk assessment for potential process-related impurities included in the active substance process relative to patient safety was performed. The sources of the impurities are sufficiently addressed.

The safety risk assessment strategy involves comparison of the theoretical worst-case concentration of impurities, assuming no removal, to calculated safety concern thresholds.

The worst-case levels of residual raw materials and reagents from the BNT162b2 active substance manufacturing process were calculated to be significantly below the pre-determined safety limits. This is found acceptable.

Characterisation

Analytical characterisation was performed on BNT162b2 active substance manufactured at commercial scale. This is found acceptable.

The physico-chemical characterisation involved primary structure, 5' cap structure, poly(A)tail and higher order structure evaluation. Primary structure was confirmed by oligonucleotide mapping and the orthogonal method, RNA sequencing using Next Generation Sequencing (NGS) technology. The results confirm the RNA sequence. The 5'-cap and 3' poly A tail were confirmed by two separate LC-UV/MS-methods. It was demonstrated that the predominant form of the 5' terminus is the full-length nucleotide sequence with the 5'-Cap. The higher order structure of BNT162b2 mRNA active substance was characterised in solution using biophysical techniques.

Overall, state-of-the-art methods were applied for physico-chemical characterisation and the results confirmed the expected sequence and quality attributes. It is recommended that the applicant should comprehensively describe the capability of a specific analytical method to detect lower amounts of product related impurity in the presence of the correct form in the active substance. **(REC9)**.

An uncertainty in the characterisation section is that no biological characterisation is presented. In response to questions during the procedure, the applicant has committed to update dossier with the strategy for potency determination and to address relevant functional assays including the in vitro expression (potency) results and results from the analysis of expressed protein size for active substance lot 20Y513C101. It is recommended that the applicant should discuss the results and the assay suitability for a certain method used for biological characterization of protein expression for the active substance **(REC10)**.

As described above, the expressed protein size results are currently not sufficiently confirmed and a specific obligation is laid down in the terms of the MA requiring their adequate characterisation **(SO1)**.

Process-related and product-related impurities as well as potential contaminants are described. A number of batches were evaluated for impurities, i.e. clinical, initial emergency supply and PPQ batches from both manufacturing sites.

The sole product-related impurity addressed is double-stranded RNA, derived from the in-vitro transcription reaction. Results from the active substance batches demonstrate that the level of double stranded RNA is low, acceptable and consistent.

In addition to double stranded RNA, there are truncated RNA, also referred to as fragmented species. Truncated RNA is reflected in the AS specification in terms of RNA integrity. However, the characterisation of BNT162b2 AS is currently not found to be complete in relation to a specific parameter. This is especially important considering that the current AS and finished product acceptance criteria allow for a proportion of fragmented species. The Applicant should provide additional data to further characterise the truncated and modified mRNA species present in the finished product. Relevant protein/peptide characterization data for predominant species should be provided **(SO1)**.

Residual DNA template is a process-related impurity derived from the linearised DNA template added to the in-vitro transcription reaction. Residual DNA template is measured as defined in the active substance specification. The levels are controlled by a specification limit which is considered suitably low.

The potential contaminants described in this section are endotoxin and bioburden. Acceptable results are shown for the Proteinase K pool, UF retentate pre recovery, UF-product pool and the active substance, for all batches investigated.

Specification

The active substance specifications contain tests for appearance (clarity, coloration (Ph. Eur.)), pH (Ph. Eur.), content (RNA Concentration) (UV Spectroscopy), Identity of Encoded RNA Sequence (RT-PCR), RNA Integrity (Capillary Gel Electrophoresis), 5'- Cap (RP-HPLC), Poly(A) Tail (ddPCR), Residual DNA Template (qPCR), dsRNA (Immunoblot), Bacterial Endotoxin (Ph. Eur.) and Bioburden (Ph. Eur.).

The proposed specification for active substance is considered acceptable for authorisation with respect to the attributes chosen for routine release testing. During the procedure the specification limits for a number of attributes were tightened in response to questions.

The length of the poly(A) tails in BNT162b2 active substance is important for RNA stability and translational efficiency and even though comparable results have been reported to date, the poly(A) tail length should be included to the active substance release testing **(SO2)**.

The rationale used to establish the acceptance criteria is described in detail and based on a limited data set representative of BNT162b2 active substance manufactured at the intended commercial scale and process. From the available data, mRNA integrity, dsRNA and Poly(A) tail acceptance criteria are considered in relation with batches used in clinical studies and with the demonstrated manufacturing capability and need to be re-assessed and revised as appropriate as further data becomes available **(SO2)**.

Potency testing is not included in the control of active substance but instead is performed at the level of finished product release testing. Considering the nature of this product, the approach is endorsed by the CHMP.

Analytical methods

All analytical methods used for testing of the active substance are sufficiently described in the dossier. The following tests are performed in accordance with Ph Eur chapters; clarity (Ph Eur 2.2.1), colour (Ph Eur 2.2.2), pH (Ph Eur 2.2.3), bacterial endotoxins (Ph Eur 2.6.14) and bioburden (Ph Eur 2.6.12).

All non-compendial analytical methods are sufficiently described. These analytical methods were suitably validated against the parameters presented in ICH Q2(R1).

The technical procedure for the quantification of the poly(A) tail is considered, in general, sufficiently described but the suitability of this method for the intended purpose remains to be confirmed **(SO2)**.

Batch analysis

Batch results are presented for active substance batches used for nonclinical toxicology, clinical trials, process performance qualification (PPQ), emergency supply and stability.

In general, the results obtained using the commercial process (Process 2) demonstrate batch to batch consistency with a few exceptions.

Reference materials

The current reference standard is referred to as the Clinical Reference Material (CRM). A stability protocol is provided. The Applicant has agreed to provide additional information such as protocol on preparation and qualification on the future reference material, as requested (**REC12**).

In future, a two-tiered system for future commercial reference material will be implemented. A primary reference material (PRM) and an initial working reference material (WRM) will be established for the active substance reference material.

Container closure

The information regarding container closure system is acceptable. Compliance with Ph. Eur. has been verified.

Stability

Based on the limited stability data presented a shelf-life at $-20 \pm 5^{\circ}\text{C}$ can be approved for the active substance when stored in the commercial container closure system. The stability program is designed to follow ICH guidelines. The test methods used are stability indicating. Data from the sites Andover, Mainz, Rentschler are included.

It is noted that the Applicant states that testing is currently in progress on the clinical batches and the dossier will be updated with data for these batches, as well as any new data available for the primary process validation batches. Thermal cycling studies have been initiated and a minimum of one process validation batch will be subjected to photostability studies at a future date.

Based on the stability data presented a shelf-life at $-20 \pm 5^{\circ}\text{C}$ can be approved for the active substance when stored in the commercial container closure system.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The BNT162b2 finished product (FP) is supplied as a preservative-free, 5 dose multidose concentrate to be diluted prior to intramuscular injection. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

Each vial, containing 0.45 mL of the finished product at pH 6.9 - 7.9 is designed to deliver a total of 5 doses after dilution by addition of 1.8 mL of sterile 0.9% sodium chloride solution to a total volume of 2.25 mL. Each dose contains 30 μg of RNA in 0.3 mL.

The overfill in the vial is required to ensure that the full five doses can be removed from the multi-dose vial after dilution and correctly administered, taking account of potential loss of product during these dilution and administration steps. The justification for the overfill is sufficiently discussed and considered to be acceptable. The applicant development data and finished product testing confirm that 5 doses can be consistently extracted from the vial and delivered after dilution.

The finished product is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap.

The full list of excipients is listed above in section 2.2.1; ALC-0315 and ALC-0159 (functional lipids), DSPC and cholesterol (structural lipids), potassium chloride, potassium dihydrogen phosphate, sodium

chloride and disodium phosphate dihydrate (buffer components), sucrose (cryoprotectant) and water for injections.

All excipients except the functional lipids ALC-0315 and ALC-0159 and the structural lipid DSPC comply with Ph. Eur. The functional lipid excipients ALC-0315 and ALC-0159, are classified as novel excipients. Both structural lipids DSPC and cholesterol are used in several already approved finished products. A justification was provided for why DSPC is not considered to be a novel excipient. DSPC is used as part of the LNP for the EU approved finished product Onpattro which is administered intravenously in a much higher dose than the intramuscular dose for this product. Additionally; DOPC, a structurally related lipid, is present in finished products approved in the EU for intramuscular administration. It was therefore concluded that the level of information provided for DSPC, is in line with the requirements for a known excipient are sufficient and appropriately justified.

The vial, stopper and seal components are compliant with the appropriate Ph. Eur. monographs for primary containers and closures.

Formulation development

The section on formulation development describes and justifies the chosen formulation and is sufficiently comprehensive.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described. The LNPs consists of four lipids, each has a functional or structural purpose. The formed RNA-containing LNPs are solid particles. Furthermore, the accumulated batch-data to date show consistent manufacture of lipid nanoparticles both with respect to size and polydispersity.

Lipid-related impurities have been identified in the finished product and have been characterized. An investigation has been initiated and is ongoing to assess and review potential root causes. The outcome of the investigation shall be provided (SO2).

Visual particulate matter has occasionally been observed in finished product batches. Characterization data have been presented and the control strategy has been discussed. The data demonstrates that the particles are comprised of components of the finished product formulation. A 100% visual inspection is performed during manufacturing and the automatic inspection system is updated to improve the inspection. Routine release or routine stability data indicate that the propensity of particles to form following storage is low. If particles are observed in the diluted vaccine the vial should be discarded.

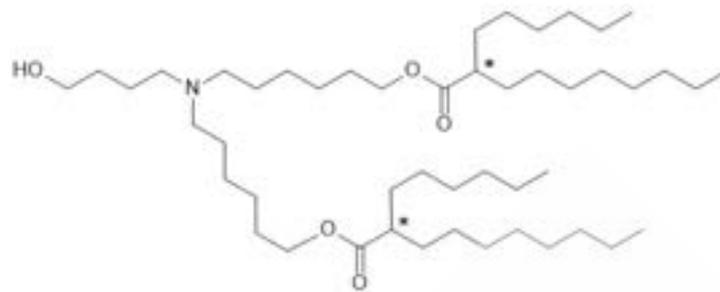
Novel excipients

Two novel excipients are included in the finished product, the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. Limited information regarding the novel excipients are provided.

ALC-0315 (cationic lipid)

The ALC-0315 novel excipient is a cationic lipid containing a tertiary amine and two ester moieties, ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate).

Figure 1 ALC-0315 structure



Asterisks (*) indicate chiral centers.

A brief description of the chemical synthesis is provided. The suppliers are defined in the dossier. A similar manufacturing process is used for ALC-0315 in clinical and commercial finished product batches.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. **(S04)**

The proposed specification is considered acceptable based on the available data. However, additional information regarding specifications that should be provided **(S04)**.

Stability data from one supplier indicate that ALC-0315 is stable when stored at the recommended storage conditions. Additionally, the excipient is stable at room temperature suitable for use in further manufacturing steps. Stability data from one supplier is considered representative for lipid from another supplier.

Lipid related impurities have been observed in some recently manufactured finished product batches, correlated with ALC-0315 lipid batches. The quality of ALC-0315 excipient is considered acceptable based on the available data on condition that specific impurities in the finished product will be further evaluated **(S02)**.

ALC-0159 (PEGylated lipid)

The ALC-0159 novel excipient is a PEGylated lipid, 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide.

Figure 2 ALC-0159 structure



A brief description of the chemical synthesis is provided.

The suppliers are defined in the dossier. The same supplier was used during development for clinical phase 1, 2 and 3 studies. The same synthetic route was used for ALC-0159 throughout development of the finished product.

In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the applicant is requested to provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **(S05)**

The proposed specification is considered acceptable based on available data. However, in order to improve impurity control strategy and to ensure batch to batch consistency of the finished product, there are additional information regarding specifications that should be provided **(S05)**.

Stability data indicate that ALC-0159 is stable when stored at the recommended storage conditions.

Manufacturing process development

The development history of the finished product is sufficiently described. The process has been transferred to commercial facilities for manufacture of later clinical materials, emergency supply and commercial supply. A table on finished product lot genealogy and usage has been provided.

The applicant states that comparability is demonstrated in a stepwise approach through a combination of release testing and extended characterization methods. It is agreed that comparability was sufficiently demonstrated with only small differences noted.

During the present regulatory procedure, release testing results of a number of recently manufactured GMP-batches was presented. The release data for the GMP-batches are compared to the clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification and that comparability has been sufficiently demonstrated subject to the specific obligations further described, for the attributes tested and given the pandemic situation. In addition, the comparison will be further extended with additional characterization testing on future batches of finished product. The applicant has confirmed that testing will be performed according to the agreed finished product comparability testing protocol and the results will be submitted in the frame of a specific obligation **(S03)**.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented and is agreed. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program at the commercial facility has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data **(S03)**.

The development of the manufacturing process is extensively described, and critical process parameters are defined. Process characterisation studies using scale-down models of individual unit operations, were performed.

Overall control strategy was presented but some parameters and ranges may be updated after PPQ and additional characterization studies completed. As for assessment of overall control strategy, a complete set of data and information is needed, this document will be assessed when finalised. A time-plan for the provision of the final data set has been agreed with the applicant **(S03)**.

The analytical testing strategy of finished product has changed throughout the development and these changes have been described. Bridging studies have been performed for analytical tests that have been changed or replaced (subvisible particles, identity of encoded RNA sequence and RNA integrity). This is found acceptable.

Container closure system

The development of the container closure system is sufficiently presented. The primary packaging is composed of glass vial and rubber stopper and are compliant with the compendial requirements of Ph. Eur.

Controlled extraction studies have been performed on the bromobutyl rubber stopper. The applicant will provide the updated results from the leachables study for assessment. **(REC13)**

Microbiological attributes

Container closure integrity testing has been performed to demonstrate that the 2 mL container closure presentation is integral.

In order to improve the control strategy, the MAH should provide validation results of alternative sterility test i.e. rapid sterility test for assessment before implementation **(REC14)**.

Compatibility

The studies described have been performed to assess physicochemical stability of the FP after dilution with 0.9% sodium chloride solution in the original glass vial as well with commonly used commercially available administration components and using worst-case conditions for dosage and administration in the clinical setting. The thawed hold time (in-use period) of undiluted finished product has been defined as 5 days at 2-8 °C and 2 hours at up to 30 °C.

Results presented support physicochemical stability of FP diluted in 0.9% sodium chloride solution for up to 24 hours at ambient or refrigerated temperatures (2-30°C) following an in-use thawed hold time of up to 5 days at 2-8 °C and 2 hours at 30 °C.

Compatibility with dosing components (syringes and needles) has been established for up to 6 hours. Furthermore, a microbiological in-use hold time study has been performed by a challenge test including five compendial micro-organisms. No significant growth ($>0.5\log_{10}$ from the start-point) was observed for any of the microorganisms within 12 hours of inoculation with storage at 20-25°C of diluted FP in 0.9% sodium chloride solution. Therefore, based on the results from the microbiological in-use hold time study, the proposed in-use period for up to 6 hours at ambient temperatures is agreed, as reflected in the product information. Furthermore, it is also stated by the applicant that the in-use period is in alignment with the WHO policy on the use of opened multi-dose vaccine vials (WHO Policy Statement: Multi-dose vial policy (MDVP) – handling of multi-dose vaccine vials after opening, rev 2014).

The compatibility of finished product is acceptably demonstrated by the dilution and administration simulation studies performed.

Manufacture of the product and process controls

The finished product is batch released by Pfizer Manufacturing Belgium NV, Puurs, Belgium or BioNTech Manufacturing GmbH, Mainz, Germany. The GMP status of the manufacturing and testing sites of the finished product have been confirmed.

The finished product manufacturing process includes the following main steps: active substance thawing and dilution, LNP formation and stabilisation, buffer exchange, concentration and filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, visual inspection, labelling, freezing and storage. Critical manufacturing steps are discussed, and relevant in-process controls are applied.

Dossier should be updated to provide more details on increase batch size including range number of AS bag and batches used, configuration of filters filter surfaces used and process controls (**REC14**). The absence of a test for residuals is considered acceptable.

Shipping validation

This section gives a summary of the qualification of the shipping process for transport of BNT162b2 finished product by passive thermal shipping containers for air and road shipments at temperature conditions of -90 to -60 °C from the finished product manufacturing and packaging site to dosing sites in the EU.

Short periods of time outside of the intended routine shipping condition of -90 to -60 °C during transport and at distribution sites have been defined.

The shipping temperature range of -90 to -60 °C is based on available stability data.

One thaw and refreeze cycle is allowed during transportation. Time during transportation out of the intended storage and shipping temperature range (-90 to -60 °C) without thaw is allowed for specified times and conditions for multiple transfers and redistribution during shipping with subsequent refreezing to -90 to -60 °C between transfers. The temperature excursion allowances are supported by data.

The selected shipping methods include shipping containers designed to maintain product temperature through a combination of insulation and dry ice. The applicant has prior experience with these passive thermal conveyances and has demonstrated that they maintain the -90 to -60 °C temperature range during product shipments, including minor shipping delays and short exposures to extreme temperatures occasionally observed during shipping and handling.

All shipments are continuously monitored using temperature data loggers.

The overall qualification strategy considered both thermal and mechanical aspects of shipping in passive thermal conveyance, supported by operational qualification and performance qualification testing. A summary of the shipping qualification strategy has been provided.

For the passive thermal conveyance, the qualification is focused on the ability of the passive system to maintain the required temperatures with specified phase change materials or dry ice when exposed to ambient temperature profiles for worst-case season. These studies are carried out in laboratory chambers to simulate the summer as worst-case ambient profiles.

A simulated distribution study demonstrated finished product and package integrity after exposure to simulated distribution hazard conditions, following the durations outlined in the worst-case extended transport lanes.

Results of thermal qualification have met specified acceptance criteria and support shipments of BNT162b2 finished product using the passive thermal conveyance shipping containers either directly or

via qualified distribution centres. Passive thermal conveyance performance qualification and the simulated shipping study finished product impact testing have been performed to complete shipping qualification assessing both thermal and mechanical aspects of shipping.

Process parameters for storage and shipping are found acceptable.

Media fills

Media fills have been performed for the filling line to validate the aseptic filling process and were run in accordance to guidelines. Results have been provided from three consecutive simulation studies and gave satisfactory results without any contaminated units. Results for the media fill cover the maximum process time for the manufacturing of finished product and simulate worst-case manufacturing conditions. The media fill validation demonstrated that aseptic conditions are maintained during the filling process. For the filling line, the maximum time will be established upon completion of media fill qualification studies. This is found acceptable.

Verification of in-process test methods

Data on verification of in-process test methods was pending at the time of the present regulatory procedure and should be provided during Q2 2021 (**REC15**).

Hold times

Hold times have been established. It is noted that any change of this section needs to be submitted to the Agency via a variation application.

Process validation plan

A FP process validation plan has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

It is described in the dossier that commercial scale PPQ-batches will be manufactured during Dec 2020 to Jan 2021 and the applicant has provided a process validation plan. In order to confirm the consistency of the finished product manufacturing process, the applicant should provide additional validation data, by March 2021. (**SO3**)

Filter validation

Acceptable information has been provided during the procedure for filter validation on the filters used for sterile filtration, describing the material, pore size and surface area. All study results met the predetermined acceptance criteria and the studies for microbial retention, membrane compatibility, extractable substances and integrity test determination have shown that the filters are appropriate for sterile filtration of the finished product. In addition, the applicant has clarified that the filter used for bioburden reduction is identical to the filters used for sterile filtration.

The MAH should provide the results for assessment from the filter validation as soon as they are available (**REC23**).

Control of excipients

ALC-0315 and ALC-0159 are novel excipients, not previously used in an approved finished product within EU. Additional information is provided separately in Section A.3 of the dossier.

DSPC is a non-compendial excipient sufficiently controlled by an in-house specification.

Cholesterol is sufficiently controlled according to the Ph. Eur. monograph with additional tests for residual solvents and microbial contamination.

The other excipients (sucrose, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injection) are controlled according to respective Ph. Eur. monograph.

The processing aids ethanol and citrate buffer are controlled according to Ph. Eur. standards and for HEPES and EDTA, reference is made to the active substance.

Product specification

The release and stability testing specifications for BNT162b2 finished product include tests for Appearance (Visual), Appearance (Visible Particulates), Subvisible Particles (Ph. Eur.), pH (Ph. Eur.), Osmolality (Osmometry), LNP Size (Dynamic Light Scattering), LNP Polydispersity (Dynamic Light Scattering), RNA Encapsulation (Fluorescence assay), RNA content (Fluorescence assay), ALC-0315 content (HPLC-CAD), ALC-0159 content (HPLC-CAD), DSPC content (HPLC-CAD), Cholesterol content (HPLC-CAD), extractable volume (Ph. Eur.), Lipid identities (HPLC-CAD), Identity of encoded RNA sequence (RT-PCR), Potency / in Vitro Expression (Cell-based flow cytometry), RNA Integrity (Capillary Gel Electrophoresis), Bacterial Endotoxin (Ph. Eur.), Sterility (Ph. Eur.) and Container Closure Integrity (Dye incursion). For all quality attributes tested on stability except for RNA integrity, the acceptance criteria for release and stability testing throughout shelf life are the same.

The specifications document for finished product in section 3.2.P.5.1 of the dossier includes a comprehensive panel of relevant tests along with corresponding acceptance criteria.

With the exception of osmolality, volume of injections in containers, HPLC-CAD (lipid identities) and RT-PCR (identity of encoded RNA sequence), which are performed only at FP release, all other analytical procedures are conducted at release and stability studies for finished product. It is stated by the applicant that the acceptance criteria used for stability during shelf-life will be the same as the acceptance criteria used for lot release.

Several questions in relation to the acceptance criteria in the FP specifications were raised during the procedure (i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity). The acceptance criteria were tightened.

For potency, RNA integrity, RNA encapsulation, lipid content and polydispersity index, the acceptance criteria will be re-assessed during Q2 2021 in order to ensure a consistent product quality by providing additional information to enhance the control strategy. This is found acceptable subject to a specific obligation. **(S02)**

The vial contains an overfill in order to ensure that the full required volume (5 doses) can be delivered following dilution and administration in line with the product information. The finished product specification includes a test to confirm the extractable volume from the vial provides 5 doses. During the procedure the applicant proposed to update the product information and instructions for use to indicate that up to 6 doses can be delivered from the vial. This proposed change to the product information was not considered acceptable as no supporting data were provided to demonstrate that 6 doses can be consistently extracted. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses **(REC21)**.

A risk evaluation regarding the risk of N-nitrosamines impurities was provided concluding that there is no risk of the presence of nitrosamines in the finished product taking into account the active

substance, the finished product formulation and primary packaging. The risk assessment is considered acceptable.

It is recommended that a risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D (**REC17**).

A question was raised during the procedure since no information and discussion was provided in the dossier on lipid-related impurities originating from the degradation of the LNP. It is argued by the applicant that with respect to potential lipid-related impurities originating from the degradation of LNPs, no degradation of the LNP FP has been observed in the stability studies at the recommended storage temperature (-70 to -90 °C) for the LNP as shown by specifications for size and polydispersity, RNA encapsulation, RNA and lipid content and RNA integrity quality attributes. This is acknowledged. In addition, further evaluation of lipid-related impurities in the finished product should be performed and the results submitted and discussed in the frame of a specific obligation (**SO2**).

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

The dossier includes release testing results of four recently manufactured GMP-batches. These finished product GMP batches were manufactured at the commercial FP manufacturing site. The release data for these GMP-batches are compared to min-max ranges of the small-scale clinical batches as well as to the results of the emergency supply lots. It is agreed that the differences noted are few and minor for all tests included in the FP specification. Therefore, it can be concluded that comparability has been sufficiently demonstrated for the attributes tested given the pandemic situation and considering that further data is to be provided in the frame of a specific obligation. In addition, the comparison will be further extended with additional characterization testing on future PPQ-batches of finished product. The applicant has confirmed that testing will be performed according to the finished product comparability testing protocol, and the results will be provided in the frame of specific obligation (**SO3**).

Reference materials

The finished product reference materials is the same as for active substance.

Stability of the product

A shelf-life of 6 months for the finished product is proposed when stored at the recommended storage condition of -90°C to -60°C.

The applicant has provided stability results up to 6 months at -80 to -60°C of one clinical batch and up to 6 months of a non-clinical batch of finished product. Two weeks data are also provided for two emergency supply under recommended storage conditions. In addition, there are newly initiated stability studies on the recently manufactured GMP-batches as well as plans to initiate stability studies on the future PPQ-batches.

Stability data have also been provided at accelerated (-40°C to +5°C) and stressed (+25°C to +30°C) storage conditions.

The stability studies are performed in accordance with ICH Q5C (Quality of biotechnological products: Stability testing of biotechnological/biological products) and the same or representative container-

closure system are used in these stability studies as will be used for commercial batches. The test methods used are stability indicating.

Overall, the presented stability data indicate no signs of degradation, significant trends or changes in terms of quality at the recommended storage condition (-90 to -60°C).

The applicant has provided updated reports from the ongoing stability studies and the presented data are considered sufficient and in support of the shelf-life claim since comparability has been sufficiently demonstrated between commercial scale GMP batches and the small-scale clinical batches.

In addition, the initial in-use period for the thawed, undiluted vial is 5 days at 2-8°C followed by storage at up to 30°C for not more than 2 hours. This is found acceptable.

Chemical and physical in-use stability has also been demonstrated for 6 hours at 2°C to 30°C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection.

It is described that the future PPQ-lots will be enrolled in the stability program and the stability protocol has been defined in the dossier. This is acceptable; however, the applicant should commit to provide the 6 months stability data for the PPQ-batches for assessment as soon as they are available. (**REC20**). Notwithstanding requests for further stability updates, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

It has been clarified by the applicant that results on photostability testing studies will be provided for assessment (**REC19**).

It is recommended that the applicant should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70°C to -20°C. In addition, the applicant should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8°C as well as the possibilities to extend the claims for transport conditions at 2-8°C (**REC22**).

A shelf-life of 6 months for the finished product at -90 to -60°C is accepted.

Adventitious agents

Adventitious agents' safety evaluation has been provided for the AS manufacturing sites and for the finished product manufacturing site.

Reagents used in active substance manufacturing and in the establishment of the MCB and WCB are the only materials of animal origin used in the manufacture of BNT162b2. The applicant has identified contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents as the main theoretical risk associated with these ingredients and it is deemed of minimal risk.

Additional clarifications were requested and provided for a number of other materials.

Sufficient details on the aseptic validation filling and media fills have been provided. Furthermore, adequate testing for bioburden and endotoxin is performed at different stages of the manufacturing process. Therefore, no additional concerns are raised.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release, the comparability between clinical and commercial material and the absence of validation data on finished product manufactured at the commercial site. These issues were classified as Major Objections (MOs).

After further information was obtained from the sites and inspectors, questions regarding the manufacturing were addressed and manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing and testing sites.

Some of the proposed sites for batch control testing are currently located in the USA. The following time-limited derogation has been introduced as a condition to the MA:

'In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by the 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.'

Additional data have been submitted by the applicant during the procedure in response to the other MOs and other questions raised.

Having considered the emergency situation and the quality documentation provided, the CHMP imposed some specific obligations (SOs) with clearly defined due dates (refer to Conclusions for details). In addition, the CHMP adopted some Recommendations (RECs) to be addressed by the Applicant.

In addition, it should be ensured that, in accordance with Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and controls (including the specifications) shall be designed to ensure product consistency and a product quality of at least shown to be safe and efficacious in clinical trials and shall introduce any subsequent changes to their manufacturing process and controls as needed.

Active substance

Overall, the information provided is satisfactory. However, certain information is still pending due to the very short time frame of product development and will either be updated in the dossier imminently or further addressed in specific obligations and other post-approval measures.

Information on the manufacturing process and process controls for the manufacturing sites Andover and BNT Mainz & Rentschler have been provided and are considered satisfactory.

Two active substance processes have been used during the development; Process 1 and 2. The major changes between AS Process 1 and 2 are: increased process scale, DNA template changed from a PCR template to linearised plasmid DNA, magnetic bead purification replaced with proteinase K digestion and UDFD steps. Based on the differences observed between batches manufactured by active substance Process 1 and 2 for the CQA mRNA integrity and lack of characterisation data, a MO was raised regarding comparability, characterisation and clinical qualification of the one proposed acceptance criteria. Biological characterisation of the active substance was limited, and additional data and discussion were requested to address functionality. Additional characterisation data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay **(SO1)**.

Truncated RNA species are regarded as product-related impurities and can be expected due to the principle of the in-vitro transcription reaction (i.e. directional polymerase activity) and (theoretical) hydrolysis during manufacturing. Analysis of RNase treated samples showed that all species detected

by the capillary gel electrophoresis (CGE)-based method are composed of RNA. Manufacturing consistency with respect to fragmented species has been sufficiently demonstrated.

There were some differences in truncated RNA species level, however further analyses revealed a comparable overall fragmentation profile among Process 1 and Process 2 active substance batches. Additionally, oligonucleotide mapping data demonstrated no significant differences observed between Process 1 and Process 2 active substance batches.

The company does not expect truncated transcripts formulated in the finished product to pose a safety or efficacy concern, as in their view no protein expression is expected from truncated transcripts. Further, clinical trials with process 1 material have not revealed major safety concerns to date. Truncated BNT162b2 RNA species lacking either the 5' cap or the poly(A) tail are expected to be rapidly targeted for degradation in the cytoplasm or would show a decrease or loss of translation efficiency. Preliminary characterization data on isolated fragment species suggest that fragment species predominantly include the 5'-cap but lack the poly(A) tail, supporting the hypothesis that most fragments would arise from premature termination in the IVT reaction.

However, as the overall characterisation of the truncated species is still limited, additional analysis of truncated species, additional translated protein characterisation, additional characterisation of lipid-related impurities and potential lipid-RNA species should be provided to support that they are not impacting clinical performance in terms of safety and/or efficacy. The current specification allows for a certain level of truncated mRNA species to be present however data from recent batches have shown levels of truncated species below that level. No related safety issues have been identified in the clinical studies thus far in subjects who received vaccine containing up to a certain level of truncated species. Therefore, the current specification is considered acceptable subject to the submission of additional data in the frame of a specific obligation (**SO1**).

Based on available data, the proposed specification for active substance is acceptable with respect to the attributes chosen for routine release testing. However, the length of the poly(A) tails in BNT162b2 active substance is critical for RNA stability and translational efficiency and therefore should be introduced in active substance release testing in the frame of a specific obligation (**SO2**). Moreover, the active substance specification acceptance limits should be re-assessed and revised as appropriate, as further data become available from ongoing clinical trials and in line with manufacturing process capability (**SO2**).

It is noted that the Applicant states that testing is currently in progress on the clinical batches and data for these batches, as well as any new data available for the primary process validation batches, will be provided. Based on the limited stability data presented, a shelf-life is approved for the active substance.

Finished product

The finished product is a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, intended for 5 doses. The finished product is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer.

The formulation development studies of the RNA containing lipid nanoparticles have been thoroughly described including studies that were performed with available active substance, representative of the mRNA platform and included in the finished product.

The development of the manufacturing process is extensively described, and critical process parameters are defined.

The manufacturing process includes lipid nanoparticle fabrication and bulk finished product formulation followed by fill and finish, and the process has been acceptably described.

Comparability between the commercial finished product and the clinical finished product has been sufficiently demonstrated for the attributes tested and will be subject to a specific obligation.

Limited data on the finished product batches manufactured at the commercial facility (entire manufacturing process at the commercial site Pfizer, Puurs, at commercial scale, active substance from process 2) were presented. A process validation plan for PPQ lots has been provided.

A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

Further data was requested in order to conclude on the consistency of finished product manufacturing, to assure comparability between the commercial product with the product used in clinical trials, and to support the claimed finished product shelf-life and storage conditions. A process validation plan for PPQ lots has been provided. Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided.

In summary, given that an acceptable validation program, also comprising the commercial facility at Puurs, Belgium, has been established, and a summary report from one PPQ validation batch was provided, the information on process validation is considered acceptable subject to the agreed specific obligation that the MAH should provide additional validation data **(S03)**.

The specifications for finished product include a comprehensive panel of relevant tests along with corresponding acceptance criteria. Several issues in relation to the acceptance criteria in the finished product specifications were raised, i.e. the LNP size, polydispersity, RNA encapsulation, in-vitro expression and RNA integrity. Whilst FP specifications were subsequently amended and overall found to be acceptable, the acceptance limits should be re-assessed, and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability **(S02)**.

Two novel excipients are included in the LNP. Complete information is not provided for both the cationic lipid ALC-0315 and the PEGylated lipid ALC-0159. In order to assure comprehensive control throughout the lifecycle of the finished product and to ensure batch to batch consistency, further information needs to be submitted regarding the synthetic process and control strategy in line with specific obligations **(S04, S05)**.

Lipid-related impurities have been observed in some recently manufactured finished product batches. For the batches with lipid-related impurities the existing quality control parameters including RNA integrity remain unchanged.

Considering the above and the emergency situation, the characterisation of the active substance and finished product is considered acceptable, and the proposed specifications for RNA Integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. These data are requested to be provided as specific obligations to the applied conditional marketing authorisation **(S01, S02)**.

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine from Process 1. The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities. The suitability of the analytical methods used for control of potency and poly(A) tail have not been fully demonstrated.

Data demonstrate the presence of significant amounts of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are poorly characterised, and the limited data provided for protein expression do not fully address the uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein.

The control strategy for active substance and finished product is important to guarantee acceptable quality and ensure batch to batch consistency of the finished product. Regarding the proposed control strategy, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Based on the above, the following uncertainties are considered to be of importance for the benefit-risk assessment:

- Truncated and modified RNA are present as impurities. Considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell there is a possibility that aberrant proteins will be expressed with possibilities for unwanted immunological events. The risk of this occurring is considered low based on the following observations and considerations:
 - Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
 - The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA.
 - The level of any individual aberrant mRNA species would in any way be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The amount of the protein would be expected to be too low to elicit an immune response. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the aberrant protein would be non-significant.
- Lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be sufficiently consistent and acceptable subject to the specific obligations abovementioned.

In general, physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in an acceptable way. While the characterisation data still

need to be completed, the results of tests carried out indicate consistency of product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product is expected to have a satisfactory clinical performance.

The submitted information indicate that currently manufactured product batches are of a quality that is appropriate and sufficiently comparable to that of clinical development batches. However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product a number of issues are expected to be addressed through fulfilment of specific obligations, within defined time frames.

The CHMP has identified the following specific obligations to address the identified quality development issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed below.

In addition, and in accordance with Article 16 of regulation (EC) No 726/2004, the MAH shall inform the Agency of any information which might influence the quality of the medicinal product concerned, such as any necessary tightening of the finished product specifications earlier than July 2021. This is also related to the general obligation to vary the terms of the marketing authorisation to take into account the technical and scientific progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

In the context of the conditional marketing authorisation, the applicant should fulfil the following specific obligations (SOs):

- SO1: In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data. **Due date: July 2021. Interim reports: March 2021.**
- SO2: In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications. **Due date: July 2021. Interim reports: March 2021.**
- SO3: In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data. **Due date: March 2021.**
- SO4: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315. **Due date: July 2021, Interim reports: January 2021, April 2021.**
- SO5: In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159. **Due date: July 2021, Interim reports: January 2021, April 2021.**

As regards SO1, the following data are requested in order to complete the information on the active substance and finished product characterisation.

- a) Additional data is to be provided to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should further address the potential for translation into

truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterization data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated. **Due date: July 2021. Interim reports: March 2021, and on a monthly basis.**

- b) The analysis of the main peak of the RNA integrity test representing the full-length RNA, should be also undertaken addressing 5'cap levels and presence of the poly (A) tail. **Due date: July 2021. Interim report: March 2021**
- c) Additional data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the *in vitro* expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated. **Due date: July 2021. Interim report: March 2021**

As regards SO2, the following data are requested to be provided in order to ensure a comprehensive control strategy, including active substance and finished product specifications:

- a) The active substance and finished product specifications acceptance limits, should be re-assessed and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that have been used in the (ongoing) clinical trials. **Due date: July 2021, Interim reports March 2021, and on a monthly basis.**
- b) Poly(A) tail length is considered a critical attribute, which should be controlled on each batch, even though comparable results were obtained until now. An active substance specification to control poly(A) length should be introduced. A suitable method should be developed and appropriate acceptance criteria should be set. **Due date: July 2021, Interim reports: March 2021**
- c) The poly(A) tail percentage is considered a critical attribute, but uncertainties remain on the suitability of the method. Additional data should be provided to support the suitability of the method used for %poly(A) tail or an alternative suitable assay should be developed and introduced. The %poly(A) tail should be characterised following any future active substance process changes. **Due date: July 2021, Interim reports: March 2021**
- d) Since mRNA integrity and polydispersity are CQAs for the efficacy of the medicinal product, the finished product acceptance criteria for these parameters should be revised as further data becomes available from ongoing clinical trials and in line with manufacturing process capability. **Due date: July 2021, Interim reports: March 2021.**
- e) Additional data should be provided to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly. **Due date: July 2021, Interim reports: March 2021**
- f) Lipid-related impurities should be further evaluated. An appropriate control strategy should be introduced, suitably justified and provided for assessment during Q2 2021. **Due date: July**

**2021, Interim reports (LMS content in commercial FP batches, investigation results):
March 2021, and on a monthly basis.**

As regards SO3, the following data are requested to be provided in order to ensure batch to batch consistency and to complete the information on process validation of the finished product manufacturing process.

- a) Full commercial scale finished product PPQ-batches will be manufactured at the commercial facility Pfizer Puurs, Belgium. The applicant should provide the summary report on the completed commercial scale process validation activities. **Due date: March 2021.**
- b) The applicant should perform testing of future process validation-batches of finished product according to the extended comparability testing protocol and the results should be provided for assessment. **Due date: March 2021.**

As regards SO4, the data are requested to be provided regarding the synthetic process and control strategy for the excipient ALC-0315 in order to improve the impurity control strategy, assure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product.

- a) A detailed description of the chemical synthesis of ALC-0315 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**
- b) Differences in the manufacturing process between two suppliers should be described and possible impact on impurity profile should be discussed **by July 2021. Interim report: January 2021**
- c) Information and justification of quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. **Due date: July 2021, Interim report: January 2021**
- d) Information and justification on critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**
- e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**
- f) The specification limit for total impurities should be re-evaluated as more batch data becomes available and revised, as appropriate. **Due date: July 2021**
- g) The specification limit for assay should be tightened based on the provided batch data to improve the quality control strategy of the finished product. **Due date: July 2021**
- h) Detailed method validation reports for assay, impurities, and residual solvents for ALC-0315 should be provided. **Due date: July 2021**
- i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

As regards SO5, the following data is requested to be provided regarding the synthetic process and control strategy for ALC-0159 in order to improve impurity control strategy, assure comprehensive control and batch-to-batch consistency throughout the lifecycle of the active product.

- a) A detailed description of the chemical synthesis of ALC-0159 (e.g. information on reagents and process conditions) should be provided. **Due date: January 2021**
- b) Information and quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. Relevant acceptance criteria for molecular weight and polydispersity should be included in the specification for the starting material carboxy-MPEG. **Due date: July 2021, Interim report: January 2021**
- c) Information and justification of critical steps and intermediates (including specifications) should be provided. **Due date: July 2021, Interim report: January 2021**
- d) The specification limit for assay should be tightened based on batch data in order to provide a more stringent quality control of the finished product. **Due date: July 2021, Interim report: April 2021**
- e) Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies. **Due date: July 2021, Interim report: April 2021**
- f) The specification limit for total impurities should be re-evaluated as more batch data are available and revised, as appropriate. **Due date: July 2021**
- g) Acceptance criteria for tetrahydrofuran should be added to the specification for ALC-0159, unless otherwise justified, as it is included as a solvent in step 2 of the synthesis. **Due date: January 2021**
- h) Detailed method validation reports for assay, impurities and residual solvents for ALC-0159 should be provided. **Due date: July 2021, Interim report: April 2021**
- i) Results of stability studies in accordance with ICH guidelines should be provided. **Due date: July 2021, Interim report: April 2021**

2.2.6. Recommendations for future quality development

In the context of the obligation of the Marketing Authorisation Holder (MAH) to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Active substance

1. The MAH should implement relevant testing strategies to ensure an adequate microbiological control for the starting materials.
2. The MAH should implement a relevant testing strategy to ensure that HEPES (Pfizer) raw material, included in the formulation buffer of FP, is free from contaminating RNases.
3. The MAH should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021.
4. The MAH should reassess the specification for the linear DNA template purity and impurities. The Applicant has already agreed to supply these by Q2 2021.
5. The MAH should perform and document a gap analysis to identify any supplemental qualification needed to align the methods used for the DNA template control with ICH requirements. The gaps identified should be addressed either prior to transferring the methods to relevant sites or during the transfer activities.
6. The MAH should provide active substance process validation data regarding the finalised

- indirect filter qualification assessment and the shipping validation between sites.
7. The MAH should provide the results of the studies performed to enhance the robustness of the DNase digestion step.
 8. The MAH should tighten the low limits of the proven acceptable ranges for the target volumes for ATP and CTP, to the levels needed to ensure a sufficiently high mRNA integrity in the active substance manufacturing process.
 9. The MAH should comprehensively describe the capability of the next generation sequencing technology platform to detect lower amounts of RNA species of alternative sequence in the presence of the correct, more abundant RNA for the active substance.
 10. The MAH should discuss the results and the assay suitability for the cell-based flow cytometry and the western blot method used for biological characterization of protein expression for the active substance.
 11. The MAH should provide a summary of the validation/verification status of the immunoblot analytical procedure used to detect double stranded RNA (dsRNA) in BNT162b2 active substance.
 12. In order to improve the control strategy, the MAH should provide the protocol on preparation and qualification of future primary and working reference standards for the active substance.

Finished Product

13. The updated results from the finished product leachables studies should be provided for assessment.
14. In order to ensure batch to batch consistency of the finished product the MAH should expand the description of the manufacturing process with more details. (1) When the batch size is twice the original one, the range number of active substance bags and active substance batches to be thawed, and the number of mixers should be stated. (2) The MAH should confirm the configuration of filters used in finished product manufacture. (3) The surface area of the sterile filter should be adapted to the batch size, unless otherwise justified; (4) process control for RNA content prior to dilution is important, particularly if several runs of TFF are performed in parallel with batch sizes
15. Data on verification of in-process test methods should be provided for assessment during Q1 2021.
16. In order to improve the control strategy, the MAH should provide results of the validation plan phase 2 of the rapid sterility test for assessment before implementation.
17. A risk assessment should be provided with respect to the potential presence of elemental impurities in the active product based on the general principles outlined in Section 5.1 of ICH Q3D and Ph. Eur. monograph Pharmaceutical Preparations (2619). A summary of this risk assessment should be submitted. The risk assessment should cover all relevant elements and sources in accordance with the guideline. The summary must enable a quantitative comparison of observed or predicted levels with the PDE's given in the guideline. It should contain what is necessary to evaluate the appropriateness and completeness of the risk assessment, including any assumptions, calculations etc. made. The control strategy for elemental impurities should be justified based on the risk assessment.
18. The MAH should provide the protocol on preparation and qualification of future primary and working reference materials for finished product testing.
19. In order to provide further information regarding the stability of finished product, Results from photostability testing and temperature cycling studies of the finished product should be provided for assessment in Q1 2021.
20. The applicant should provide the 6 months stability data for the finished product process performance qualification batches for assessment as soon as they are available.
21. This applicant proposed change to the product information to indicate that up to 6 doses can

be delivered from the vial was not considered acceptable as no supporting data was provided. In order to support such a change in the product information, a variation should be submitted to update the specification limits for extractable volume, supported by appropriate pharmaceutical development data to support the claim of 6 doses.

22. The MAH should investigate the opportunities for an increased temperature at long term storage conditions for the finished product from -70 °C to -20 °C. In addition, the MAH should investigate the possibility to prolong the in-use storage time (before dilution) of 5 days at 2-8 °C as well as the possibilities to extend the claims for transport conditions at 2-8 °C.
23. The MAH should provide the results for assessment from the filter validation as soon as they are available.

2.3. Non-clinical aspects

GLP inspections

The pivotal toxicological studies are stated to be GLP compliant by the Applicant. There were some issues identified during the assessment with repeat-dose toxicity study #38166 regarding the documentation which have led to a study audit GLP inspection conducted by the local German GLP Compliance Monitoring Authority at the facility where the study was performed, in November 2020. All the answers to the issues were acknowledged by the CHMP. The Applicant gave also comments on these issues. In light of all the elements provided, the issues identified were considered resolved.

With regard to repeat-dose toxicity study #20GR142 the only major concern identified was resolved with the answers from the Applicant that were considered satisfactory by the CHMP.

2.3.1. Pharmacology

The pharmacology dossier is based on initial studies of the functionality of the BNT162b2 (V9) RNA-based product and the encoded SARS-CoV-2 P2 S protein as well as on supporting studies of SARS-CoV-2 P2 S protein structure. This is followed by characterisation of the humoral and cellular immune response in mouse and nonhuman primate upon immunization with BNT162b2 (V9) and ends up with a SARS-CoV-2 challenge study of BNT162b2 (V9) immunized nonhuman primates.

No secondary pharmacodynamic, safety pharmacology or pharmacodynamic drug interaction studies have been conducted with BNT162b2 due to the nature of the RNA-based vaccine product, which is according to applicable guidelines (WHO guideline on nonclinical evaluation of vaccines, WHO Technical Report Series, No. 927, 2005).

Mechanism of action

SARS-CoV-2 infects the body by the use of the Spike protein (S) to attach to specific cell surface receptors, of which the angiotensin converting enzyme 2 (ACE2) may constitute a major part, as recently suggested. In addition to the initial attachment to a host cell, the S protein is also responsible for viral envelope fusion with the host cell membrane resulting in genome release. Due to its indispensable role, the S protein is a major target of virus neutralizing antibodies and has become a key antigen for vaccine development. By immunisation with the modified RNA (modRNA) product BNT162b2, encoding for the S protein, the intention is to trigger a strong and relatively long-lasting production of high affinity virus neutralizing antibodies, which can act through blocking the S-protein and its receptor-binding domain (RBD) interaction with host cell receptors but also by opsonisation mediated virus clearance. In addition, the immunisation with BNT162b2 is also intended to elicit a concomitant T cell response of the Th1 type, supporting the B cells responsible for the production of S-specific antibodies and cytotoxic T cells that kill virus infected cells.

The S protein is a trimeric class I fusion protein that exists in a metastable prefusion conformation before engaging with a target cell. BNT162b2 encodes a P2 mutant (P2 S) variant of S where two consecutive proline mutations have been introduced in order to lock the RBD in the prefusion conformation. In addition, BNT162b2 is nucleoside-modified by a substitution of 1-methylpseudouridine for uridine and thus its inherent adjuvant activity mediated by binding to innate immune sensors such as toll-like receptors (TLRs) 7 and 8, is dampened, but not abrogated. Furthermore, the structural elements of the vector backbones of the BNT162b2 are optimised for prolonged and strong translation of the antigen-encoding RNA.

The potency of the RNA vaccine is further optimised by encapsulation of the RNA into lipid nano particles (LNPs), which protects the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (i.m.) delivery. The functional and ionizable lipid, ALC-0315, is identified as the primary driver of delivery as it allows the LNPs to have a neutral charge in a physiological environment to facilitate internalization; the endosomal environment exhibits a positive charge and therefore triggers the translocation of RNA into the cytosol (Midoux & Pichon, 2015; Hassett et al, 2019; Patel et al, 2019); ALC-0159 is included in the formulation to provide a steric barrier to: 1) facilitate the control of particle size and homogeneity during manufacturing and product storage, and 2) regulate the association of plasma and proteins with the LNP surface. The composition of the LNPs may also affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity.

Administration of LNP-formulated RNA vaccines IM results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Primary pharmacodynamic studies

Primary pharmacodynamic studies in vitro

To confirm the functionality of the BNT162b2 (V9) RNA-based product, protein expression, transfection frequency from BNT162b2 and cell surface expression of the SARS-CoV-2 P2 S protein antigen was assessed. BNT162b2 (V9) transfection of HEK293T cells indicated SARS-CoV-2 P2 S was correctly expressed on the cell surface, as indicated by flow cytometry staining of non-permeabilized cells with an anti-S1 monoclonal antibody. In addition, the cellular localisation of expressed S1 protein was investigated. The S protein co-localized with an ER marker, as detected by immunofluorescence experiments in HEK293T cells expressing BNT162b2-RNA, suggesting the S protein is processed within the ER.

In a set of supportive studies, it was investigated whether BNT162b2 RNA encodes for an amino acid sequence that authentically express the ACE2 binding site (RBD). Recombinant P2 S was expressed from DNA encoding for the same amino acid sequence as BNT162b2 RNA encodes for. Flow cytometry staining with spike protein (S) binding agents, as human ACE2 and monoclonal antibodies known to bind to authentic S-protein all indicated an authentically presented P2 S protein and ACE2 binding site. Low nanomolar affinity of P2 S binding to ACE2 PD and B38 mAb was demonstrated with the use of biolayer Interferometry.

To further structurally characterize the P2 spike protein, a cryo-electron microscopy (cryoEM) investigation of purified P2 S, expressed from DNA, was conducted. The cryoEM revealed, according to

the Applicant, a particle population closely resembling the prefusion conformation of SARS-CoV-2 spike protein. By fitting a previously published atomic model on to a processed and refined cryoEM dataset, a rebuilt model was obtained showing good agreement with reported structures of prefusion full-length wild type S and its ectodomain with P2 mutations. In the prefusion state the RBD undergo hinge-like conformational movements and can either be in an “up” position (open for receptor binding) or in a “down” position (closed for receptor binding). Three-dimensional classification of the dataset showed a class of particles that was in the conformation one RBD ‘up’ and two RBD ‘down’. This partly open conformation represented 20.4% of the trimeric molecules. The remainder were in the all RBD ‘down’ conformation. Although potent neutralizing epitopes have been described when the RBD is in the “heads down” closed conformation, the “heads up” receptor accessible conformation exposes a potentially greater breadth of neutralizing antibody targets. It is concluded that antibodies to both the up and down conformations will potentially be formed upon immunisation with the P2 S encoding BNT162b2.

Primary pharmacodynamic studies in vivo

The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates. The choice and relevance of the mouse for pharmacological animal model studies was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Non-human primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. The selection of rats as the toxicology test species is consistent with the World Health Organization (WHO) guidance documents on nonclinical evaluation of vaccines (WHO, 2005). The documents recommend conducting vaccine toxicity studies in a species which mounts an immune response to the vaccine. The Wistar Han (WH) rat developed an antigen-specific immune response following BNT162b2 vaccination.

Balb/c, females were immunized IM on day 0 with 0.2, 1 or 5 µg RNA/animal of BNT162b2 (V9), or with buffer alone (n=8). Blood samples were collected on Days 7, 14, 21 and 28 after immunization. The IgG antibody response to SARS-CoV-2- RBD or S1 was analysed by ELISA. Immunization with BNT162b2 induced IgGs that bound to S1 and RBD, as detected by ELISA, and on day 28 after immunization showed a binding affinity of KD 12 nM or 0.99 nM (geometric mean) respectively, as detected by surface plasmon resonance.

To further characterise the antibody response to BNT162b2 and its potential capacity to reduce SARS-CoV-2 infections, a pseudo virus type neutralization assay (pVNT) was used as a surrogate of virus neutralization since studies with authentic SARS-CoV-2 requires a BSL3 containment. The pVNT was based on a recombinant replication-deficient vesicular stomatitis virus (VSV) vector that had been pseudotyped with SARS-CoV-2 S protein according to published protocols. A dose-dependent increases in SARS-CoV-2-S VSV pseudovirus neutralizing antibodies were observed in sera from BNT162b2-immunized mice. On day 14, the difference of the group treated with 5 µg RNA compared to the buffer control was statistically significant (p = 0.0010). On days 21 and 28, the differences of the groups treated with 1 µg and 5 µg BNT162b2 compared to the buffer control were statistically significant. The relevance of the pseudovirus assay for authentic SARS-CoV-2 was not discussed. For technical reasons, it was not possible to determine a ratio of neutralizing to non-neutralizing antibodies.

Immunisation of mice with BNT162b2 also induced IFN-γ secreting cells of both the CD4+ and CD8+ T-cell subsets. This was shown by ELISPOT after *ex vivo* re-stimulation of splenocytes with an S-protein overlapping peptide pool Day 28 after immunization. Cytokine profiling was also carried out by Multiplex analysis of cytokine release from the Day 28 Splenocytes. High levels of the Th1 cytokines IFNγ and IL-2 but minute amounts of the Th2 cytokines IL-4, IL-5 and IL-13 were detected after re-stimulation with S but not RBD overlapping peptide mix. The much higher immune cellular responses

elicited against the S1 protein compared to the RBD domain could be explained by the presence of significantly more T cell epitopes in the larger full-length S peptide mix (in addition, S1 covers the RBD domain). It should be emphasized that cellular immune reactivity is much more important against S1 than against the RBD domain, where neutralizing antibodies are more important to the latter. In addition, an elevated secretion of TNF α , GM-CSF, IL-1 β , IL-12p70 and IL-18 was recorded after re-stimulation. In order to characterize the immunophenotype of B- and T-cells appearing in lymph nodes from mice immunized with BNT162b2 (V9), B- and T-cell subsets in draining lymph node cells were quantified by flow cytometry 12 days after immunization. Higher numbers of B cells were observed in the samples from mice that received BNT162b2 compared to controls. That included plasma cells, class switched IgG1- and IgG2a-positive B cells, and germinal centre B cells. T-cell counts were elevated, particularly numbers of T follicular helper (Tfh) cells, including subsets with ICOS upregulation, which play an essential role in the formation of germinal centres (Hutloff 2015).

In the nonhuman primate (rhesus macaques) studies, BNT162b2 (V9) was shown to be immunogenic after intramuscular administration. The serum concentrations of both S1-binding and the SARS-CoV-2 neutralizing antibody titres were at least an order of magnitude higher after BNT162b2 immunization of rhesus macaques than for the panel of SARS-CoV-2 convalescent human sera. In this study, total antibody response is measured using a luminex assay and results expressed on U/ml and for the neutralization assay results are expressed in VNT 50.

Antigen specific S-reactive T-cell response after BNT162b2 immunization of the macaques was measured by ELISPOT and ICS. While S-specific T cells were low to undetectable in naïve animals, strong IFN γ but minimal IL-4 ELISpot responses were detected after the second 30 or 100 μ g dose of the BNT162b2. Intra cellular staining (ICS) confirmed that BNT162b2 immunization elicited strong S-specific IFN γ producing T cell responses, including a higher frequency of CD4+ T cells that produced IFN γ , IL-2, or TNF-alpha but a lower frequency of CD4+ cells that produce IL-4. An S-specific IFN γ producing CD8+ T cell response was also recorded.

A challenge study in rhesus macaques was conducted as nonclinical proof of concept (PoC). Rhesus macaques share a 100% homology with the human ACE2 sequence that interacts with the RBD of the S protein. BNT162b2 (V9) immunized macaques were challenged with SARS-CoV-2 intra nasally and intratracheally 55 days after the second immunization with BNT162b2. Rhesus macaques were immunized on days 0 and 21, in order to align with the clinical vaccination regimen. Some other COVID-19 vaccine candidates have different prime-boost intervals, such as 4 weeks for both ChAdOx1 (Graham et al., 2020) and mRNA-1273 (Corbett et al., 2020). At the time of challenge, SARS-CoV-2 neutralising titres ranged from 260 to 1,004 in the BNT162b2 (V9)-immunized animals. Neutralising titres were undetectable in animals from the control-immunized and sentinel groups. The presence of SARS-CoV-2 RNA was monitored by nasal and oropharyngeal (OP) swabs and bronchoalveolar lavage (BAL). Viral RNA was detected in BAL fluid from 2 of the 3 control-immunized macaques on Day 3 after challenge and from 1 of 3, on Day 6. At no time point sampled was viral RNA detected in BAL fluid from the BNT162b2 (V9)-immunized and SARS-CoV-2 challenged macaques. The difference in viral RNA detection in BAL fluid between BNT162b2-immunized and control-immunized rhesus macaques after challenge is statistically significant ($p=0.0014$). From control-immunized macaques, viral RNA was detected in nasal swabs obtained on Days 1, 3, and 6 after SARS-CoV-2 challenge; from BNT162b2 (V9)-immunized macaques, viral RNA was detected only in nasal swabs obtained on Day 1 after challenge and not in swabs obtained on Day 3 or subsequently. The pattern of viral RNA detection from OP swabs was similar to that for nasal swabs. No signs of viral RNA detected vaccine-elicited disease enhancement were observed. The viral RNA levels between control-immunized and BNT162b2-immunized animals after challenge were compared by a non-parametric analysis (Friedman's test), and the p-values are 0.0014 for BAL fluid, 0.2622 for nasal swabs, and 0.0007 for OP swabs.

Despite the presence of viral RNA in BAL fluid from challenged control animals, none of the challenged animals, immunized or control, showed clinical signs of illness (weight change, body temperature change, blood oxygen saturation and heart rate). The Applicant concluded, the absence of clinical signs in any of the challenged animals, immunised or control, despite the presence of viral RNA in BAL fluid from challenged control animals, indicates that the 2-4 year old male rhesus monkey challenge model appears to be an infection model, but not a clinical disease model. However, a further investigation by lung radiograph and computerized tomography (CT) was conducted. Radiographic evidence of pulmonary abnormality was observed in challenged controls but not in unchallenged sentinels nor in challenged BNT162b2-immunized animals except for a CT-score signal in 1 of 6 pre infection and 2 out of six at Day 10/EOP in BNT162b immunised animals. The CT score signal was at the same level as the control at Day 10/EOP. No radiographic evidence of vaccine-elicited enhanced disease was observed.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were conducted with BNT162b2, which is acceptable to the CHMP.

Safety pharmacology studies

No safety pharmacology studies were conducted with BNT162b2. The Applicant refers to that they are not considered necessary according to the WHO guideline (WHO, 2005). In addition, no findings on vital organ functions have been recorded in the repeat dose toxicology studies. Thus, the absence of safety pharmacology studies is endorsed by the CHMP.

Pharmacodynamic drug interactions studies

No pharmacodynamics drug interaction studies were conducted with BNT162b2. This is agreeable to the CHMP.

2.3.2. Pharmacokinetics

The applicant has determined the pharmacokinetics of the two novel LNP excipients ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) in plasma and liver as well as their elimination and metabolism in rats. Furthermore, the Applicant has studied the biodistribution of the two novel lipids (in rats) and the biodistribution of a LNP-formulated surrogate luciferase RNA in mice (IV), as well as the biodistribution of a [³H]-Labelled Lipid Nanoparticle-mRNA Formulation in rats (IM).

No traditional pharmacokinetic or biodistribution studies have been performed with the vaccine candidate BNT162b2.

In study PF-07302048_06Jul20_072424, the applicant has used a qualified LC-MS/MS method to support quantitation of the two novel LNP excipients. The bioanalysis methods appear to be adequately characterized and validated for use in the GLP studies.

PK studies with the two novel LNP-excipients ALC-0315 and ALC-0159:

Wistar Han rats were IV bolus injected with LNP formulated luciferase-encoding RNA at 1 mg/kg and ALC-0315 and ALC-0159 concentrations at 15,3 mg/kg and 1,96 mg/kg respectively. ALC-0315 and ALC-0159 levels in plasma, liver, urine and faeces were analysed by LC-MS/MS at different time-points up to 2-weeks.

ALC-0315 and ALC-0159 were rapidly cleared from plasma during the first 24 hours with an initial $t_{1/2}$ of 1.62 and 1.72 h, respectively. 24 hours post-dosing, less than 1% of the maximum plasma concentrations remained. A slower clearance rate was observed after 24 hours with ALC-0315 and ALC-0159 terminal elimination $t_{1/2}$ of 139 and 72.7 h, respectively.

Following plasma clearance, the liver appears to be the major organ to which ALC-0315 and ALC-0159 distribute. The applicant has estimated the percent of dose distributed to the liver to be ~60% for ALC-0315 and ~20% for ALC-0159. The observed liver distribution is consistent with the observations from the biodistribution study and the repeat-dose toxicology, both using IM administration.

For ALC-0315 (aminolipid), the maximum detected concentration in the liver (294 $\mu\text{g/g}$ liver) was reached 3 hours after IV injection. ALC-0315 was eliminated slowly from the liver and after 2-weeks the concentration of ALC-0315 was still ~25% of the maximum concentration indicating that ALC-0315 would be eliminated from rat liver in approximately 6-weeks. For ALC-0159 (PEG-lipid), the maximum detected concentration in the liver (15.2 $\mu\text{g/g}$ liver) was reached 30 minutes following IV injection. ALC-0159, was eliminated from the liver faster than ALC-0315 and after 2-weeks the concentration of ALC-0159 was only ~0.04% of the maximum detected concentration. The applicant was asked to discuss the long half-life of ALC-0315 and its effect, discussion on the comparison with patisiran, as well as the impact on the boosts and post treatment contraception duration. The applicant considered that there were no non-clinical safety issues based on the repeat dose toxicity studies at doses (on a mg/kg basis) much greater than administered to humans; this was acceptable to the CHMP.

Both patisiran lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives. According to the applicant, it is difficult to further contextualize the pharmacokinetic data and therefore to understand the safety of these molecules, beyond consideration of dose. There is a large dose differential between the human BNT162b2 dose and the dose used in the toxicity studies (300-1000x) which provides an acceptable safety margin.

Moreover, according to the Applicant given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. Finally, the applicant is of the opinion that these results support no requirements for contraception. The CHMP found this position agreeable.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159.

Biodistribution of a LNP-formulated luciferase surrogate reporter:

To determine the biodistribution of the LNP-formulated modRNA, the applicant did study distribution of the modRNA in two different non-GLP studies, in mice and rats, determined the biodistribution of a surrogate luciferase modRNA formulated with a LNP with identical lipid composition used in BNT162b2 (mouse study) or the biodistribution of a [3H]-Labelled Lipid Nanoparticle-mRNA Formulation (rat study).

The mouse study used three female BALB-c mice per group and luciferase protein expression was determined by *in vivo* bioluminescence readouts using an *In Vivo* Imaging System (IVIS) following injection of the luciferase substrate luciferine. The readouts were performed at 6h, 24h, 48h, 72h, 6d and 9d post IM injection (intended clinical route) in the right and left hind leg with each 1 μg (total of 2 μg) of LNP-formulated luciferase RNA.

In vivo luciferase expression was detected at different timepoints at the injection sites and in the liver region indicating drainage to the liver. As expected with an mRNA product, the luciferase expression was transient and decreased over time. Luciferase signals at the injection sites, most likely reflecting distribution to the lymph nodes draining the injection sites, peaked 6h post injection with signals of

approximately 10 000 times of buffer control animals. The signal decreased slowly during the first 72 hours and after 6 and 9 days the signals were further weakened to approximately levels of 18 and 7 times the signals obtained from animals injected with buffer control.

The signals from the liver region peaked 6h post injection and decreased to background levels 48h after injection. The liver expression is also supportive of the data from the rat PK study and the findings in the rat repeat-dose toxicological study showing reversible liver vacuolation and increased γ GGT levels.

The biodistribution was also studied in rats using radiolabeled LNP and luciferase modRNA (study 185350). The radiolabeling data, measuring distribution to blood, plasma and selected tissues, of IM injection of a single dose of 50 μ g mRNA over a 48-hour period is considered more sensitive than the bioluminescence method and indicate a broader biodistribution pattern than was observed with bioluminescence. Over 48 hours, distribution from the injection site to most tissues occurred, with the majority of tissues exhibiting low levels of radioactivity.

Radioactivity was detected in most tissues from the first time point (0.25 h) and results support that injections site and the liver are the major sites of distribution. The greatest mean concentration was found remaining in the injection site at each time point in both sexes. Low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, distribution was mainly observed to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of radiolabeled LNP+modRNA outside the injection site was greatest in the liver (up to 21.5%) and was much less in spleen ($\leq 1.1\%$), adrenal glands ($\leq 0.1\%$) and ovaries ($\leq 0.1\%$). The mean concentrations and tissue distribution pattern were broadly similar between the sexes. No evidence of vaccine-related macroscopic or microscopic findings were found in the ovaries in the repeat-dose toxicity studies (Study 38166 and Study 20GR142) and no effects on fertility were identified in the DART study.

Immunogenicity of a LNP formulated luciferase modRNA:

Activation of the innate immune system following IM injection of a LNP-formulated luciferase reporter RNA into mice was assessed in a Luminex-based multiplex assay where serum samples (day -1 (pre), 6 h and day 9) were tested for levels of the following chemokines and cytokines: MCP-1, MIP-1 β , TNF- α , IFN- α , IFN- γ , IL-2, IL-6, IL-10, IL1- β , IP-10. The applicant tested 3 different LNPs, all formulated together with luciferase RNA. The results suggest that the LNP formulation used in BNT162b2 (LNP8) slightly increased levels of MCP-1, IL-6, and IP-10 at 6h post immunisation. All chemokine/cytokine levels dropped to background levels at day 9.

In addition to innate immune activation, LNP formulated luciferase modRNA was able to induce IFN- γ T-cell responses (when challenged with MHC I-specific luciferase peptide pools) measured in splenocytes isolated from the mice at day 9. The LNP formulated luciferase modRNA did not induce the formation of luciferase-specific IgGs as measured by ELISA.

In an additional hPBMC study (R-20-0357), overall, low levels of pro-inflammatory cytokines (TNF, IL-6, IFN γ , IL-1 β) and low or medium levels of chemokines (IP-10, MIP-1 β , MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. IP-10, MIP-1b, MCP-1 were seen to be increased among donors, because of transfection of antigen presenting cells after infection.

Metabolism of the two novel LNP-excipients ALC-0315 and ALC-0159:

Metabolism studies were conducted to evaluate the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid). No metabolic studies were performed with the modRNA or the other two lipids of the LNP. Overall, it seems as both ALC-0159 and ALC-0315 are metabolised by hydrolytic

metabolism of the amide or ester functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

The metabolism of the novel excipients, ALC-0159 and ALC-0315, were examined *in vitro* using blood, liver S9 fractions and hepatocytes, all from mouse, rat, monkey and human. The *in vivo* metabolism was examined in rat plasma, urine, faeces, and liver from a rat pharmacokinetics study where a luciferase-encoding modRNA formulated in an LNP was used.

Metabolism of ALC-0315 appears to occur via two sequential ester hydrolysis reactions, first yielding the monoester metabolite followed by the doubly de-esterified metabolite. The monoester metabolite was observed *in vitro* in rat blood, monkey S9 fraction, and *in vivo* in rat plasma and rat liver. The doubly de-esterified metabolite was observed *in vitro* in mouse and rat blood; monkey liver S9 fraction; and *in vivo* in rat plasma, urine, faeces and liver. Subsequent metabolism of the doubly de-esterified metabolite resulted in a glucuronide metabolite which was observed in urine only from the rat pharmacokinetics study. Additionally, 6-hexyldecanoic acid, the acid product of both hydrolysis reactions of ALC-0315, was identified *in vitro* in mouse and rat blood; mouse, rat, monkey and human hepatocytes; mouse, rat and human liver S9 fractions; and *in vivo* in rat plasma.

ALC-0315 was stable over 120 min (>93% remaining) in liver microsomes and S9 fractions and over 240 min (>93% remaining) in hepatocytes in all species and test systems.

The primary route of metabolism for ALC-0159 appears to involve amide bond hydrolysis yielding *N,N*-ditetradecylamine. This metabolite was identified in mouse and rat blood as well as hepatocytes and liver S9 from mouse, rat, monkey and human.

ALC-0159 was stable over 120 min (>82% remaining) in liver microsomes and S9 fractions and over 240 min (>87% remaining) in hepatocytes in all species and test systems.

Excretion of the two novel LNP-excipients ALC-0315 and ALC-0159:

Excretion of the two novel lipids in the LNP, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid) was studied in the rat PK study. No excretion studies were performed with the modRNA or the other two lipids of the LNP which is considered acceptable by the CHMP.

While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in faeces was ~1% for ALC-0315 and ~50% for ALC-0159. Since almost no unchanged ALC-0315 was detected in urine or faeces, metabolism may play a bigger role in the elimination of ALC-0315 than ALC-0159.

2.3.3. Toxicology

The toxicological dossier for BNT162b2 is based on a total of three pivotal toxicological experimental studies; two repeat-dose toxicity rat studies and one DART fertility-EFD rat study. The test substance in the repeat-dose toxicity studies is BNT162b2 (100 µg of variant 8 in one study (study 38166) and 30 µg of the clinically relevant variant 9 in the second study (study 20GR142)), which consists of a modified RNA in a lipid nanoparticle (LNP) formulation. The differences between the variants are due to codon optimization. The LNP contains four excipients whereof two are considered novel (ALC-0315 and ALC-0159).

Repeat dose toxicity

The two general/repeat-dose toxicity studies involved IM exposure of Han Wistar rats to BNT162b2 for a total of 17 days (three weekly administrations) followed by three weeks of recovery. Overall, the

study designs only included a single experimental group each with a variant of BNT162b2 (V8 or V9 variant), with no dose-response assessment or specific experimental groups for the LNP alone or its novel excipients. No test substance-linked mortality or clinical signs were observed (except a slight increase [$<1^{\circ}\text{C}$] in body temperature). No ophthalmological and auditory effects were found. The animal model of choice, the rat, has not been assessed in the pharmacological dossier but a limited absorption/distribution study has been conducted in pharmacokinetics dossier. Immunogenicity was assessed in the toxicology studies.

Body weight and food intake: Exposure generated a slight reduction of absolute BW statistically significant at D9 (-6.8% to -11.3%; BNT162b2 V8) alternatively a weak body weight increase reduction [BNT162b2 v9]. No changes in food intake were observed.

Gross pathology and organ weights: At 100ug BNT162b2 V8 and 30ug BNT162b2 V9, the tissue at the injection site was thickened/enlarged with oedema and erythema at the end of exposure in a reversible manner. The spleen was enlarged (reversible) with up to 60% for both vaccine variants and doses. There was also an enlargement of the draining and inguinal lymph nodes at 100ug (BNT162b2 V8). Overall, there were signs of a significant immune response which is likely linked to the test substance. There was a trend of slightly enlarged liver in females at 100ug (BNT162b2 V8) but not at 30ug (BNT162b2 V9).

Histopathology: At 100ug BNT162b2 V8, there were observations of various inflammatory signs at the injection site (e.g. fibrosis, myofiber degeneration, oedema, subcutis inflammation and epidermis hyperplasia). Also, there was inflammation of the perineural tissue of the sciatic nerve and surrounding bone in most rats at d17. The bone marrow demonstrated increased cellularity and the lymph nodes showed plasmacytosis, inflammation and increased cellularity. The spleen demonstrated increased haematopoiesis in half the animals at d17. The liver showed hepatocellular periportal vacuolation at d17 (fully reversed during recovery) which may be related to hepatic clearance of ALC0315. Histopathology assessment of 30ug BNT162b2 V9 generated similar results as 100ug BNT162b2 V8 although not on as extensive level (possibly due to a lesser dose). Minimal to moderate inflammation and oedema was observed at the injection site (usually resolved after $\sim 3\text{d}$). There was minimal to moderate increased plasma cell cellularity in the lymph nodes and germinal center cellularity plus hematopoietic cell cellularity in the spleen at d17 (reversible at end of recovery). There was minimal increase cellularity in the bone marrow. Reversible vacuolisation in the liver was also observed.

The Applicant explained that peri-portal liver vacuolization was observed in both pivotal studies but are not related to any microscopic evidence of liver/biliary injury in animals (cellular hypertrophy, inflammation) nor any clinical data from Phase 1 study. Vacuoles are considered by the Applicant to be a result of ALC-0315 accumulation in liver and not PEG.

A novel finding at 30ug was minimal extra-capsular inflammation in the joints at d17.

Moreover, increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 μg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells does not provide additional information. The CHMP found this agreeable.

Immunogenicity: Treatment of rats with 100 ug BNT162b2 V8 generated SARS-CoV-2 neutralizing titers (based on a vesicular stomatitis virus (VSV)-based pseudovirus neutralization assay) and IgG antibodies against the S1 fragment and the RBD (based on ELISA) in serum samples. Treatment of

rats with 30 ug BNT162b2 V9 generated SARS-CoV-2 neutralizing antibodies (not a pseudovirus neutralization assay).

Haematology: At 30ug BNT162b2 V9 and 100ug BNT162b2 V8, there was a moderate to strong reduction of reticulocytes (48-74%, not specified for V9) coupled to lowered red cell mass parameters (RBC, HGB, and HCT). There was a moderate to strong increase (>100%) in large unclassified cells [LUC], neutrophils, eosinophils, basophils and fibrinogen that may be related to the inflammatory/immune response. The changes were reversible. No effects on coagulation were observed for V8 whereas a slight increase in fibrinogen was observed with V8 and V9.

Clinical pathology: A very strong but reversible increase (>100%) in pro-inflammatory acute phase proteins in the blood (A1AGP, A2M) was seen with both 30ug BNT162b2 V9 and 100ug BNT162b2 V8. Also, indicative of pro-inflammation, a slight to moderate reduced albumin/globulin ratio was seen for both variants. V8 (100ug) exposure generated increased levels of γ GT (>200%) and increased γ GT enzyme activity and increased AST levels (+ ~19%). V9 (30ug) exposure led to slight to moderate increases in AST and ALP levels (+20-100%), possible indicative of liver effects but no changes in γ GT levels. There were no changes in cytokine levels (IFN γ , TNF α , IL-1b, IL6, IL-10) after 100ug V8 exposure (not measured for V9). For 100ug V8, there were no changes measured in urine whereas there was a slight-moderate reduction in pH for 30ug V9.

Genotoxicity

No genotoxicity studies have been provided. This is acceptable as the components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥ 1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 μ g/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

Reproduction Toxicity

In the DART study, the test substances used were BNT162b1, BNT162b2 and BNT162b3, which were given to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 μ g RNA/dosing day). The test substances were administered intramuscularly (IM) to F0 female Wistar rats 21 and 14 days before the start of mating (M-21 and M-14, respectively) and then on Gestation Day (GD) 9 and GD20, for a total of 4 doses. A subgroup was terminated at GD21 and another (litter) group was terminated at PND21. SARS-CoV-2 neutralizing antibody titers were found in the majority of females just prior to mating (M-14), in most females and foetuses at the end of gestation (GD21), and in most offspring at the end of lactation (PND21). There was transient reduced body weight gain and food consumption after each dose. No effects on the estrous cycle or fertility index were observed. There was an increase ($\sim 2x$) of pre-implantation loss (9.77%, compared to control 4.09%) although this was within historical control data range (5.1%-11.5%). Among foetuses (from a total of n=21 dams/litters), there was a very low incidence of gastroschisis, mouth/jaw malformations, right sided aortic arch, and cervical vertebrae abnormalities, although these findings were within historical control data. Regarding skeletal findings, the exposed group had comparable to control group levels of presacral vertebral arches supernumerary lumbar ribs, supernumerary lumbar short ribs, caudal vertebrae number < 5). There were no signs of adverse effects on the postnatal

pups (terminated at PND21). It is noted that there is currently no available data on the placental transfer of BNT162b2. This information is reflected in section 5.3 of the SmPC.

Local Tolerance

No dedicated local tolerance studies have been conducted; however the assessment of local tolerance was performed in repeat-dose toxicity studies. At 100ug BNT162b2 V8, there was mostly slight to moderate oedemas but in some cases severe oedema. The severity increased with the 2nd and 3rd injections. The data for 30ug BNT162b2 V9 exposure indicated less severe but similar effects.

2.3.4. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/4447100 Corr 2), due to their nature vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this Application for Marketing Authorisation, which is considered acceptable.

2.3.5. Discussion on non-clinical aspects

Pharmacology

The proposed medicinal product is composed of a modRNA formulated with functional and structural lipids forming lipid nano particles (LNPs), the latter having the purpose to protect the modRNA from degradation and enable transfection of the modRNA into host cells after IM injection. The composition of the LNPs is likely to affect the distribution of injected BNT162b2. In addition, it cannot be excluded the LNP composition contributes to the overall immunogenicity (see also toxicology below).

The general immune activating mode of action of LNP-formulated RNA vaccines have been described in the literature. The administration of LNP-formulated RNA results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs. In general, following endocytosis of LNPs, the mRNA is released from the endosome into the host cell cytosol (Sahay et al, 2010; Maruggi et al, 2019). The process of an RNA vaccine-elicited immune response has been demonstrated in both murine and nonhuman primate models (Pardi et al, 2015; Liang et al, 2017).

Whether other cells than professional APCs may transiently express the vaccine derived spike protein and therefore from a theoretical point of view, as compared to SARS-CoV-2 infected cells, also could potentially be targets for previously primed spike protein reactive cytotoxic T cells, if present, is not known. However, no overt signs of such adverse pharmacological responses have been recorded in the repeat dose toxicity study or in the clinical trials. In the clinical trial, a second dose was administered to patients who had been immunologically primed by the first dose. Moreover, in the clinical trials it appeared around 270 patients that was shown to have been seropositive for SARS-COV-2 before vaccination. In these cases, the expression of the spike protein on host cells occurred in the presence of a primed immune response to the spike protein but no overt adverse pharmacological response has been observed. The low amount of vaccine product in a single dose may limit the distribution of modRNA/LNP mainly to the injection site and to migrating APCs. Due to the transient expression of the modRNA, no persistent expression is expected.

Regarding the structural and biophysical characterization of the modRNA, a schematic description shows that 5 different sequences are included in the BNT162b2, of which two being coding sequences.

Concerning the protein expression obtained from the V8 and V9 variants, specific immune responses (total IgG binding Ab + neutralizing Ab) were obtained at significant levels against the Spike S protein in animals with both variants (in mice and rats), indicating the efficiency of the *in vivo* expression of Spike S protein. An additional study was provided (R-20-0360) further demonstrating *in vitro* protein expression. Transfection efficiency, expression rate and cellular viability were analysed in HEK293T cells, upon transfection with different constructs (saRNA, uRNA, modRNA V8 and V9). HEK293T cells were efficiently transfected by both modRNA V8 and modRNA V9 with higher transfection rate for V9, but quite similar the expression rate by V8 and V9.

Although some of the structural and biophysical characterization of P2 S as a vaccine antigen has been provided, it was investigated in supportive studies based on P2S expressed from DNA and not the product modRNA. While it is not considered to be of critical importance for the assessment in this procedure, it still provides a scientific understanding supporting the nonclinical key studies of humoral and cellular immune response, including SARS-CoV-2 neutralizing antibodies, as well as SARS-CoV-2 challenge nonclinical PoC.

In-vivo pharmacodynamics: The humoral and cellular immune response following IM administration of BNT162b2 (V9) was investigated in mice and nonhuman primates and was based on the in-depth knowledge about the suitability, dosing and immunization regimen of BALB/c mice for RNA-based vaccine development. Nonhuman primates were chosen as they are a higher-ordered species, more closely related to humans, which may better reflect immune responses in humans. This is accepted but a more in-depth discussion on the suitability of these pharmacological animal models have not been provided (e.g. susceptibility for SARS-CoV-2 infection and similarity to COVID 19 disease; potential bias for Th1- or Th2-skewed responses has been well characterized for certain mice strains). Only single immunisation was conducted in mice, as compared to the clinical 2-dose regimen, which was adequate since only characterization of the immune response, but no challenge study was carried out in mice. Also, no or limited attention to the induction of long-term memory responses nor immunogenicity and protection in aged animals has been paid. That being said, the induction of virus neutralizing antibodies in both mice (VSV-SARS-CoV-2 S) and primates (SARS-CoV-2) indicated that BNT162b2 immunization has the potential to induce neutralizing antibodies also in humans. Thus, vaccination with modRNA is expected to induce robust neutralising antibodies and a concomitant T cell response to achieve protective immunity.

In mice, the immune response was assessed by single immunization only. Taking the phenotyping of B and T cells in aggregate, the data indicates a concurrent induction of SARS-CoV-2 S-specific neutralizing antibody titers and a Th1-driven T-cell response by immunization with BNT162b2 (this was also seen in nonhuman primates).

Concerning the nonhuman primate (rhesus macaques) studies, the applicant considers the human convalescent serum panel as an assessable benchmark to judge the quality of the immune response to the vaccine; this is accepted by the CHMP.

Concerning the characterization of the T cell responses, the Applicant suggests the S-specific IFN γ producing T cell responses, including a high frequency of CD4+ T cells that produced IFN γ , IL-2, or TNF- α but a low frequency of CD4+ cells that produce IL-4, indicates a Th1-biased response occurred after the BNT162b2 (V9) immunization. This reasoning appears acceptable to the CHMP. The role of such a Th1 biased response was put in the context of antigen-specific T-cell responses playing an important role in generation of antigen-specific antibody response as well as in elimination of infected cells to mediate protection against disease.

When immunised macaques were challenged with SARS-CoV-2, a clear and statistically significant effect was observed on reduced presence of viral RNA in bronchoalveolar lavage (BAL) and oropharyngeal (OP) swabs. A clear effect was also recorded by blinded X ray scoring of the lungs. A

protective effect is also evident in the CT score Day 3 after challenge, however at Day 10/EOP, there was a CT signal in 2 out of six BNT162b immunized monkeys at the same level as observed in the control group. That signal is of unclear significance since also in 1 out of 6 pre infection BNT162b immunized animals a similar CT-score signal was observed. During this time period the SARS-CoV-2 neutralizing GMT in the BNT162b2-immunised rhesus macaques continued to decrease but remained above the GMT of a human convalescent serum panel.

In conclusion of the preclinical pharmacology, the presented data, including immunogenicity, triggering of neutralizing antibodies and Th1 response and reduced presence of viral RNA in challenged animals as well as radiological lung parameters, provide support for the vaccination approach. Due to species differences in the immune system between animal model species and humans, the conclusion whether this candidate vaccine will be sufficiently effective in humans needs to be established in clinical studies.

Pharmacokinetic

Pharmacokinetic (regarding the two novel LNP excipients): The two novel lipid excipients play different roles in the formulation and have different pharmacokinetics. It is worth to notice that the lipid displaying a persistent kinetic over time in liver is ALC-0315.

ALC-0159 is comprised of a polyethylene glycol (PEG) headgroup (~2000 M.Wt.) attached to hydrophobic carbon chains (ie, the lipid anchor). ALC-0159 is present in BNT162 at a low mol% (<2 mol%), and therefore dose, relative to the other lipids. PEGylated lipid can exchange out of the LNP after administration, thus allowing the desired binding of endogenous proteins (eg, Apolipoprotein E) and removing the steric barrier that would otherwise restrict interactions of the LNP with target cells and proteins.

ALC-0315 is an ionizable aminolipid in BNT162b2 and is the most important lipid component for efficient self-assembly and encapsulation of the mRNA within the LNP, and for providing successful delivery of mRNA into target cells.

The PEG-lipid (ALC-0159) is designed to largely exchange out of the LNP after administration and before uptake into target cells, whereas the aminolipid (ALC-0315) is critical to the efficient intracellular delivery of the mRNA through endosomal uptake and release and must remain with the LNP.

ALC-0159 is much more hydrophilic, in large part due to the presence of the PEG molecule which is known to be a strongly hydrophilic molecule (Ma et al, 1990). Due to the more hydrophilic and essential neutral nature of this molecule, ALC-0159 has a much lower affinity for tissues and relative to ALC-0315 there will be freer compound available for redistribution from tissue to plasma; thus, elimination will be more rapid.

The Applicant pointed out that during the course of the 2-week pharmacokinetic study, liver concentrations of ALC-0315 fell 4-fold from their maximum value indicating that 75% of the material delivered to the liver was eliminated over this two-week period.

ALC-0315 has no known biology. In the absence of this 'biological relevance' the applicant used an estimation of >95% elimination of ALC-0315 to represent the essential elimination from the body. The elimination half-life of ALC-0315 in the liver following IV administration in the rat is approximately 6-8 days. These data indicate that 95% elimination of ALC-0315 will occur approx. 30-40 days following final administration in the rat.

Based on the understanding of the process involved in the terminal half-life, redistribution from tissues into which the lipid nanoparticle is delivered, a similar half-life and time to 95% elimination in human is expected (Mahmood et al, 2010). Examination of the scaling of the comparable lipids (PEG2000-C-DMG, DLin-MC3-DMA) in patisiran indicates that the half-life of these lipids appears to scale with a value approaching the typically used exponent for half-life (0.25). If this is the case for ALC-0315 we may

expect a half-life approximating 20-30 days in human for ALC-0315 and 4-5 months for 95% elimination of the lipid (Mahmood et al, 2010).

Both lipids showed an essentially similar PK profile in clinic with a strongly biphasic profile and long terminal half-lives.

Given the large difference in dose between the toxicity studies and the clinically efficacious dose (300-1000x), it is unlikely that the administration of a booster dose will lead to significant accumulation. This is noted by the CHMP.

Biodistribution: Several literature reports indicate that LNP-formulated RNAs can distribute rather non-specifically to several organs such as spleen, heart, kidney, lung and brain.

In line with this, results from the newly transmitted study 185350, indicate a broader biodistribution pattern with low and measurable radioactivity in the ovaries and testes. Given the current absence of toxicity in the DART data, the absence of toxicological findings in gonads in the repeat-dose studies and that the radioactivity in the gonads were low (below 0,1% of total dose), the current data does not indicate it to be a safety concern. The relative high dose used in the rats (500x margin to human dose based on weight) also supports a low risk from distribution to the gonads in humans.

RNA stability and kinetics are not expected to be the same for all RNAs and are influenced by the nucleosides of the RNA and although expression of the full-length spike (S) protein is expected to follow similar kinetics of that of the luciferase with a transient expression fading over time, it cannot be excluded that differences in stability/persistence of the signal could differ between the luciferase protein and the spike (S) protein.

In an additional hPBMC study (R-20-0357), low levels of pro-inflammatory cytokines (TNF, IL-6, IFN γ , IL-1 β) and low or medium levels of chemokines (IP-10, MIP-1 β , MCP-1) were secreted when assayed in an exploratory *in vitro* reactogenicity assay using human PBMCs from three donors. The Applicant underlines that no specific general trend in cytokine secretion can be observed, given variability among donors and based on the low numbers of donors in the experiment.

Toxicology

Although no extensive pharmacological assessment has been conducted in rat (only in mouse and non-human primate), the rat was used as a toxicological animal model in the repeat-dose toxicity studies. The positive neutralization assay results in the repeat-dose toxicity studies demonstrate that V8 and V9 generate an immune response in this species (i.e. SARS-CoV-2 antibodies), partially supporting the use of the rat as an animal model. Other SARS-CoV-2 immune responses in rat remain unclear. The immune responses, especially at the injection sites (e.g. oedema, erythema), seem to increase with each injection in the studies (n=3). There was a marked increase in acute phase proteins, fibrinogen and reduced albumin-globulin ratio (but no increase in cytokines with V8, unclear for V9). There was also a general increase in immune cells (LUC, neutrophils, eosinophils, basophils) and a decrease in red blood cell parameters (reticulocytes, RGB, HGB, HCT). The spleen was enlarged at both 30ug V9 and 100ug V9 and the draining and inguinal lymph nodes were enlarged mostly at 100ug (V8) but also in a few animals at 30ug (V9).

Systemic complement activation (which sometimes may be induced by liposomal drugs and biologicals and potentially result in hypersensitivity reactions) was not investigated as no signs indicative of such clinical manifestations were detected. An absence of dose-response designs in the studies increases the difficulty to interpret the effects. Overall, the V8 and V9 test substances invoked a strong but mostly reversible immune-linked response in rats after 17d exposure. Increases in neutrophils, monocytes, eosinophils and basophils were observed in study 20GR142. For the Applicant, increases in neutrophils, monocytes, eosinophils and basophils observed in the Study 20GR142 were related to the

inflammatory/immune response to BNT162b2 administration. Similar findings were also identified in Study 38166 in animals administered 100 µg BNT162b2. The applicant stated that the increases in eosinophils and basophils are a minor component of the inflammatory leukogram, which is dominated by increases in neutrophils. The Applicant also informed that characterisation of large unstained cells was not conducted since the identification of these cells would not provide additional information. The CHMP agreed with this position.

With regards to the vaccine components, only the whole formulation (modified RNA in LNPs) were used, so there is no toxicological data on the LNP alone or its specific novel excipients. The novel LNP components, these are not considered primarily as adjuvant substances.

No genotoxicity nor carcinogenicity studies have been provided. The components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The novel excipient ALC-0159 contains a potential acetamide moiety. Risk assessment performed by the Applicant indicates that the risk of genotoxicity relating to this excipient is very low based on literature data where acetamide genotoxicity is associated with high doses and chronic administration (≥ 1000 mg/kg/day). Since the amount of ALC-0159 excipient in the finished product is low (50 µg/dose), its clearance is high and only two administrations of the product are recommended for humans, the genotoxicity risk is expected to be very low.

As the pharmacokinetic distribution studies in rat demonstrated that a relatively large proportion - second to the levels at the injection site - of the total dose distributes to the liver (up to 18%, and far more than levels seen in spleen [$< 1.1\%$], adrenal glands [$< 0.1\%$] and ovaries [$< 0.1\%$]). While there was no severe pathogenesis in liver, there were some reversible functional hepatic and/or biliary effects with V8 and V9 (enlarged liver, vacuolation, strongly increased γ GT levels at $> 200\%$ and activity, minor-moderate increase in levels of AST and ALP) which may be linked to the LNP. The γ GT changes were not observed with 30ug V9, which may be due to variant differences and/or, more likely, a lower dose. The applicant is of the view that the vacuoles are a result of primarily ALC-0315 accumulation in liver. It can be noted that ALC-0159 needs to be lost from the surface of the LNP to facilitate efficient uptake into target cells. At the same time, ALC-0315 is present in the LNP at a high mol% (50 mol%) relative to the other lipids in the BNT162 vaccine, suggesting that this lipid is more likely to be present within the cells (and possibly in the vacuoles).

The assessment of the data available as regards to the DART study shows that there is no clear adverse signs on fertility and early embryogenesis effects. There were no effects on the oestrous cycle in dams but there was an $\sim 2x$ increase in pre-implantation loss ($\sim 9.77\%$ vs 4.1% in controls) but these effects are within historical control data (5.1% to 11.5%) so these findings do not raise any specific concern. It can be noted that the choice of rat as an DART animal model is supported by means of the repeat-dose toxicity rat studies which demonstrates an immune response to the vaccine candidates [V8 and V9] and the publication of Bowman et al (2013; PUBMED ID [PMID] 24391099) that reports that foetal-maternal IgG ratios are relatively low during organogenesis but that these ratios approach 1 by the end of gestation in both rat and human.

2.3.6. Conclusion on the non-clinical aspects

The applicant sufficiently addressed other concerns raised to be granted MA from a non-clinical perspective.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

Some rats intramuscularly administered Comirnaty (receiving 3 full human doses once weekly, generating relatively higher exposure in rats due to body weight differences) developed some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) which is consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible. These findings are described in SmPC section 5.3.

As per guidance, no genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential. This is acceptable to the CHMP.

Finally, the combined fertility and developmental toxicity study showed that SARS-CoV-2 neutralising antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, gestation, or embryo-foetal or offspring development up to weaning. The CHMP noted that no data are available on vaccine placental transfer or excretion in milk.

2.4. Clinical aspects

2.4.1. Introduction

Pfizer and BioNTech have developed a vaccine that targets SARS-CoV-2, intended to prevent COVID-19, for which BioNTech initiated a FIH study in April 2020 in Germany (BNT162-01) and Pfizer initiated a Phase 1/2/3 study (C4591001) shortly afterwards in the US which expanded to include global sites upon initiation of the Phase 2/3 part of the study.

Phase 1/2 Study BNT162-01

Study BNT162-01 is the ongoing, FIH, Phase 1 dose level-finding study, in which healthy adults 18 to 55 years of age all receive active vaccine. This study is evaluating the safety and immunogenicity of several different candidate vaccines at various dose levels. The protocol was later amended to allow inclusion of older adult participants up to 85 years of age. The available Phase 1 safety and immunogenicity data for adults 18 to 55 years of age are reported in this application. Multiple vaccine candidates are being evaluated in this study. For each vaccine candidate, participants received escalating dose levels (N=12 per dose level) with progression to subsequent dose levels based on recommendation from a Sponsor Safety Review Committee (SRC).

Phase 1/2/3 Study C4591001

Study C4591001 is the ongoing, randomized, placebo-controlled, Phase 1/2/3 pivotal study for registration. It was started as a Phase 1/2 study in adults in the US, was then amended to expand the study to a global Phase 2/3 study planning to enrol ~44,000 participants to accrue sufficient COVID-19 cases to conduct a timely efficacy assessment; amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. In Phase 1, two age groups were studied separately, younger participants (18 to 55 years of age) and older participants (65 to 85 years of age). The study population includes male and female participants deemed healthy as determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Exclusions included screened individuals with high risk of exposure to SARS-CoV-2 infection due to exposure in the workplace and/or medical conditions that represent risk factors, clinically important prior illness or laboratory abnormalities, serological evidence of prior SARS-CoV-2 infection or current SARS-CoV-2 infection as measured by polymerase chain reaction (PCR).

GCP

The Applicant claimed that the Clinical trials included in the application were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In addition, to seek further reassurance of the GCP compliance of the studies included in this dossier, in the context of the COVID-19 pandemic, EMA gathered additional information as indicated below from EU and non-EU regulatory authorities, and shared them with the CHMP to be considered in the assessment:

- a full inspection report from GCP inspection by Regierungspräsidium Karlsruhe and Paul-Ehrlich-Institut conducted at one of the investigator sites and at a CRO in Germany for the study BNT 162-01;
- Establishment Inspection Reports from GCP inspection by Food and Drug Administrations (USA Regulatory Authority) of six investigator sites in USA for study C4591001 (BNT 162-02);
- A full inspection Report and the summaries of the outcome from two GCP inspections by the National Administration of Drugs, Foods and Medical Devices (Argentinian Regulatory Authority) conducted at the single site located in Argentina for the study C4591001(BNT 162-02).

Based on the review of clinical data and the above-mentioned reports, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

- Tabular overview of clinical studies

Table 1 Overview of the Clinical Development

Sponsor	Study Number (Status)	Phase Study Design	Test Product (Dose)	Number of Subjects	Type of Subjects (Age)
BioNTech	BNT162-01 (ongoing)	Phase 1/2 randomized, open-label, dose-escalation, first-in-human	BNT162b2 (1, 3, 10, 20, 30 µg)	Phase 1: 60	Adults (18-55 years of age)
BioNTech (Pfizer)	C4591001 (ongoing)	Phase 1/2/3 randomized, observer-blind, placebo-control	Phase 1: BNT162b2 (10, 20, 30 µg) Placebo Phase 2: BNT162b2 (30 µg) Placebo Phase 3: BNT162b2 (30 µg) Placebo	Phase 1: 90 randomized 4:1 (within each dose/age group) Phase 2: 360 randomized 1:1 Phase 3: ~44,000 randomized 1:1 (includes 360 in Phase 2)	Phase 1: Adults (18-55 years of age, 65-85 years of age) Phase 2: Adults (18-55 years of age, 65-85 years of age) Phase 3: Adolescents, Adults (12-15 years of age, 16-55 years of age, >55 years of age)

Note: study information relevant to the scope of data presented in this application are summarized in this table.

Table 2 Overview of the pivotal phase 3 study

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Diagnosis Incl. criteria	Primary Endpoint
C4591001	131 United States 9 Turkey 6 Germany 4 South Africa 2 Brazil 1 Argentina.	randomized, multinational, placebo-controlled, observer-blind,	2 doses of 30 µg given 21 days apart	Primary: To evaluate the efficacy of BNT162b2 against confirmed severe COVID-19 occurring from 7 and 14 days after the 2nd dose in participants with and without evidence of infection before vaccination	Healthy volunteers at risk of COVID-19	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection

2.4.2. Pharmacokinetics

Not applicable.

2.4.3. Pharmacodynamics

Mechanism of action

The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

Immunogenicity studies

For vaccines, pharmacodynamics relates to investigation of immunogenicity. The available data were generated from the phase 1/2 study BNT162-01 conducted in Germany, and from the phase 1 and 2 parts of the phase 1/2/3 study C4591001, conducted in the USA (later phases were multinational). Both studies were designed to choose the optimal vaccine candidate and an appropriate dose and schedule for further studies. Among the four prophylactic SARS-CoV-2 RNA vaccines initially tested the following two candidates were selected for further development:

BNT162b1: RNA-lipid nanoparticle (LNP) vaccine containing nucleoside-modified messenger ribonucleic acid (modRNA) that encodes the RBD (receptor-binding domain)

BNT162b2: RNA-LNP vaccine containing modRNA that encodes SARS-CoV-2 full-length, P2 mutant (see section 2.2.2), prefusion spike glycoprotein (P2 S).

Key features of the two studies are summarised in the below table.

Study id	BNT162-01	C4591001
Title	A multi-site, Phase 1/2, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using	A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine

	different dosing regimens in healthy adults	Candidates Against COVID-19 in Healthy Individuals
Design	This is an open-label, multi-site, Phase 1/2, 2-part, dose-escalation study. Part A of the study includes the first in human dose and dose ranging groups in healthy adults (aged 18 to 85yrs).	This is a Phase 1/2/3, randomized, multinational, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in healthy individuals. The study consists of 2 parts: Phase 1 to identify preferred vaccine candidate(s) and dose level(s); and Phase 2/3 as an expanded cohort and efficacy part.
Immunogenicity objectives	To describe the immune response in healthy adults after dose 1 only or after both dose 1 and dose 2 measured by a functional antibody titre	To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses
Study population	Healthy adults aged 18 to 55yrs <u>BNT162b1</u> : N=84 (12/group) <u>BNT162b2</u> : N=60 (12/group) Healthy adults aged 56-85 yrs <u>BNT162b1</u> : N=36 (12/group) <u>BNT162b2</u> : N=36 (12/group)	Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive Phase 1 comprised 15 participants (randomization ratio of 4:1 so that 12 received active vaccine and 3 received placebo) per group; 13 vaccine groups were studied, corresponding to a total of 195 participants (the 100 µg dose was only used in the younger adult cohort)
IMP and dose level	<u>BNT162b1</u> : 1µg, 3µg, 10µg, 20µg, 30µg, 50µg, and 60µg. <u>BNT162b2</u> : 1µg, 3µg, 10µg, 20µg, 30µg	<u>BNT162b1</u> : 10 µg, 20 µg, 30µg, 100 µg <u>BNT162b2</u> : 10µg, 20µg, 30µg Placebo: normal saline
Dosing frequency	Two injections ~21d apart	Two injections ~21d apart
Immunogenicity endpoints	Virus neutralization test (VNT). Antibody binding assay, CMI assays, e.g. ELISpot and intracellular cytokine staining (ICS).	SARS-CoV-2 neutralization assay S1-binding IgG level assay RBD-binding IgG level assay N- binding antibody assay

Endpoints and Assays used to evaluate immunogenicity

In Study BNT162-01, immunogenicity was evaluated in Phase 1 using a SARS-CoV-2 serum neutralization assay to determine neutralizing titres and the fold rise in SARS-CoV-2 serum neutralizing titres. Immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1 (Day 8); and at Day 22 (before Dose 2) and 7 days, 14 days, and 21 days after Dose 2. Only qualified assays were used. In addition, T cells isolated from peripheral blood mononuclear cells (PBMCs) obtained from

whole blood samples of vaccinated Phase 1 participants were evaluated by enzyme-linked immunosorbent assay (ELISPOT) and intracellular cytokine staining visualized with fluorescence activated cell sorting (FACS). Blood samples were collected from study participants prior to the first vaccine dose and on Day 29 (7 days) after the second vaccine dose. Assessments included cytokines associated with Th1 responses such as IFN γ and IL-2 and those associated with Th2 responses such as IL-4, to analyse the induction of balanced versus Th1-dominant or Th2-dominant immune responses.

In Study C4591001, immunogenicity was evaluated in Phase 1 and Phase 2 using a SARS-CoV-2 serum neutralization assay to determine titres and a SARS-CoV-2 RBD- or S1-binding IgG direct Luminex immunoassay to determine antibody binding levels. Fold rises were assessed also. Only qualified assays were used. In Phase 1, immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1; and at Day 21 (before Dose 2) and 7 days, 14 days, and 1 month after Dose 2. Data were summarized for each dose level and age group. In Phase 2, immunogenicity was assessed at Day 1 (before Dose 1) and 1 month after Dose 2. Data were summarized for each age strata group and by evidence of prior SARS-CoV-2 infection at baseline per NAAT (PCR) or N-binding IgG assay. To facilitate interpretation of immunogenicity data generated in Study C4591001, a human convalescent serum (HCS) panel was obtained from Sanguine Biosciences (Sherman Oaks, CA), MT Group (Van Nuys, CA), and Pfizer Occupational Health and Wellness (Pearl River, NY). The 38 sera in the panel were collected from SARS-CoV-2 infected or COVID-19 diagnosed individuals 18 to 83 years of age \geq 14 days after PCR-confirmed diagnosis at a time when they were asymptomatic. The serum donors had predominantly had symptomatic infections (35 of 38) including 1 who had been hospitalized. In Phase 3, exploratory immunogenicity assessments are planned at time points up to 24 months, to be reported at a later time.

These are the immunogenicity assays that were used in clinical trials:

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 S1-binding IgG in Human Serum

Single-plex Direct Luminex Assay for Quantitation of SARS-CoV-2 RBD-binding IgG in Human Serum

Roche Elecsys SARS-CoV-2 N Binding Antibody Assay

mNeonGreen SARS-CoV-2 Microneutralization Assay

ELISpot Assay

Intracellular Cytokine Staining (ICS) for BNT162b1 and BNT162b2

The SARS-CoV-2 Wuhan-Hu-1 isolate spike glycoprotein (GenBank accession # QHD43416.1) is the reference sequence for the recombinant S1 and RBD proteins used in the Luminex assays. The SARS-CoV-2 neutralisation assay used a previously described strain of SARS-CoV-2 (USA_WA1/2020).

Study BNT162-01

Immunogenicity - functional antibody responses (secondary objectives)

Functional antibody titre data are available up until Day 43 for younger adults (18 to 55 yrs) dosed with 1, 10, 30, 50, and 60 μ g BNT162b1 on Days 1 (all dose levels) and 22 (all dose levels except 60 μ g) (n=12 per group). Data are available for the 10 and 30 μ g up until Day 50 for younger adults dosed with 1, 10, 20, and 30 μ g BNT162b2 on Days 1 and 22 (dose level 1 μ g, n=9; dose levels 10, 20, and 30 μ g, n=12).

Virus neutralizing antibody GMTs for participants aged 18 to 55 years after dosing with BNT162b1, are shown in Figure 3. On Day 22, at 21 d after the first dose, virus neutralizing antibody GMTs had increased in a dose-dependent manner for all dose groups. At 7 d after the second dose (Day 29), neutralizing GMTs showed a strong, dose level dependent booster response. In the 60 μ g dose group,

which was only dosed once, neutralizing GMTs remained at a lower level, indicating that a booster dose is necessary to increase functional antibody titres.

On Day 43 (21 d after the second dose of BNT162b1), neutralizing GMTs decreased (with exception of the 1 µg dose level). Day 43 virus neutralizing GMTs were 0.7-fold (1 µg) to 3.6-fold (50 µg) those of a COVID-19 HCS panel.

The COVID-19 HCS panel is comprised of 38 human COVID-19 HCS sera drawn from individuals aged 18 to 83 yrs at least 14 d after confirmed diagnosis and at a time when the individuals were asymptomatic.

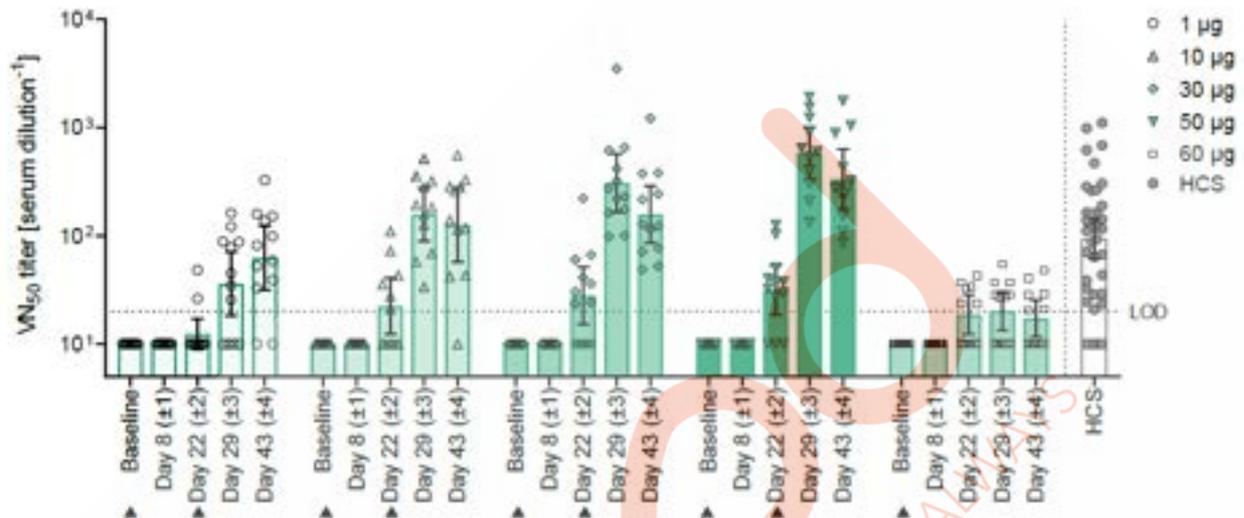


Figure 3: BNT162b1 – Functional 50% SARS-CoV-2 neutralizing antibody titers (VN50) – IMM

VN₅₀ titers with 95% confidence intervals are shown for younger participants (aged 18 to 55 years) immunized with 1, 10, 30, 50, or 60 µg BNT162b1. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). Dose 2 was not performed in the 60 µg dose group. The dotted horizontal line represents the LOD. IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum

For virus neutralizing antibody GMTs for participants aged 18 to 55 yrs after dosing with BNT162b2, see Figure 4. Participants dosed with BNT162b2 showed a strong IMP-induced antibody response. Virus neutralizing GMTs were detected at 21 d after Dose 1 (Day 22) and had increased substantially in younger participants (aged 18 to 55 yrs) immunized with ≥3 µg BNT162b2, and older participants (aged 56 to 85 yrs) immunized with 20 µg BNT162b2 by 7 d after Dose 2 (Day 29). Day 29 virus neutralizing GMTs were comparable between the younger and older adult in the 20 µg dose level cohorts. The lowest tested dose of 1 µg BNT162b2 elicited only a minimal neutralizing response in participants aged 18 to 55 yrs.

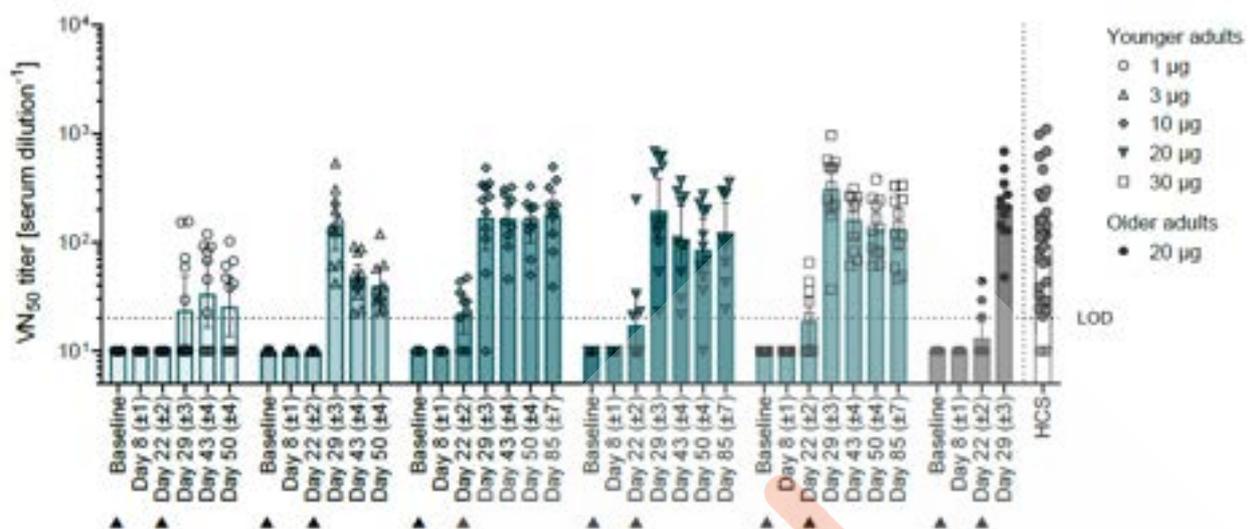
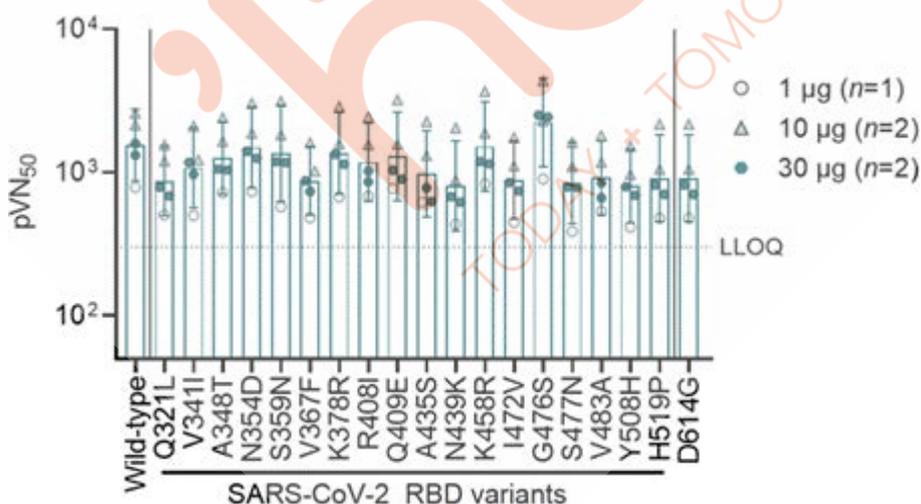


Figure 4: BNT162b2 – Functional 50% SARS-CoV-2 neutralizing antibody titres (VN50) – IMM
 VN50 titres with 95% confidence intervals are shown for younger adults (aged 18 to 55 years) immunized with 1, 3, 10, 20, or 30 µg BNT162b2, and older adults (aged 56 to 85 yrs) immunized with 20 µg BNT162b2. Values smaller than the limit of detection (LOD) are plotted as 0.5*LOD. Arrowheads indicate baseline (pre-Dose 1, Day 1) and Dose 2 (Day 22). The dotted horizontal line represents the LOD.
 IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralizing antibody titers; HCS = human COVID-19 convalescent serum.

Neutralisation of different spike protein mutants

Different pseudoviruses including RBD sequence variants have been tested in a pseudovirus neutralization assay with sera from BNT162b1- and BNT162b2-immunized participants in the BNT162-01 study. Efficient neutralization of spike protein mutants was observed with sera from BNT162b1- and BNT162b2-immunized participants demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies.



BNT162b2-induced virus neutralization titers with pseudovirus 50% neutralization titers (pVNT50) across a pseudovirus panel with 19 SARS-CoV-2 spike protein variants including 18 RBD mutants and the dominant spike protein variant D614G. LLOQ = Lower level of quantification (at 300). Data shown as group (total n=5) GMT with 95% CI.

Cell mediated immunity (CMI)

CMI were measured in terms of IFN γ - producing CD4+ and CD8+ T cells by ELISpot. Both vaccine candidates elicited clear responses (baseline vs post-dose 2). Further characterisation was determined using intracellular cytokine staining for Th1 cytokines (IFN γ , IL-2) and Th2 cytokines (IL-4). Both vaccine candidates stimulated predominantly Th1 responses, both in CD4 and CD8 T cells.

Study C4591001

Methods

The statistical analyses of immunogenicity data from Study C4591001 were based on the evaluable immunogenicity populations and all-available immunogenicity populations. Phase 1 and Phase 2 data were reported as the following, for SARS-CoV-2 serum neutralizing titers and SARS-CoV-2 S1-binding and RBD-binding IgG concentrations:

- geometric mean titers/concentrations (GMTs/GMCs)
- geometric mean-fold rise (GMFR)
- geometric mean ratio (GMR) (for Phase 1 only)
- proportions of participants with ≥ 4 -fold rise (for Phase 1 only)
- antibody titers/levels at defined thresholds (for Phase 2 only)

For immunogenicity results of SARS-CoV-2 serum neutralizing titers and S1- or RBD-binding IgG concentrations, GMTs or GMCs were computed with associated 95% CIs.

The GMFR was calculated by exponentiating the mean of the difference of logarithm transformed assay results: (later time point) – (earlier time point) with two-sided CIs. The GMR was calculated as the mean of the difference of logarithm transformed assay results: (SARS-CoV-2 serum neutralizing titers) – (SARS-CoV-2 anti-S binding antibody) for each participant, then exponentiating the mean, with two-sided CIs.

Results

The study set out to evaluate 2 SARS-CoV-2 RNA vaccine candidates, as a 2-dose (separated by 21 days) schedule, at different dose levels (BNT162b1: 10, 20, 30, and 100 μg , BNT162b2: 10, 20, and 30 μg) and in different age groups (18-55 y; 65-85 y), to select a vaccine and dose level for further testing in Phase 2/3. Cut-off date: 24-Aug-2020 (1 month post-dose 2 = D52).

Immunogenicity results are available for both adult age groups up to 1 month post-Dose 2 for the BNT162b1 and BNT162b2 vaccine candidates at the 10- μg , 20- μg , and 30- μg dose levels, and up to 7 weeks after Dose 1 of BNT162b1 at the 100- μg dose level (younger age group only).

Results for the 7 days after Dose 1 time point are only analysed and presented in the younger age group (18 to 55 years of age) for 10 μg and 30 μg BNT162b1.

Immunogenicity results SARS-CoV-2 Neutralizing Titres

BNT162b1

In the younger age group, SARS-CoV-2 50% neutralizing GMTs modestly increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b1 (Figure 5).

Generally similar trends were observed in the older age group, with higher GMTs observed in the 20- μg and 30- μg dose groups of BNT162b1 compared to the 10- μg dose group (Figure 6). In the older age

group, the SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.

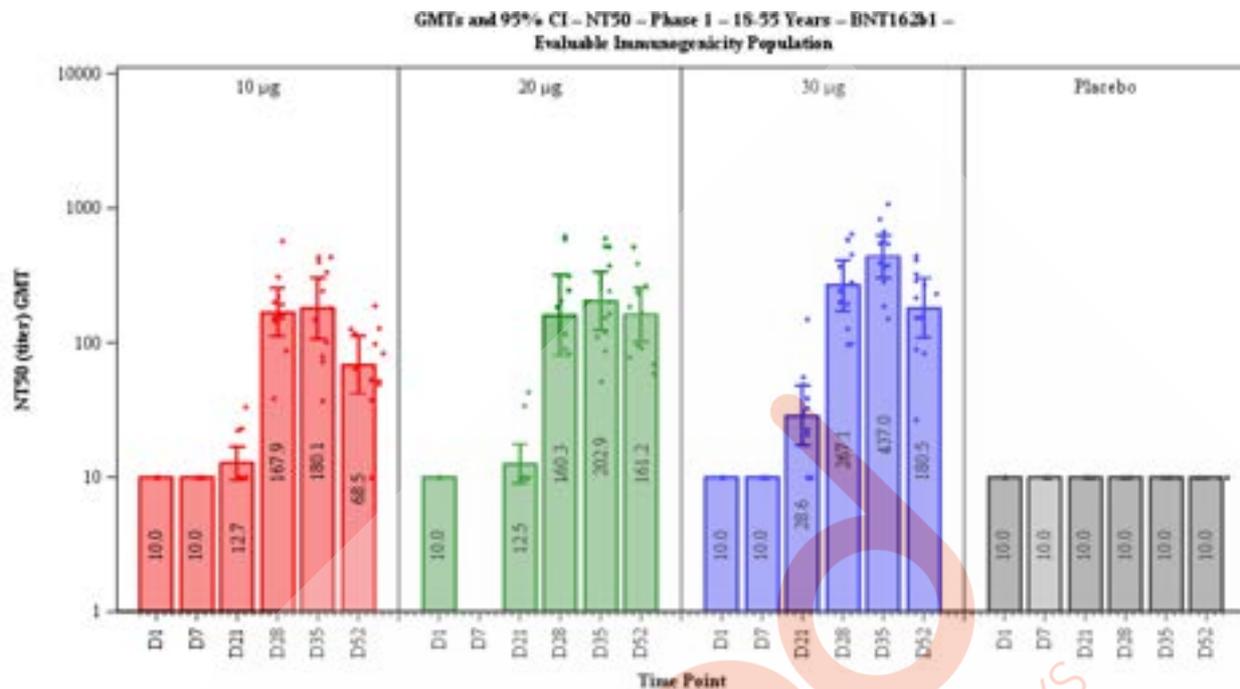


Figure 5. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

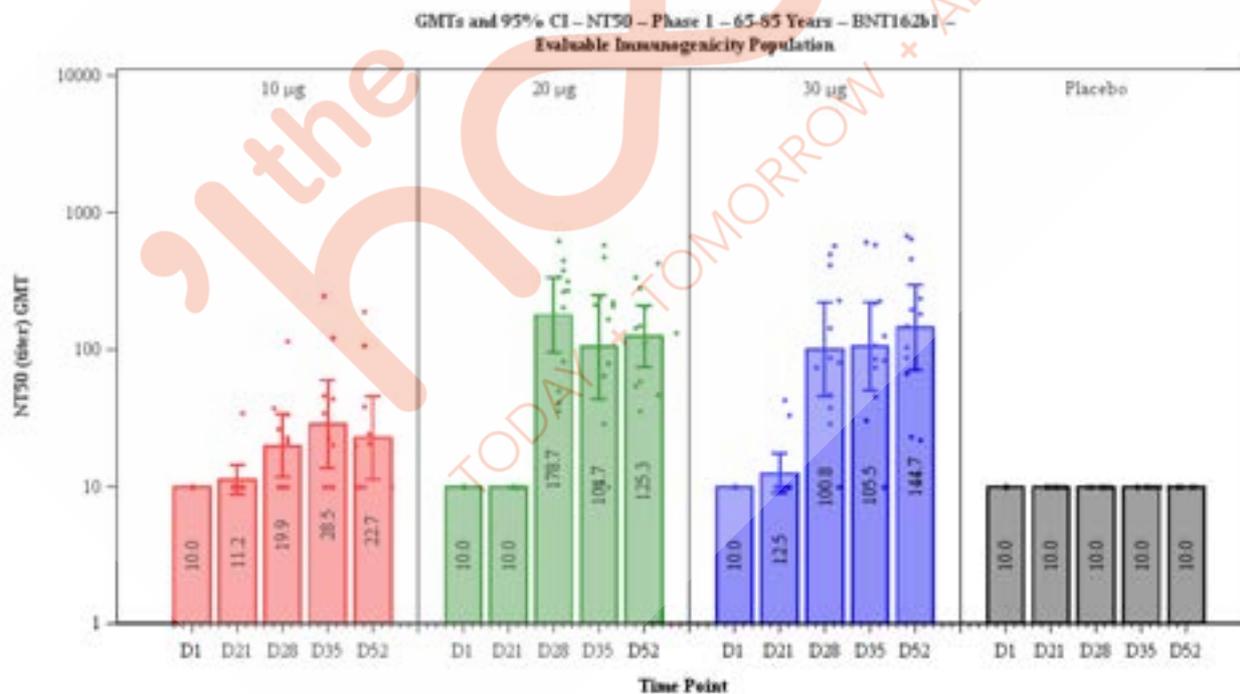
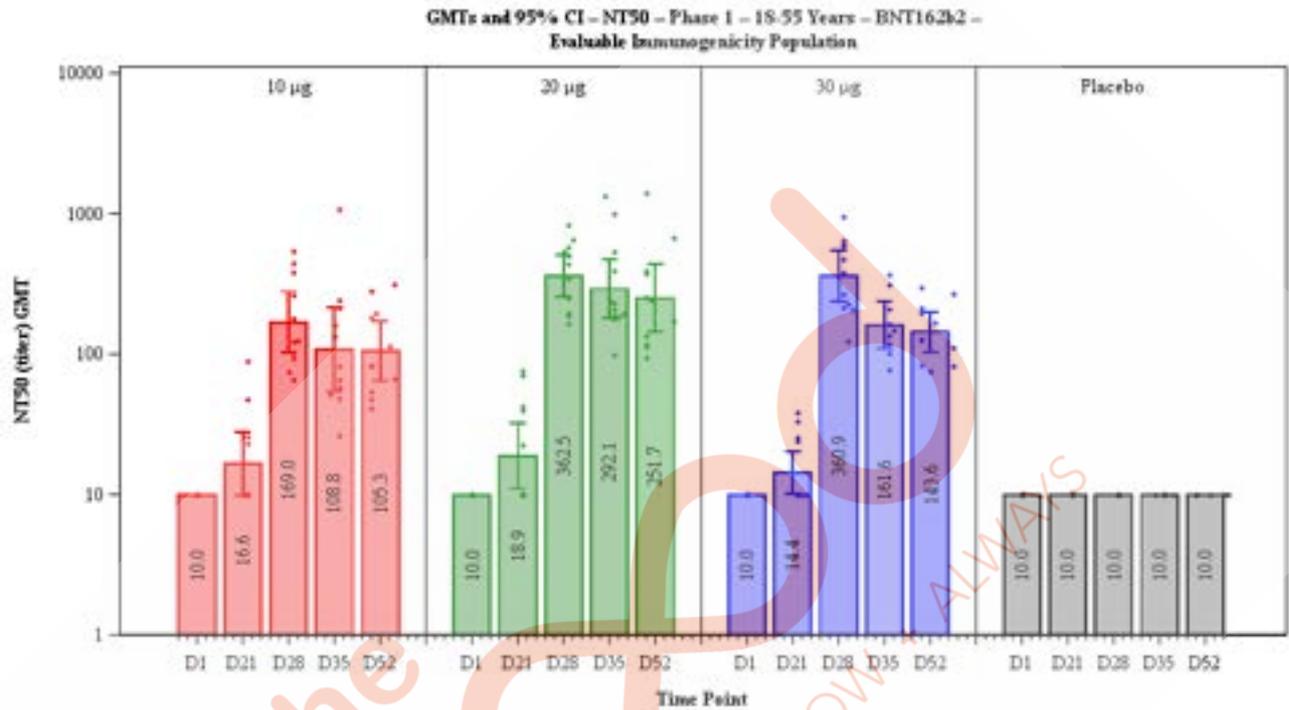


Figure 6. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b1 – Evaluable Immunogenicity Population

BNT162b2

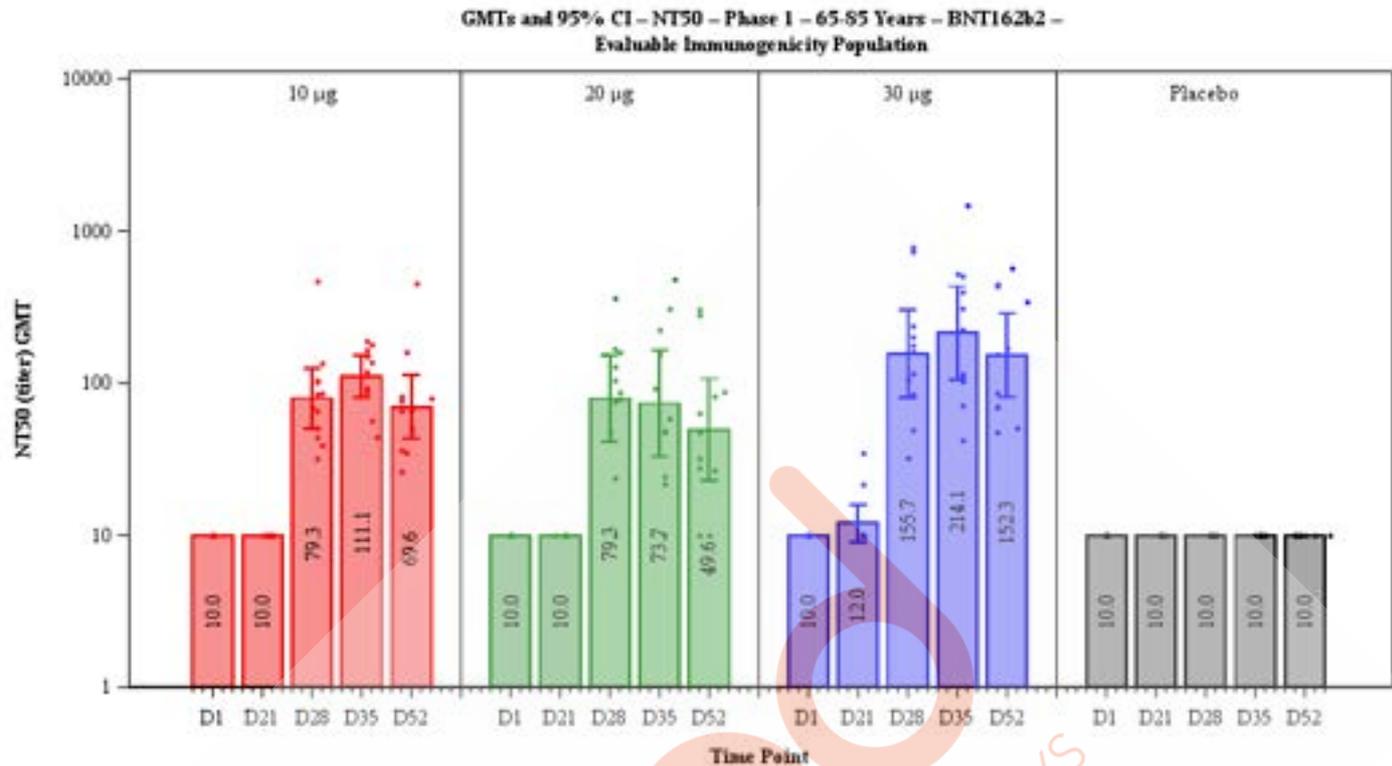
In the younger age group, SARS-CoV-2 50% neutralizing GMTs increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b2 (Figure 7).

Similar trends were generally observed in the older age group, with higher GMTs observed in the 30-µg dose groups compared to the 20-µg and 10-µg dose groups (Figure 8). In the older age group, SARS-CoV-2 50% neutralizing GMTs were generally lower than the GMTs in the younger age group.



Abbreviations: GMT = geometric mean titer, NT50 = 50% neutralizing titer, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
 Note: Dots present individual antibody levels.
 Note: Number within each bar denotes geometric mean.
 PFIZER CONFIDENTIAL, SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
 (Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: AndamC4591001_1A_P1_Serology/adva_f002_sars_50_18_b2_p1

Figure 7. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMT = geometric mean titer, NT50 = 50% neutralizing titer, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
 Note: Dots present individual antibody levels.
 Note: Number within each bar denotes geometric mean.
 PFIZER CONFIDENTIAL. SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
 (Cutoff Date: 34AUG2020, Snapshot Date: 17SEP2020) Output File: And3/C4591001_IA_P1_Serology/adv_a_f002_sars_50_65_b2_p1

Figure 8. Geometric Mean Titres and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 65-85 Years of Age – BNT162b2 – Evaluable Immunogenicity Population

2.4.4. Discussion on clinical pharmacology

The choice and dose of vaccine candidate was based on the results of two clinical phase I studies. Immune responses and safety of the two candidates were studied in both studies. The immune responses in terms of neutralising antibody responses clearly demonstrated that two doses resulted in increased geometric mean titres (GMTs) compared to responses after only the first dose. Thus, in the absence of a serological correlate of protection, these data supported that two doses would be needed in adults. The responses were numerically higher in higher dose groups compared to lower doses but did not substantially differ between 10ug and 30ug. The neutralising antibody responses between the two vaccine candidates are considered similar although no formal comparison was made. The responses to the vaccines were higher compared to a pool of human convalescent sera in study BNT162-001. In both studies subjects 55 years of age and older were included as well as younger adults. The responses in elderly were lower compared to younger adults, but the difference is likely of no clinical relevance, also considering the delayed peak.

For BNT162b1 and BNT162b2, the S1- and RBD-binding IgG kinetics were comparable to the kinetics of neutralizing antibodies, with lower IgG concentrations in older age group than in younger age group.

Further evaluation of antibody persistence is ongoing. Neutralizing antibody titres will be followed until the end of 162 days post-dose 2 for study BNT162-01 and up to 2-years for study C459001. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation).

Immune responses induced by the vaccine against emerging circulating strains of SARS-CoV-2 will be also be investigated. Effectiveness studies included in the RMP will be important to understand the performance of the vaccine in case of e.g. mutating variants.

Efficient neutralization of spike protein mutants including RBD sequence variants was observed with sera from vaccine-immunized study BNT162-01 participants, demonstrating the neutralization breadth of vaccine-elicited polyclonal antibodies. This may be important to consider when facing emerging variants with mutations in the spike proteins, e.g. the UK variant, as the vaccine might still be able to confer sufficient cross-neutralisation.

Further characterisation of immune responses was included in study BNT162-001. Cellular immune responses were demonstrated in terms of IFN γ -producing CD4 and CD8 T cells. In addition, a clear Th1-polarised response, i.e. IFN γ /IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED. For the 30 μ g dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults, whereas for the 30 μ g dose cohort vaccinated with BNT162b1, RBD-specific IL-2 producing CD4+ and CD8+ T cells were reduced in older adults.

2.4.5. Conclusions on clinical pharmacology

The immune response data overall support the choice of vaccine candidate, BNT162b2, and the choice of a 2-dose schedule of 30 μ g. Final study report from study C4591001 is requested to be submitted as soon as available (specific obligation), including data on persistence of immune responses.

2.5. Clinical efficacy

2.5.1. Dose response study

See section 2.4.3.

2.5.2. Main study

Title of study

Study C4951001: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Methods

Study Participants

Main Inclusion criteria:

- Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥ 12 years (Phase 2/3) at randomization.
- Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks

before enrolment, could be included. Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfil the criteria specified in the protocol.

- Phase 2/3 only: Participants who, in the judgment of the investigator, were at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).
- Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent

Exclusion criteria:

- Other medical or psychiatric condition including recent or active suicidal ideation/behaviour or laboratory abnormality that increased the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention.
- Receipt of medications intended to prevent COVID-19.
- Previous clinical or microbiological diagnosis of COVID-19.
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding.
- Previous vaccination with any coronavirus vaccine.
- Individuals who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids were administered short term (<14 days) for treatment of an acute illness, participants should not have been enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.
- Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation
- Previous participation in other studies involving study intervention containing lipid nanoparticles.

Treatments

The vaccine candidate selected for Phase 2/3 evaluation was BNT162b2 at a dose of 30 µg. In phase 2/3 the participants were randomized 1:1 to receive vaccine or placebo, normal saline (0.9% sodium chloride solution for injection). The injection was intramuscular for both vaccine and the placebo.

Available safety, efficacy and immunogenicity data pertain to vaccine made according with the manufacturing process employed for clinical trial batches.

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply (commercial process) will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. Data are expected in February 2021. See the Quality section regarding comparability of clinical lots and commercial lots.

Objectives

The outcomes of the primary efficacy objectives were included in the Clinical Study Report submitted in this application. Results of the secondary objectives are expected during 2021.

Primary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination

Primary safety objectives

- To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)
- To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3
- To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3

Secondary efficacy objectives

- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination
- To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination
- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination

- To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination.

Secondary immunogenicity objectives

- To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age (data not included in this report)

Exploratory objectives

- To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination
- To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study
- To describe the serological responses to the BNT vaccine candidate in cases of:
 - Confirmed COVID-19
 - Confirmed severe COVID-19
 - SARS-CoV-2 infection without confirmed COVID-19
- To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease
- To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by two different manufacturing processes (see under Treatment).

Outcomes/endpoints

Immunogenicity

See pharmacodynamics section for description of immunological methods used in phase 1 and 2 of this study. The same methods are used also in phase 3, but results are not yet available.

Primary Efficacy Endpoints

First primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥ 7 days after Dose 2.

Second primary endpoint: COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥ 7 days after Dose 2.

Secondary Efficacy Endpoints

COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥ 14 days after Dose 2.

Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥ 7 days after Dose 2 or (2) ≥ 14 days after Dose 2.

COVID-19 Case Definitions

Participants who developed any potential COVID-19 symptoms were to contact the site immediately and, if confirmed, to participate in an in-person or telehealth visit as soon as possible (within 3 days of symptom onset and at the latest 4 days after symptom resolution). At the visit (or prior to the visit, if a self-swab was used), investigators were to collect clinical information and results from local standard-of-care tests sufficient to confirm a COVID-19 diagnosis. Investigators were to obtain a nasal swab (mid-turbinate) for testing at a central laboratory using a validated reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA) to detect SARS-CoV-2. If the evaluation was conducted by telehealth, the participant was to self-collect a nasal swab and ship for assessment at the central laboratory. A local nucleic acid amplification test (NAAT) result was only acceptable if it met protocol specified criteria and if a central laboratory result was not available.

Two definitions of SARS-CoV-2 related cases, and SARS-CoV-2 related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

Confirmed COVID-19 (defined for FDA guidance): presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):

- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste or smell;
- Sore throat;
- Diarrhoea;
- Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC:

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.

Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥ 30 breaths per minute, HR ≥ 125 beats per minute, SpO₂ $\leq 93\%$ on room air at sea level, or PaO₂/FiO₂ < 300 mm Hg);

- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death.

In addition, evidence of prior infection was determined by virological testing via NAAT on mid-turbinate swab and serological testing for IgG to the SARS-CoV-2 N-antigen. A serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result.

In addition, prior infection with SARS-CoV-2 was assessed also at Dose 2 (NAAT) and is being evaluated for up to 24 months. The purpose is to assess persistence of efficacy, explore efficacy against asymptomatic SARS-CoV-2 infections, and ensure safety in both seronegative and seropositive participants.

Sample size

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being non-evaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

Randomisation and Blinding (masking)

Allocation of participants to vaccine groups were performed through the use of an IRT system (IWR). Participants were randomised 1:1 to active vaccine or placebo.

The trial included participants ≥ 12 years of age, stratified as follows: 12 to 15, 16 to 55 years or >56 years. It was intended that a minimum of 40% of participants were to be enrolled in the >56-year stratum.

The study staff receiving, storing, dispensing, preparing, and administering the study interventions were unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, were blinded to study intervention assignments.

Exceptions to blinding for e.g. DMC activities were described and found acceptable.

Efficacy Analysis Methods

During Phase 2/3, interim analyses were pre-specified in the protocol to be conducted after accrual of at least 62, 92, and 120 evaluable COVID-19 cases, where overwhelming efficacy could be declared if the primary endpoint was met with a posterior probability that the true VE is >30% (i.e., $\Pr[VE > 30\% | \text{data}] > 99.5\%$ at an interim analysis or $> 98.6\%$ at the final analysis). The success threshold for each interim analysis was calibrated to protect overall type I error at 2.5%. Futility was also assessed, and the study could be stopped for lack of benefit if the predicted probability of demonstrating vaccine efficacy at the final analysis was <5% at any of the first 2 planned interim analyses. Efficacy and futility boundaries were applied in a nonbinding way. The calculation of posterior probability and the credible interval were adjusted for surveillance time. For subgroup analyses of the primary efficacy endpoint, a 2-sided 95% confidence interval (CI) was calculated. VE is defined as $100\% \times (1 - \text{IRR})$, where illness rate ratio (IRR) is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. VE is demonstrated if there is convincing evidence (i.e., posterior probability greater than 99.5% at an interim analysis or greater than 98.6% at the final analysis) that the true VE of BNT162b2 is >30% using a beta-binomial model, where VE represents efficacy for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of prior SARS-CoV-2 infection before and during the vaccination regimen. Participants with positive or unknown NAAT results at any illness visit prior to 7 days after Dose 2 were not included in the evaluation for VE. Cases were counted from 7 days after Dose 2.

The interim analysis was performed for the first primary efficacy endpoint only. Other efficacy data analysed for the interim analysis were summarized with descriptive summary statistics, including COVID-19 case counts in the BNT162b2 and placebo groups on the basis of:

- evidence of prior SARS-CoV-2 infection at baseline per NAAT or N-antigen binding assay
- subgroup status (i.e., age, sex, race, ethnicity baseline SARS-CoV-2 status)
- COVID-19 cases meeting protocol criteria as severe after the first and second doses.

Overwhelming efficacy success criteria were met at the first interim analysis, so further formal interim analyses would not be conducted. The final analysis of all protocol specified primary and secondary efficacy endpoints was pre-specified in the protocol to be conducted after accrual of the final number of COVID-19 cases (at least 164 cases). Subgroup analyses of VE were performed for the primary endpoints and secondary endpoint of severe COVID-19 cases. Additional post hoc analyses of subgroups defined by comorbidity risk assessment were performed. Secondary efficacy was analysed in the same manner as primary efficacy (Section 2.5.4.1.2.2), using the cases definitions for severe COVID-19 and CDC criteria for COVID-19.

Statistical methods

The estimands to evaluate the efficacy objectives were based on evaluable populations for efficacy. These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE was also analysed by all-available efficacy population.

The evaluable efficacy population included all eligible randomized participants who received all vaccination(s) as randomized, with Dose 2 received within the predefined window (19-42 days after Dose 1), and had no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2. This was the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy populations, including all randomized participants who completed 1 and 2 vaccination doses respectively, were also performed.

The two primary endpoints were tested hierarchically. Key secondary efficacy endpoints were evaluated sequentially in a prespecified order after the primary endpoints were met. Missing data were not imputed for the primary or secondary analyses. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with MNAR assumption.

VE was estimated as follows: $100 \times (1 - \text{IRR})$, where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose.

A Bayesian approach was used for the primary and secondary endpoints. A beta prior, beta (0.700102, 1), was used for $\theta = (1-\text{VE})/(2-\text{VE})$. The prior was centred at $\theta = 0.4118$ (VE=30%). The 95% interval for θ is (0.005, 0.964) and the corresponding prior 95% interval for VE is (-26.2, 0.995). The Bayesian approach was not used for the point estimate for VE. At final analysis, efficacy was to be declared if the posterior probability of VE greater than or equal to 30% ("p") > 98.60%.

During Phase 2/3, 4 interim analyses (IAs) were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. The final analysis was to be performed when 164 cases were observed. However, only one interim analysis was performed, at 94 cases. The final analysis was performed with 170 cases. At the time of the IAs, futility and VE with respect to the first primary endpoint were planned to be assessed. The IA that was performed was successful, as was the final analysis, and results were consistent with the IA.

The success threshold for each interim analysis was to be calibrated to protect overall type I error at 2.5%. The risk of falsely concluding the VE to be above 30% (the type I error rate) with the proposed Bayesian model and over the interim analyses and final analysis under assumption of 30% vaccine efficacy is 0.021 (one sided). Hence the type I error rate for the primary endpoint is controlled. Although only one interim analysis was performed, the overall Type I error (overall probability of success when true VE=30%) was controlled at 0.025 with the originally proposed success/futility boundaries.

Although Bayesian analysis are not usually accepted as confirmatory evidence in pivotal trials, the magnitude of the effect in this study, makes this concern redundant. Hence, the conclusions of the inference are considered robust.

Results

Disposition of All Randomised Subjects – ~38000 Subjects for Phase 2/3 Analysis

	Vaccine Group (as Randomized)		Total (N ^a =37796) n ^b (%)
	BNT162b2 (30 µg) (N ^a =18904) n ^b (%)	Placebo (N ^a =18892) n ^b (%)	
Randomized	18904 (100.0)	18892 (100.0)	37796 (100.0)
Not vaccinated	46 (0.2)	43 (0.2)	89 (0.2)
Vaccinated			
Dose 1	18858 (99.8)	18849 (99.8)	37707 (99.8)
Dose 2	18555 (98.2)	18533 (98.1)	37088 (98.1)
Completed 1-month post-Dose 2 visit (vaccination period)	16902 (89.4)	16804 (88.9)	33706 (89.2)
Discontinued from vaccination period but continue in the study	121 (0.6)	111 (0.6)	232 (0.6)
Discontinued after Dose 1 and before Dose 2	121 (0.6)	107 (0.6)	228 (0.6)

Discontinued after Dose 2 and before 1-month post-Dose 2 visit	0	4 (0.0)	4 (0.0)
Reason for discontinuation from vaccination period			
No longer meets eligibility criteria	48 (0.3)	81 (0.4)	129 (0.3)
Withdrawal by subject	45 (0.2)	9 (0.0)	54 (0.1)
Adverse event	20 (0.1)	12 (0.1)	32 (0.1)
Pregnancy	4 (0.0)	4 (0.0)	8 (0.0)
Physician decision	2 (0.0)	1 (0.0)	3 (0.0)
Lost to follow-up	0	2 (0.0)	2 (0.0)
Medication error without associated adverse event	0	1 (0.0)	1 (0.0)
Other	2 (0.0)	1 (0.0)	3 (0.0)
Withdrawn from the study	180 (1.0)	259 (1.4)	439 (1.2)
Withdrawn after Dose 1 and before Dose 2	132 (0.7)	164 (0.9)	296 (0.8)
Withdrawn after Dose 2 and before 1-month post-Dose 2 visit	44 (0.2)	84 (0.4)	128 (0.3)
Withdrawn after 1-month post-Dose 2 visit	4 (0.0)	11 (0.1)	15 (0.0)
Reason for withdrawal from the study			
Withdrawal by subject	84 (0.4)	157 (0.8)	241 (0.6)
Lost to follow-up	80 (0.4)	86 (0.5)	166 (0.4)
Adverse event	8 (0.0)	5 (0.0)	13 (0.0)
Death	2 (0.0)	3 (0.0)	5 (0.0)
Physician decision	1 (0.0)	2 (0.0)	3 (0.0)
No longer meets eligibility criteria	1 (0.0)	2 (0.0)	3 (0.0)
Medication error without associated adverse event	1 (0.0)	0	1 (0.0)
Refused further study procedures	0	1 (0.0)	1 (0.0)
Other	3 (0.0)	3 (0.0)	6 (0.0)

Note : 1 subject was randomised but did not sign informed consent and is not included in any analysis population

Note: because of a dosing error, 2 subjects received an additional dose of BNT162b2 (30µg) and one dose of placebo

Note: HIV-positive subjects are included in this summary but not included in the analysis of the overall study objectives.

a. N=number of randomised subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations

b. n=number of subjects with the specific characteristics

Recruitment

This study is ongoing, and participants are continuing to be enrolled and evaluated in Phase 3.

Subject First Visit: 29 April 2020

Data Cut-off dates:

- 24 August 2020 (Phase 1 safety and immunogenicity data through 1 month after Dose 2)
- 02 September 2020 (Phase 2 safety data 7 days after Dose 2 only)
- 06 October 2020 (Phase 2/3 safety data 1 month after Dose 2 for the first 6610 participants, and available safety data for all 36,855 participants)
- 04 November 2020 (Phase 2/3 first interim analysis for efficacy at 94 cases)

As a result, 44,822 subjects have been enrolled and 43,386 subjects have been randomised at 153 centres, in 6 countries worldwide, including: United States (131 centres, 33,068 subjects), Argentina (1 site, 5,776 subjects), Brazil (2 sites, 2,900 subjects), Turkey (9 sites, 342 subjects), South Africa (4 sites, 800 subjects) and Germany (6 sites, 500 subjects).

Conduct of the study

This study has gone through extensive changes or amendments. The amendments of the phase 1 of the study are deemed acceptable for a dose-finding design. Protocol amendments concerning the phase 3 of the study are overall adequately motivated and acceptable, since they are not expected to affect the conclusions on efficacy. Main Amendments have allowed to include adolescents from 12 to 15 years in the study and added corresponding objectives. Furthermore, secondary efficacy endpoints to include COVID-19 cases that occurred from 14 days after the second dose were added. The SAP was amended twice in line with protocol amendments.

Baseline data

Overall, demographic characteristics were well balanced between study groups.

Demographics (population for the primary efficacy endpoint)^a

	Comirnaty (N=18,242) n (%)	Placebo (N=18,379) n (%)
Sex		
Male	9318 (51.1)	9225 (50.2)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥12 through 15 years	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
75 through 85 years	799 (4.4)	807 (4.4)
>85 years	5 (0.0)	5 (0.0)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other ^b	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities^c		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

- All eligible randomised participants who receive all vaccination(s) as randomised within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
- Includes multiracial and not reported.

- c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
- Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
 - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
 - Obesity (body mass index ≥ 30 kg/m²)
 - Diabetes (Type 1, Type 2 or gestational)
 - Liver disease
 - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

Baseline comorbidities - safety population 38,000 subjects- at final analysis:

Table 3. Baseline Charlson Comorbidities ~ 3800 Subjects for Phase 2/3 Analysis – Safety Population

Charlson Comorbidity Index Category	Vaccine Group (as Administered)		Total (N ^a =37706) n ^b (%)
	BNT162b2 (30 µg) (N ^a =18860) n ^b (%)	Placebo (N ^a =18846) n ^b (%)	
Subjects with any Charlson comorbidity	3934 (20.9)	3809 (20.2)	7743 (20.5)
AIDS/HIV	59 (0.3)	62 (0.3)	121 (0.3)
Any Malignancy	733 (3.9)	662 (3.5)	1395 (3.7)
Cerebrovascular Disease	195 (1.0)	166 (0.9)	361 (1.0)
Chronic Pulmonary Disease	1478 (7.8)	1453 (7.7)	2931 (7.8)
Congestive Heart Failure	88 (0.5)	83 (0.4)	171 (0.5)
Dementia	7 (0.0)	11 (0.1)	18 (0.0)
Diabetes With Chronic Complication	99 (0.5)	113 (0.6)	212 (0.6)
Diabetes Without Chronic Complication	1473 (7.8)	1478 (7.8)	2951 (7.8)
Hemiplegia or Paraplegia	13 (0.1)	21 (0.1)	34 (0.1)
Leukemia	12 (0.1)	10 (0.1)	22 (0.1)
Lymphoma	22 (0.1)	32 (0.2)	54 (0.1)
Metastatic Solid Tumor	4 (0.0)	3 (0.0)	7 (0.0)
Mild Liver Disease	125 (0.7)	89 (0.5)	214 (0.6)
Moderate or Severe Liver Disease	1 (0.0)	2 (0.0)	3 (0.0)
Myocardial Infarction	194 (1.0)	188 (1.0)	382 (1.0)
Peptic Ulcer Disease	52 (0.3)	71 (0.4)	123 (0.3)
Peripheral Vascular Disease	124 (0.7)	117 (0.6)	241 (0.6)
Renal Disease	123 (0.7)	133 (0.7)	256 (0.7)
Rheumatic Disease	62 (0.3)	56 (0.3)	118 (0.3)

Note: MedDRA (v23.1) coding dictionary applied.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic. Subjects with multiple occurrences within each category are counted only once. For 'Subjects with any Charlson comorbidity', n = number of subjects reporting at least 1 occurrence of any Charlson comorbidity.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:04) Source Data: admh Table Generation: 17NOV2020 (16:21)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2_unblinded/C4591001_IA_P3_2MPD2/admh_s002_risk_p3_saf

The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease

not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

Numbers analysed

The disposition of the efficacy populations is described in the Table below. There was an imbalance between the two study groups on the number of subjects excluded from the evaluable efficacy population. The two reasons responsible for this imbalance were "Dosing/administration error, subject did not receive correct dose of vaccine" (n=105 in vaccines and n=3 in placebo) and "IP administered that was deemed not suitable for use by Almac" (n=144 in vaccines and n=0 in placebo). There may be several explanations for this imbalance as listed below:

- As the placebo was a fixed volume of saline, with no dilution required, the likelihood of a dosing error in the placebo group was lower compared to vaccine, which did required dilution.
- An isolated dosing/administrative error event in one clinical centre affecting a higher number of participants receiving BNT162b2 (n=52 participants) has contributed to this imbalance.
- Almac was responsible for determining suitability for use of investigational product that was subject to a temperature excursion. Due to the differences in the required storage conditions (ambient for the placebo versus ultracold for the BNT162b2), temperature excursions were not an issue for the placebo but were for BNT162b2.

The protocol design was such that, if a participant experienced any of the specified trigger symptoms that could indicate COVID-19, a potential COVID-19 illness visit should occur, including obtaining a swab for the central laboratory.

Table 4 Efficacy Populations

	Vaccine Group (as Randomized)		
	BNT162b2 (30 µg) n ^a (%)	Placebo n ^a (%)	Total n ^a (%)
Randomized ^b	21823 (100.0)	21828 (100.0)	43651 (100.0)
Dose 1 all-available efficacy population	21768 (99.7)	21783 (99.8)	43551 (99.8)
Subjects without evidence of infection before Dose 1	20314 (93.1)	20296 (93.0)	40610 (93.0)
Subjects excluded from Dose 1 all-available efficacy population	55 (0.3)	45 (0.2)	100 (0.2)
Reason for exclusion ^c			

Did not receive at least 1 vaccination	54 (0.2)	45 (0.2)	99 (0.2)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Dose 2 all-available efficacy population	20566 (94.2)	20536 (94.1)	41102 (94.2)
Subjects without evidence of infection prior to 7 days after Dose 2	18701 (85.7)	18627 (85.3)	37328 (85.5)
Subjects without evidence of infection prior to 14 days after Dose 2	18678 (85.6)	18563 (85.0)	37241 (85.3)
Subjects excluded from Dose 2 all-available efficacy population	1257 (5.8)	1292 (5.9)	2549 (5.8)
Reason for exclusion ^c			
Did not receive 2 vaccinations	1256 (5.8)	1292 (5.9)	2548 (5.8)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Evaluable efficacy (7 days) population	20033 (91.8)	20244 (92.7)	40277 (92.3)
Subjects without evidence of infection prior to 7 days after Dose 2	18242 (83.6)	18379 (84.2)	36621 (83.9)
Evaluable efficacy (14 days) population	20033 (91.8)	20243 (92.7)	40276 (92.3)
Subjects without evidence of infection prior to 14 days after Dose 2	18219 (83.5)	18315 (83.9)	36534 (83.7)
Subjects excluded from evaluable efficacy (7 days) population	1790 (8.2)	1584 (7.3)	3374 (7.7)
Subjects excluded from evaluable efficacy (14 days) population	1790 (8.2)	1585 (7.3)	3375 (7.7)
Reason for exclusion ^c			
Randomized but did not meet all eligibility criteria	36 (0.2)	26 (0.1)	62 (0.1)
Did not provide informed consent	1 (0.0)	0	1 (0.0)
Did not receive all vaccinations as randomized or did not receive Dose 2	1550 (7.1)	1561 (7.2)	3111 (7.1)
within the predefined window (19-42 days after Dose 1)			
Had other important protocol deviations on or prior to 7 days after Dose 2	311 (1.4)	60 (0.3)	371 (0.8)
Had other important protocol deviations on or prior to 14 days after Dose 2	311 (1.4)	61 (0.3)	372 (0.9)
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.			
a. n = Number of subjects with the specified characteristic.			
b. These values are the denominators for the percentage calculations.			
c. Subjects may have been excluded for more than 1 reason.			

Outcomes and estimation

Primary Efficacy Endpoints – Final Analysis

The result for the first primary efficacy analysis is shown in Table 5. VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%, with 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 95.2%, with 8 and 165 cases in the BNT162b2 and placebo group.

Table 5 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Efficacy Endpoint	Vaccine Group (as Randomized)						Pr (VE >30% data) ^f
	BNT162b2 (30 µg) (N ^a =18198)		Placebo (N ^a =18325)		VE (%)	(95% CI ^e)	
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)			
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SARS-CoV-2 =severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of subjects in the specified group.

b. n1 = Number of subjects meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of subjects at risk for the endpoint.

e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details

For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with or without evidence of prior SARS-CoV-2 infection through 7 days after Dose 2. Cases were counted from 7 days after Dose 2 (Table 6). VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 94.6%, with 9 and 169 cases in the BNT162b2 and placebo groups respectively.

The vaccine efficacy of BNT162b2 for the same primary efficacy endpoint based on the Dose 2 all-available efficacy population was 94.8%, with and 9 and 172 cases in the BNT162b2 and placebo group, respectively.

Table 6 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Efficacy Endpoint	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N ^a =19965)		Placebo (N ^a =20172)		VE (%)	(95% CI) ^e	Pr (VE >30% data) ^f
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)			
First COVID-19 occurrence from 7 days after Dose 2	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.9, 97.3)	>0.9999

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

However the seropositive subjects were not many: among 38,000 subjects there were 407 individuals seropositive in the vaccine group and 436 in the placebo group in the age strata 16-55 YOA, and 150 individual seropositive in the vaccine group and 152 in the placebo group in the >55 YOA age strata.

All Confirmed Cases of COVID-19 After Dose 1

An analysis of the cases occurring from dose 1 and until dose 2 or 1 week after dose 2 provides information on onset of protection.

All reports of COVID-19 with onset at any time after Dose 1 are accounted for in Table 7, which provides a summary of cases for all participants in the Dose 1 all-available efficacy (modified intention-to-treat) population, regardless of evidence of infection before or during the vaccination regimen. Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group (Table 7). Notably, in the BNT162b2 group, most cases occurred before Dose 2.

Figure 9 displays cumulative incidence for the first COVID-19 occurrence after Dose 1 among all vaccinated participants based on Dose 1 all-available efficacy (modified intention-to-treat) population. Disease onset appears to track together for BNT162b2 and placebo until approximately 14 days after Dose 1, at which point the curves diverge, with cases steadily accumulating in the placebo group, while remaining virtually flat in the BNT162b2 group. From table 7 and figure 9 it is evident that the first dose offers partial protection, while few cases occur after the second dose.

Table 7 Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All- Available Efficacy Population

Efficacy Endpoint Subgroup	Vaccine Group (as Randomized)		Placebo Group (as Randomized)		VE (%)	(95% CI ^e)
	BNT162b2 (30 µg) (N ^a =21669)	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b		
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
≥10 days after Dose 1 to before Dose 2	6		45		86.7	(68.6, 95.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

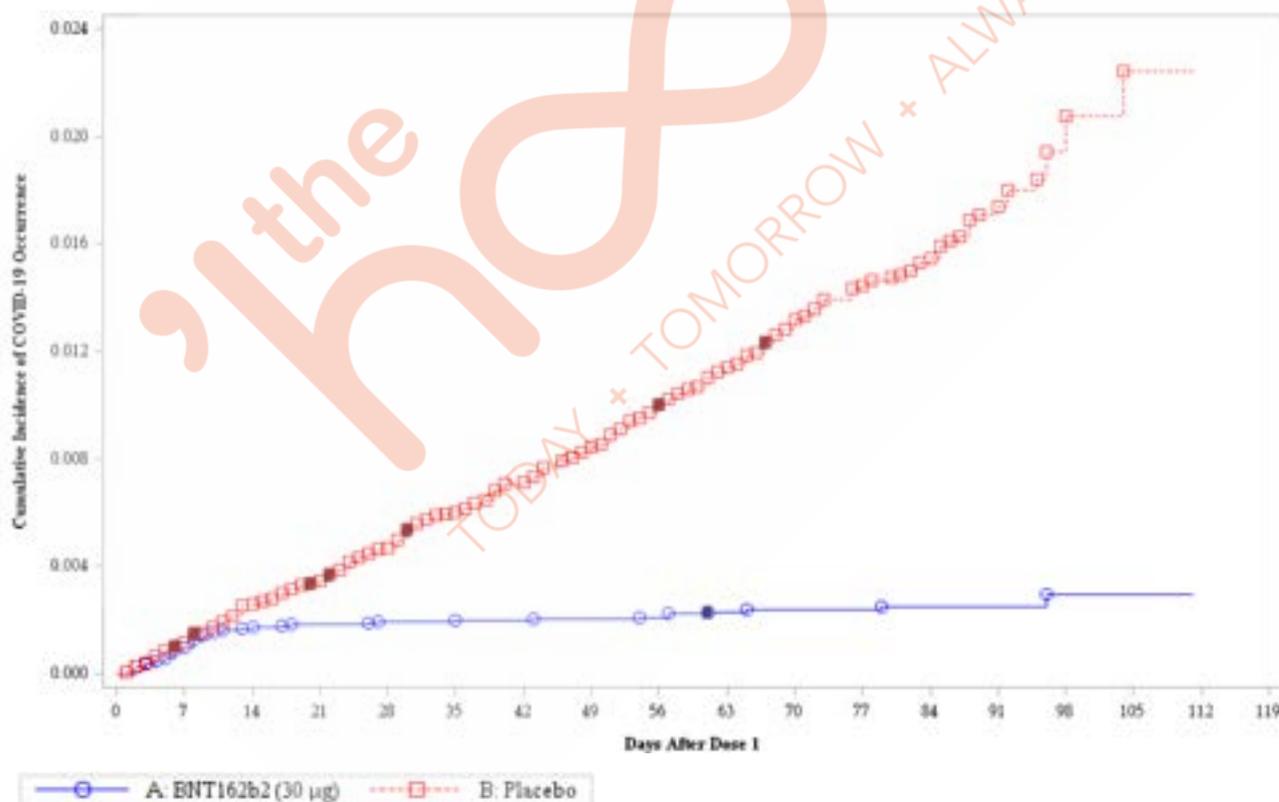


Figure 9. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All- Available Efficacy Population

Immunogenicity results

The immunogenicity part of study C4591001 are presented in this section and aimed to confirm the conclusions on safety and immunogenicity from phase 1. These are the only immunogenicity results from a larger study population available at this stage, and further results from phase 3 are expected post approval. In addition, any data generated in attempts to establish a serological correlate of protection are expected to be reported when available.

The results of the immunogenicity analyses here reported are generated from the Dose 2 evaluable immunogenicity population; baseline positive participants (by N-binding antibody or positive NAAT at Visit 1) were not excluded from these analyses.

SARS-CoV-2 Neutralizing Titres and S1-Binding IgG Concentrations GMTs/GMCs

At 1 month after Dose 2 (Day 52) of BNT162b2, there were substantial increases in SARS-CoV-2 50% neutralizing GMTs (Figure 10) and S1-binding IgG concentrations (GMCs) (Figure 11). GMTs/GMCs were higher in younger participants (18 to 55 years of age) than in older participants (56 to 85 years of age). Similar trends were observed for the SARS-CoV-2 90% neutralizing GMTs (data not shown in this report).

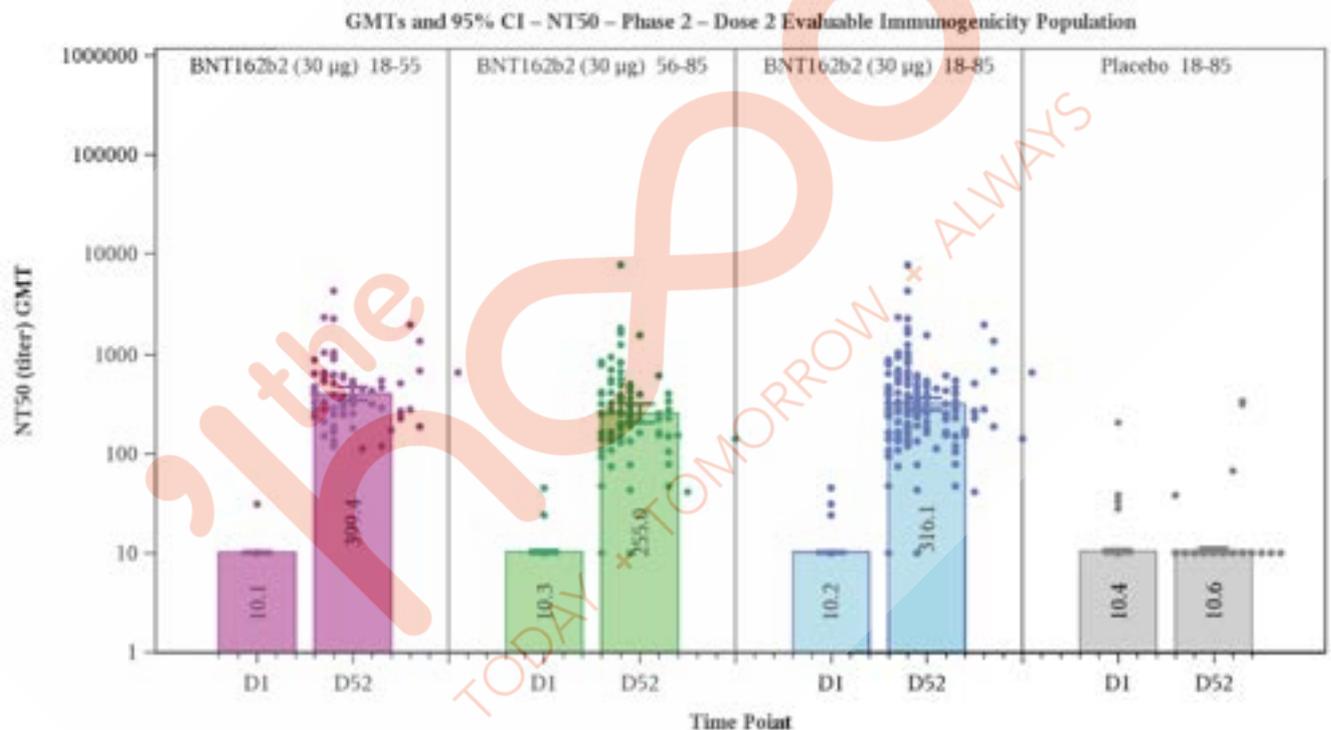


Figure 10. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay – NT50 – Phase 2 – Dose 2 Evaluable Immunogenicity Population

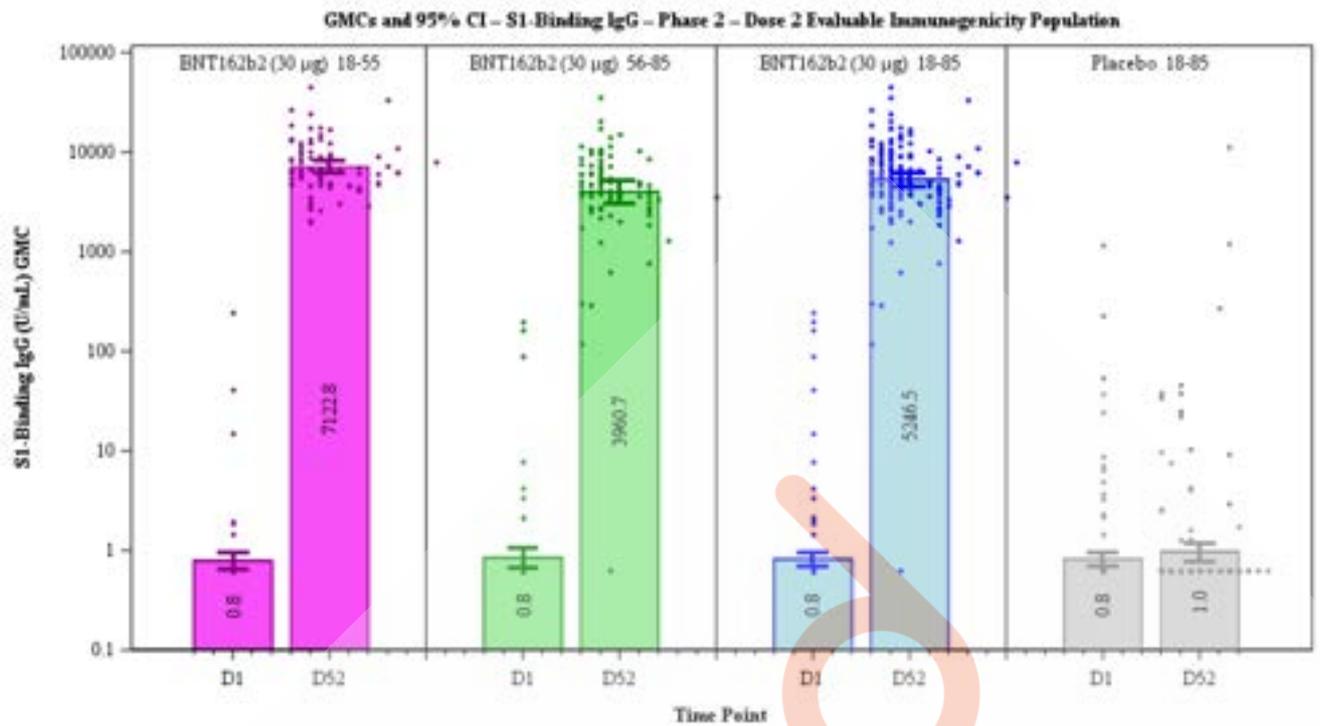


Figure 11. Geometric Mean Concentrations and 95% CI: S1-Binding IgG Level Assay - Phase 2 Dose 2 Evaluable Immunogenicity Population

A few participants in the Dose 2 evaluable immunogenicity population had a positive baseline SARS-CoV-2 status. These SARS-CoV-2 status positive participants were analysed separately from the baseline negative participants. In general, at 1 month after Dose 2 among BNT162b2 recipients, SARS-CoV-2 50% neutralizing GMTs and S1-binding IgG GMCs in participants with a positive baseline SARS-CoV-2 status (n=3) were numerically higher than those observed in participants with a negative baseline SARS-CoV-2 status (n=163).

Ancillary analyses

Vaccine Efficacy by Subgroup

For both primary endpoints, VE was also evaluated for subgroups of participants by age, sex, race/ethnicity, and country, without evidence of prior infection (Table 8). Results for additional age groups are shown in Table 9.

Post hoc analyses of efficacy by risk status were performed. For these analyses, at-risk participants were defined as those who had at least one Charlson Comorbidity Index condition or who were obese (defined as BMI ≥ 30 kg/m²) (table 11). Results for the all-available population were similar; no clinically meaningful differences were observed in VE on the basis of subgroup.

These subgroup analyses are considered of importance. There is no evidence of significantly reduced efficacy in older age groups, i.e. >90% vaccine efficacy even in over 75-year-old subjects, although not statistically significant as there were only few cases in this age stratum. There were no cases in the 16-17-year-old age stratum, but efficacy is not anticipated to be lower in younger age groups compared to the overall study population. Additionally, it is reassuring that other factors, e.g. ethnicity/race, gender did not impact efficacy. Efficacy was not demonstrated in subjects who were

seropositive at baseline, but the subgroup was very small and results are considered inconclusive rather than negative at this stage.

Table 8 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	Vaccine Group (as Randomized)				VE (%)	(95% CI ^e)
	BNT162b2 (30 µg) (N ^a =18198)		Placebo (N ^a =18325)			
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)		
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
16 to 55	5	1.234 (9897)	114	1.239 (9955)	95.6	(89.4, 98.6)
>55	3	0.980 (7500)	48	0.983 (7543)	93.7	(80.6, 98.8)
≥65	1	0.508 (3848)	19	0.511 (3880)	94.7	(66.7, 99.9)
Sex						
Male	3	1.124 (8875)	81	1.108 (8762)	96.4	(88.9, 99.3)
Female	5	1.090 (8536)	81	1.114 (8749)	93.7	(84.7, 98.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
All others ^f	1	0.160 (1405)	9	0.155 (1355)	89.3	(22.6, 99.8)
Ethnicity						
Hispanic/Latino	3	0.605 (4764)	53	0.600 (4746)	94.4	(82.7, 98.9)
Non-Hispanic/non-Latino	5	1.596 (12548)	109	1.608 (12661)	95.4	(88.9, 98.5)
Country						
Argentina	1	0.351 (2545)	35	0.346 (2521)	97.2	(83.3, 99.9)
Brazil	1	0.119 (1129)	8	0.117 (1121)	87.7	(8.1, 99.7)
USA	6	1.732 (13359)	119	1.747 (13506)	94.9	(88.6, 98.2)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = number of subjects in the specified group.
- n1 = Number of subjects meeting the endpoint definition.
- Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of subjects at risk for the endpoint.
- Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.
- All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

Table 9 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Subgroup – Subjects With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N ^a =19965)		Placebo (N ^a =20172)		VE (%)	(95% CI ^e)
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)		
First COVID-19 occurrence from 7 days after Dose 2						
Overall	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.6, 97.6)
Age group (years)						
16 to 55	6	1.309 (10653)	120	1.317 (10738)	95.0	(88.7, 98.2)
>55	3	1.022 (7892)	49	1.028 (7956)	93.8	(80.9, 98.8)
≥65	1	0.530 (4044)	19	0.532 (4067)	94.7	(66.8, 99.9)
Sex						
Male	4	1.183 (9457)	85	1.170 (9342)	95.3	(87.6, 98.8)
Female	5	1.149 (9102)	84	1.176 (9366)	93.9	(85.2, 98.1)
Race						
White	7	1.975 (15294)	153	1.990 (15473)	95.4	(90.3, 98.2)
Black or African American	0	0.187 (1758)	7	0.188 (1758)	100.0	(30.4, 100.0)
All others ^f	2	0.170 (1507)	9	0.167 (1477)	78.2	(-5.4, 97.7)
Ethnicity						
Hispanic/Latino	3	0.637 (5074)	55	0.638 (5090)	94.5	(83.2, 98.9)
Non-Hispanic/non-Latino	6	1.681 (13380)	114	1.693 (13509)	94.7	(88.1, 98.1)
Country						
Argentina	1	0.366 (2664)	36	0.367 (2684)	97.2	(83.5, 99.9)
Brazil	2	0.134 (1274)	8	0.132 (1257)	75.4	(-23.5, 97.5)
USA	6	1.816 (14141)	124	1.830 (14287)	95.1	(89.1, 98.2)
South Africa	0	0.015 (362)	1	0.015 (363)	100.0	(-3818.9, 100.0)
Prior SARS-CoV-2 Status						
Positive at baseline ^g	1	0.056 (526)	1	0.060 (567)	-7.1	(-8309.9, 98.6)
Negative at baseline but positive prior to 7 days after Dose 2 ^h	0	0.003 (27)	1	0.004 (34)	100.0	(-6004.9, 100.0)
Negative prior to 7 days after Dose 2 ⁱ	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Unknown	0	0.059 (595)	5	0.060 (596)	100.0	(-9.6, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; VE= vaccine efficacy.

a. N = number of subjects in the specified group.

b. n1 = Number of subjects meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of subjects at risk for the endpoint.

e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

f. All others = American Indian or Alaska native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported race categories.

g. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.

h. Negative N-binding antibody result and negative NAAT result at Visit 1, positive NAAT result at Visit 2 or at unscheduled visit, if any, prior to 7 days after Dose 2.

i. Negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1 and Visit 2, and negative NAAT result at unscheduled visit, if any, prior to 7 days after Dose 2.

Table 10 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Requested Subgroup – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N ^a =18198)		Placebo (N ^a =18325)		VE (%)	(95% CI ^e)
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)		
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Age group (years)						
12 to 15	0	0.000 (14)	0	0.000 (13)	NE	(NE, NE)
16 to 17	0	0.002 (52)	0	0.003 (55)	NE	(NE, NE)
18 to 64	7	1.703 (13497)	143	1.708 (13563)	95.1	(89.6, 98.1)
65 to 74	1	0.406 (3074)	14	0.406 (3095)	92.9	(53.1, 99.8)
≥75	0	0.102 (774)	5	0.106 (785)	100.0	(-13.1, 100.0)
Race						
White	7	1.889 (14504)	146	1.903 (14670)	95.2	(89.8, 98.1)
Black or African American	0	0.165 (1502)	7	0.164 (1486)	100.0	(31.2, 100.0)
American Indian or Alaska native	0	0.011 (100)	1	0.010 (96)	100.0	(-3429.0, 100.0)
Asian	1	0.092 (764)	4	0.093 (769)	74.6	(-156.6, 99.5)
Native Hawaiian or other Pacific Islander	0	0.006 (46)	1	0.003 (29)	100.0	(-2266.9, 100.0)
Multiracial	0	0.042 (414)	1	0.036 (359)	100.0	(-3231.3, 100.0)
Not reported	0	0.010 (81)	2	0.012 (102)	100.0	(-563.3, 100.0)

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of subjects in the specified group.

b. n1 = Number of subjects meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of subjects at risk for the endpoint.

e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.

Table 11 Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Risk Status – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Efficacy Endpoint Subgroup	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N ^a =18198)			Placebo (N ^a =18325)		
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)	VE (%)	(95% CI ^e)
First COVID-19 occurrence from 7 days after Dose 2						
Overall	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
At risk ^f						
Yes	4	1.025 (8030)	86	1.025 (8029)	95.3	(87.7, 98.8)
No	4	1.189 (9381)	76	1.197 (9482)	94.7	(85.9, 98.6)
Age group (years) and at risk						
16-64 and not at risk	4	0.962 (7671)	69	0.964 (7701)	94.2	(84.4, 98.5)
16-64 and at risk	3	0.744 (5878)	74	0.746 (5917)	95.9	(87.6, 99.2)
≥65 and not at risk	0	0.227 (1701)	7	0.233 (1771)	100.0	(29.0, 100.0)
≥65 and at risk	1	0.281 (2147)	12	0.279 (2109)	91.7	(44.2, 99.8)
Obese ^g						
Yes	3	0.763 (6000)	67	0.782 (6103)	95.4	(86.0, 99.1)
No	5	1.451 (11406)	95	1.439 (11404)	94.8	(87.4, 98.3)
Age group (years) and obese						
16-64 and not obese	4	1.107 (8811)	83	1.101 (8825)	95.2	(87.3, 98.7)
16-64 and obese	3	0.598 (4734)	60	0.609 (4789)	94.9	(84.4, 99.0)
≥65 and not obese	1	0.343 (2582)	12	0.338 (2567)	91.8	(44.5, 99.8)
≥65 and obese	0	0.165 (1265)	7	0.173 (1313)	100.0	(27.1, 100.0)
Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.						
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.						
a. N = number of subjects in the specified group.						
b. n1 = Number of subjects meeting the endpoint definition.						
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.						
d. n2 = Number of subjects at risk for the endpoint.						
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted for surveillance time.						
f. At risk is defined as having at least one of the Charlson Comorbidity Index (CMI) category or obesity (BMI ≥30 kg/m ²).						
g. Obese is defined as BMI ≥30 kg/m ² .						

Vaccine efficacy by different age subgroup is shown below in line with the information included in the SmPC.

Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection and participants with or without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	COVID-19 mRNA Vaccine N^a=18,198 Cases n1^b Surveillance time^c (n2^d)	Placebo N^a=18,325 Cases n1^b Surveillance time^c (n2^d)	Vaccine efficacy % (95% CI)^f
All subjects ^e	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

- N = number of participants in the specified group.
- n1 = Number of participants meeting the endpoint definition.
- Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- n2 = Number of subjects at risk for the endpoint.
- No confirmed cases were identified in participants 12 to 15 years of age.
- Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Vaccine efficacy for Severe COVID-19 cases, Final analysis

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, the estimated VE against severe COVID-19 occurring at least 7 days after Dose 2 was 66.4%, with 1 and 3 cases in the BNT162b2 and placebo groups respectively (Table 12). The posterior probability for the true vaccine efficacy greater than 30% is 74.29%, which did not meet the prespecified success criterion of >98.6% for this endpoint due to the small number of severe cases observed after Dose 2 in the study.

Consequently, statistical testing of subsequent secondary endpoints (i.e., the additional secondary endpoints related to severe disease with pre-specified control of overall type 1 error) ended. However, descriptive summaries for the additional endpoints were provided.

Table 12 Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

Efficacy Endpoint	Vaccine Group (as Randomized)				VE (%)	(95% CI ^e)	Pr (VE >30% data) ^f
	BNT162b2 (30 µg) (N ^a =18198)		Placebo (N ^a =18325)				
	n1 ^b	Surveillance Time ^c (n2 ^d)	n1 ^b	Surveillance Time ^c (n2 ^d)			
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
 Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of subjects in the specified group.
 b. n1 = Number of subjects meeting the endpoint definition.
 c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
 d. n2 = Number of subjects at risk for the endpoint.
 e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
 f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial C4591001

Title: A Phase 1/2/3, Placebo-Controlled, Randomized, Observer- Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals				
Study identifier	C4591001			
Design	Phase 1/2/3 randomized, observer-blind, placebo-controlled			
	<table border="1"> <tr> <td>Follow-up for efficacy</td> <td>Until nov 14, 2020</td> </tr> <tr> <td>Follow-up for safety</td> <td>At least 1 month, median 2 months</td> </tr> </table>	Follow-up for efficacy	Until nov 14, 2020	Follow-up for safety
Follow-up for efficacy	Until nov 14, 2020			
Follow-up for safety	At least 1 month, median 2 months			
Hypothesis	Superiority of vaccine vs placebo for vaccine efficacy			
Treatments groups	Active arm BNT162b2 (30 µg), 2 doses, 21 days apart, randomized 22 000			

	Control arm		Saline placebo, 2 doses, 21 days apart, randomized 22 000
Endpoints and definitions	First Primary endpoint	VE-7d-no-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥ 7 days after Dose 2
	Second Primary endpoint	VE-7d-no/yes-SARS-Cov-2	COVID-19 incidence per 1000 person-years of follow-up in participants with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥ 7 days after Dose 2.
	Secondary Endpoint	VE-14d-no/yes-SARS-Cov-2	COVID-19 confirmed at least 14 days after Dose 2: COVID-19 incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed ≥ 14 days after Dose 2
	Secondary Endpoint	VE-7d/14d-no-no/yes-SARS-Cov-2-Severe	Severe COVID-19: incidence per 1000 person-years of follow-up in participants either (1) without or (2) with and without evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed either (1) ≥ 7 days after Dose 2 or (2) ≥ 14 days after Dose 2
Database lock	November 14, 2020		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population	Per protocol, Evaluable Efficacy population		
<p>Effect estimate per comparison</p> <p>VE=100x (1- IRR)</p> <p>IRR= caseN/groupN</p> <p>Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.,</p> <p>Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time.</p>	Primary endpoint	VE-7d-no-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=8/18198 Cases in Placebo arm N=162/18325
		Vaccine Efficacy VE %	95.0
		95% Credible Interval	90.3, 97.6
		Pr (VE >30% data)	>0.9999
	Co-Primary	VE-7d-no/yes-SARS-CoV-2 Evaluable Efficacy population	Cases in Active arm N=9/18559 Cases in Placebo arm N=169/18708
		Vaccine Efficacy VE %	94.6
		95% Credible Interval	89.9, 97.3

		Pr (VE >30% data)	>0.9999
	Secondary endpoint	VE-14d-no- SARS-CoV-2	Cases in Active arm N=8/18175 Cases in Placebo arm N=139/18261
		Vaccine Efficacy VE %	94.2
		95% Credible Interval	88.7, 97.2
		Pr (VE >30% data)	>0.9999
	Secondary endpoint	VE-14d-no/yes-SARS-CoV-2	Cases in Active arm N=8/19965 Cases in Placebo arm N=144/20171
		Vaccine Efficacy VE %	94.4
		95% Credible Interval	89.1, 97.3
		Pr (VE >30% data)	>0.9999
	Secondary endpoint	VE-7d-no-SARS-CoV-2-Severe	Cases in Active arm N=1/18198 Cases in Placebo arm N= 3/18325
		Vaccine Efficacy VE %	66.4
		95% Credible Interval	-124.8, 96.3
		Pr (VE >30% data)	0.7429
Notes	Subgroup analyses support the overall results, e.g. elderly and patients with risk factors appear to be protected as well.		

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the selected vaccine BNT162b2 was investigated in one pivotal trial, BNT162-02 study. This is a phase 1/2/3, multicentre, multinational, randomized, placebo-controlled, observer blind, dose finding, vaccine candidate efficacy and safety study in subjects that are healthy or have clinically stable comorbidities. Safety and immunogenicity data generated during the phase 1 portion of this study supported the selection of BNT162b2 at 30 µg, as a prime/boost regimen (separated by 21 days) as the vaccine candidate to proceed into Phase 2/3.

Phase 2/3 was designed to evaluate the efficacy of BNT162b2, and to provide additional safety and immunogenicity data in a larger population. The study design for the pivotal phase 3 study is overall acceptable and in line with applicable guidelines. In the Phase 2/3 portion, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo separated by 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for

up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. It is an observer-blind study, which is considered acceptable as placebo and vaccine differed in appearance. Randomisation and blinding were considered acceptable.

Overall inclusion and exclusion criteria are acceptable and the study population is considered representative of the target population for vaccination, including subjects at higher risk of severe disease, i.e. age above 65 years (>20% with no upper age limit) and relevant underlying diseases (46%, e.g. obesity, chronic pulmonary diseases, diabetes, hypertension, and cardiovascular disease). Immunocompromised subjects and pregnant or breastfeeding women were excluded from the study. Subjects with known stable infection with HIV, HBV, HCV could be enrolled. Further, individuals who had previous clinical or microbiological diagnosis of COVID-19 were excluded, since the natural infection would affect the immunogenicity of the vaccine.

The study mainly recruited in the USA, but other sites worldwide were also included.

The primary endpoint (laboratory confirmed symptomatic COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection up to 7 days after receipt of the second dose, and then in all participants regardless of serostatus) is considered relevant for the purpose of establishing vaccine efficacy.

SARS-CoV-2 genomic RNA has been detected in nasal swab samples using Cepheid Xpert Xpress SARS-CoV-2 PCR assay on the GeneXpert Molecular Diagnostic System. This method detects 2 structural genes of SARS-CoV-2: E and N2. A validation of this method was performed, and in addition the test was issued a EUA by FDA. In order to assess the analytical detection limit, live virus and commercial control (AccuPlex™ SARS-CoV-2) were used. Clinical sensitivity and specificity were evaluated in comparison with results obtained using another FDA authorised real-time RT-PCR method with positive or negative clinical specimens and pre-pandemic samples. Results showed that Cepheid Xpert Xpress PCR assay is a sensitive and specific method for the detection of SARS-CoV-2 RNA in nasal swabs. The positive rate of self-swab is similar to site-swab, 3.7% and 4.7% positive from self-swab and site-swab respectively in the BNT162b2 group.

The third main secondary endpoint evaluated vaccine efficacy against severe cases of the disease (defined as confirmed COVID-19 with the presence of at least one of pre-defined severity criteria), to determine whether the vaccine decreased the incidence of confirmed severe COVID-19 in participants with no serological or virological evidence of past SARS-CoV-2 infection, 7 to 14 days after the second dose. Prevention of severe disease is an important endpoint, but the relative rarity of severe cases would require either a very large study population and/or a very long study duration to be certain to achieve sufficient statistical power. Therefore, it is acceptable as a secondary endpoint.

The immunogenicity secondary and exploratory endpoints are considered acceptable.

This is an event-driven study. This case-driven approach is deemed appropriate as the rate of accumulation of cases was not certain which could allow a rapid assessment of efficacy in case of a high attack rate. With assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. The randomisation procedure is considered appropriate to control confounding factors.

The statistical methods are overall acceptable. The Bayesian approach used is not expected to affect the decisions from the hypothesis testing procedure. For consistency and ease of interpretation, the Clopper Pearson confidence intervals will be included in the SmPC rather than the Bayesian credible intervals. Of the four pre-planned interim analyses only one was performed, and the final analysis was also submitted. These analyses give highly consistent results with VE far from the null hypothesis limit

of 30%. Confidence intervals were not adjusted for multiplicity, which is considered acceptable in this context.

While it could be argued that alpha could be allocated according to a group sequential design, since no failed interim analysis has been performed, the alpha allocated to the interim analysis may be recycled to the final analysis. Hence the final analysis could have been performed at full alpha level and the coverage probability of the “naïve” confidence interval is therefore considered correct.

The interim and final analyses are conducted in an evaluable efficacy population of participants who receive the two doses within the predefined window and excluding subjects with other major protocol deviation, in order to obtain a best-case estimate of vaccine efficacy. However, this approach could result in bias due to exclusion of subjects. For this reason, sensitivity analyses assessing VE based on all laboratory-confirmed cases with symptom onset at any time after the first dose (dose 1 all-available efficacy population) and 7 days after the second dose (dose 2 all-available efficacy population) have been performed without excluding participants with major protocol deviations.

Overall, the study report including the final analysis is considered adequate. This is not the final report for the study, as the study is expected to continue for a total of 24 months.

Baseline data

At the cut-off date of 14 November 2020, the disposition of the 38,000 participants were similar in the BNT162b2 and placebo groups. Overall, 0.2% of participants did not receive study vaccine. A small percentage of participants discontinued study vaccine after Dose 1 and before Dose 2 (0.6%). The reasons for discontinuation were also balanced. The most frequently reported reasons for discontinuation included: no longer meets eligibility criteria (0.3% BNT162b2; 0.4% placebo; the most common reason was previous clinical or microbiological diagnosis of COVID-19), withdrawal by participant, and AEs (0.1% in both treatment groups).

The distribution of demographics and other baseline characteristics was similar between both arms among participants without evidence of infection up to 7 days after dose 2 in the final analysis evaluable efficacy population. Overall, most participants were White (82.8%) and non-Hispanic/non-Latino (72.7%) (26.8% of Hispanic/Latino ethnicity), median age was 52.0 years, and approximately 49% were female. There were 42.6% of participants in the older age group (>50 years), 26% of participants over 65 years of age and 0.7% (112 subjects) of participants adolescents (12-17 years). In 75-85 years and >85 years age groups, 837 and 5 participants respectively had been vaccinated with BNT162b2 (Dose 2 all-available efficacy).

Across both treatment groups, 20.5% had any comorbidity (per the Charlson comorbidity index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%) and were reported at similar frequencies in each group. Obese participants made up 35.1% of the safety population. Overall, 120 subjects were HIV-positive and were evenly distributed between treatment groups.

Efficacy data and additional analyses

The population for the analysis of the primary efficacy endpoint included 36,621 participants 12 years of age and older (18,242 in the Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

The first interim analysis for vaccine efficacy (VE) was conducted on 08-Nov-2020 by an IDMC. The data cut-off date was 04-Nov-2020, when a total of 94 confirmed COVID-19 cases were accrued. There were 4 COVID-19 cases in the BNT162b2 group compared to 90 COVID-19 cases reported in the

placebo group. These data gave a vaccine efficacy of 95.5% (95%CI: 88.8%, 97.5%) among participants without evidence of infection up to 7 days after Dose 2, and a >99.99% posterior probability for the true vaccine efficacy greater than 30% conditioning on available data. Participants included in the first interim analysis were also included in the final analysis.

The date for data cut-off for the final efficacy analysis was November 14, 2020, when a total of 170 confirmed COVID-19 cases were accrued.

The protective efficacy in subjects without prior evidence of SARS-CoV-2 infection from 7 days after dose 2 was high, 95.0% (95% CI: 90.0; 97.9) in the primary efficacy population (8 cases and 162 cases in the BNT162b2 and placebo groups, respectively). The posterior probability of >99.99% for the true VE greater than 30% met the pre-specified success criterion of >98.6% for this endpoint.

Among participants without evidence of SARS-CoV-2 infection before and during vaccination regimen, VE against confirmed COVID-19 occurring at least 14 days after dose 2 was 94.2%, 95%CI (88.7%, 97.2%) (8 and 139 cases in the BNT162b2 and placebo groups respectively) with a posterior probability (VE≥30%/data) of >99.99%.

Slightly more subjects in the placebo group had symptoms of COVID-19 without being a confirmed case by PCR. This is also reflected in slightly more subjects in the placebo arm with result not available from the swab. Sensitivity analysis of missing laboratory data was performed for the primary endpoint with the available data, assuming a higher than the observed case rate when imputing missing efficacy endpoints from participants in the BNT162b2 group only, to reflect potentially unknowable missing not at random (MNAR) effects that are unfavourable for efficacy results of the study. 500 imputations were performed that were generated using SAS PROC MI Fully Conditional Specification (FCS) method. Each imputation filled in the missing laboratory results based on a logistic regression model at the subject level. VE after imputation was over 80% also with up to 15-fold increase of positivity rate applied to the BNT162b2 group. Hence, there is no concern that this slight imbalance has introduced any significant bias to the results presented below.

The 2-dose schedule is considered justified both based on immune responses and on the actual efficacy results. In dose 1 all-available efficacy (mITT) population, regardless of evidence of infection before or during the vaccination regimen, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group (n=21,314 subjects) compared to 275 cases in the placebo group (n=21,258 subjects). Notably, in the BNT162b2 group, most cases (36/(50)) occurred before Dose 2. The estimated VE against confirmed COVID-19 occurring after dose 1 was 82% (2-sided 95% CI: 75.6 %, 86.9%), with an estimated VE of 52.4% (2-sided 95% CI: 29.5%, 68.4%) against confirmed COVID-19 occurring after dose 1 but before dose 2.

The cumulative incidence curves for the first COVID-19 occurrence after dose 1 (all-available efficacy population) showed that COVID-19 disease onset seems to occur similarly for both BNT162b2 and placebo groups until approximately 14 days after Dose 1, then cumulative curves diverge with more cases accumulating in the placebo group than in the BNT162b2 group. During the follow-up time of approximately 2 months post-dose 2, the BNT162b2 cumulative curve is stable which would not suggest waning protection. A longer follow-up is necessary to investigate the duration of the efficacy of the vaccine in protecting against the disease.

For both primary endpoints, no clinically meaningful differences in VE by subgroup were observed by age group, country, ethnicity, sex, or race in the dose 2 evaluable efficacy population, with VE estimates that ranged from 91.2% to 100.0%. Efficacy was consistent across relevant subgroups.

The results in elderly are of great importance, as increasing age is an identified risk factor for severe disease and death. The results from this study are therefore reassuring suggesting a high protective efficacy in subjects ≥65 years of age (95%, 95% CI: 66.8; 99.9). There was no indication of

decreasing efficacy in subjects ≥ 75 years although the number of cases was small (0 in the vaccine group and 5 in placebo). In addition, the number of subjects >85 YOA is very limited (5 subjects) hence the impact of immunosenescence on vaccine efficacy in these very old individuals remain uncertain.

Among participants without prior evidence of SARS-CoV-2 infection before and during vaccination regimen, VE for participants at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, obese with body mass index (BMI) ≥ 30 kg/m², chronic pulmonary disease, diabetes mellitus, hypertension) was 95.3%, as compared with 94.7% for those not at risk. VE for participants ≥ 65 years of age and at risk was 91.7%, as compared with 100% for those ≥ 65 years of age and not at risk. VE was similar in obese (95.4%) and non-obese (94.8%) participants. The VE by comorbidity status are as follows: cardiovascular (VE 100.0 (-0.8, 100.0)), Chronic pulmonary disease (93.0 (54.1, 99.8)), diabetes (94.7 (66.8, 99.9)), Hypertension (95.4 (82.6, 99.5)).

Severe disease cases were uncommon in the study: 1 case in the vaccine group and 4 cases in the placebo group (one case in the all evaluable population) after 7 days post second vaccination. None of the severe cases were baseline positive for SARS-CoV-2.

In the evaluable efficacy population, subjects without evidence of prior SARS-CoV-2 infection, the estimated VE against severe COVID-19 occurring at least 7 days after dose 2 was 66.4% (95% CI: -124.8%: 96.3%). The posterior probability for the true VE greater than 30% is 74.29% (7 days) and 74.32% (14 days), which did not meet the pre-specified success criterion for this endpoint, therefore no reliable conclusion can be drawn at this stage. While data on severe COVID-19 are limited, the experience with other vaccines (rotavirus and influenza vaccines with known efficacy against mild disease but better efficacy against severe disease) coupled with the high observed vaccine efficacy observed for BNT162b2 on all COVID-19 cases in populations with any comorbidity gives reassurance that the vaccine is likely to prevent severe disease. However, a precise estimate of its protective effect is presently lacking. The final study report may include additional data to the extent that the study is continued in a randomised fashion with a placebo group.

The second primary endpoint -VE in participants with and without prior evidence of SARS-CoV-2 infection- yielded similar results as the one in the population excluding those without evidence of prior infection. However, analysis is largely driven by events in subjects without evidence of prior infection, and therefore does not provide additional information.

It is not possible to conclude on vaccine efficacy in subjects with prior COVID-19, or signs of infection with SARS-CoV2 because only a small number of subjects were found to be seropositive at baseline (approximately 550 in each vaccine and placebo group), and only 2 cases of disease were reported in this subset (1 in each group). Further data may become available as the trial proceeds, but it is unlikely that the study will be able to deliver conclusive evidence for a number of reasons (e.g. it is very likely that the number of subjects seropositive will remain limited, and that there will be a lower incidence of disease in seropositive placebo recipients compared to seronegative placebo recipients due to existing partial protection). The extent of additional protection in seropositive subjects is presently uncertain. Effectiveness studies may give us some information on this regard.

Genome sequencing of the SARS-CoV-2 strains in the BNT162b2 vaccine and placebo groups has not been performed. However, this work is planned by the Applicant.

The primary analysis of efficacy was conducted when the pre-defined number of 164 COVID-19 cases had occurred. This correspond to about 1.5 months of median follow-up time duration after completion of the full vaccination regimen. Therefore, available efficacy data are limited in term of follow-up duration, and the efficacy of the vaccine over longer-time remains unknown. Data are expected to become available post-authorisation.

Immune responses in terms of neutralising antibodies were measured in the phase 1 and 2 part of the study. Overall, the immune responses measured in the phase 1 and 2 part of the pivotal study are consistent and in line with the phase 1 study BNT162-01 results. As expected, both neutralising antibody levels and S-protein binding antibody levels were higher in the youngest age stratum compared to the older age stratum. Serum titres in vaccinated subjects were numerically higher compared to human convalescent sera, up to 1 month after dose 2. There is presently no established correlate of protection.

Very limited results by baseline serostatus were provided, but updated immunogenicity data is expected to become available.

Cell mediated immune responses were demonstrated in the phase 1 part of the study as well as in the other phase 1/2 study BNT162-01, but in a small cohort of subjects only. A clear Th1-polarised response, i.e. IFN γ /IL-2 ICS and limited IL-4 ICS was shown, which is reassuring in terms of lack of VAED.

In total 14 adolescents aged 12-15 years were included in the vaccine group and 13 in the placebo group, and 52 adolescents aged 16-17 years in the vaccine and 55 in the placebo group. Vaccine efficacy could not be estimated for these subjects as no cases of disease were reported. No immune response data are available. However extrapolation of efficacy is possible from young adults because, from an immune system perspective, adolescents do not differ from young adults, thus there are no reasons to believe that the vaccine will not be as efficacious at least in the age subgroup proposed for the current indication (>16 years).

At cut-off date (14-Nov-2020), 120 subjects HIV positive were vaccinated with BNT162b2. Immunogenicity and efficacy data are not available at this time but will be provided post-authorisation.

Additional efficacy data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.5.4. Conclusions on clinical efficacy

Excellent vaccine efficacy (preventing symptomatic COVID-19) was shown in subjects without evidence of prior SARS-Cov2 infection (VE 95.0% (95% CI: 90.3%, 97.6%), which was consistent across relevant subgroups. It is likely that the vaccine also protects against severe COVID-19, though these events were rare in the study, and statistically certain conclusion cannot be drawn. It is presently not known if the vaccine protects against asymptomatic infection, or its impact on viral transmission. The duration of protection is not known.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- The final clinical study report will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA. This will provide long-term data.

Regarding missing data to confirm efficacy in subpopulations that were not studied or whose data are limited please refer to sections 2.7 and 3.3.

2.6. Clinical safety

The candidate vaccine BNT162b2 at 30 µg given twice 21 days apart was assessed a first-in-human (FIH) study in April 2020 in Germany (BNT162-01) and a Phase 1/2/3 study (C4591001) was initiated shortly afterwards in the United States (US). Hence, the safety data base for BNT162b2 constitutes of two Phase 1 studies (BNT162-01 and C4591001) and one Phase 2/3 study still ongoing (C4591001).

The cut-off for safety data included in this assessment is 14 November 2020.

The two Phase 1 trials (BNT162-01 and C4591001) are described in previous sections. Study C4591001 was initially started as a Phase 1/2 study in the USA and was then amended to expand to a global Phase 3 study.

Phase 2/3 of Study C4591001 included subjects that were stratified into two age groups: 18-55 years and >55-85 years. The Phase 3 part however was subsequently amended (6 Sept 2020 protocol amendment) to include subjects from 16 years of age in the younger age group (and then from 12 years of age) and subjects >85 years of age in the older age group.

AEs were collected during the Phase 2/3 study from the signing of the informed consent document through and including 1 month after Dose 2 (visit no. 3). In addition, in all follow-up visits where blood samples for immunogenicity data are taken, any AEs and SAEs as appropriate occurring up to 48 hours were recorded after each visit. Immunogenicity follow-up is planned to occur during that period with visits 1-month, 6-months, 12-months and 24-months post the first vaccination. AEs are categorized by frequency, maximum severity, seriousness, and relationship to study intervention using SOC and PT according to MedDRA. SAEs are recorded for up to 6 months after Dose 2 (ongoing at the time of this submission). In addition, any potential COVID-19 illness will lead to extra visits followed by convalescent visits. At the cut-off date 14-Nov-20, the longest follow-up time available was 12-13 weeks after Dose 2 (N=780: N=382 BNT162b2 and N=398 placebo).

Overall the study enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up.

The assessment is based on the following safety data (cut-off date 14 Nov 2020):

- Phase 1: i) Study C4591001 (N=72 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=18); ii) Study BNT162-01 (N=60 any dose of BNT162b2; N=12 BNT162b2 30µg; placebo N=0).
- Phase 2/3 participants with a follow-up ≥ 2 months after Dose 2 (N=19,037) of either BNT162b2 (N=9531) or placebo (N=9536). This subset constitutes the core safety data set in this assessment.
- All enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of duration of follow-up. In this population, the total number of subjects 16-17 years were 283 (N=138 BNT162b; N=145 placebo) and 100 participants were 12 to 15 years of age (N=100; 49 in the BNT162b2 group and 51 in the placebo group).
- Phase 2/3 participants (N=37,706) randomised before 9 October 2020 who received BNT162b2 (N=18,860) or placebo (N=18,846). These subjects had a median follow-up time of 2 months after Dose 2 (at least 1 month after dose 2). Among these, 1,148 subjects had a positive SARS-CoV-2 baseline status (vaccinated N=558; placebo N=590).
- Reactogenicity was evaluated based on a subset of subjects in the Phase 2/3 study, i.e. 8,183 (N=4,093 BNT162b2; N=4,090 placebo), who reported on local reactions, systemic events,

and antipyretic/pain medication usage for 7 days after each dose by using an e-diary. Eight subjects aged 16-17 years were included in this subset (BNT162b2 N=5; placebo N=3).

2.6.1. Patient exposure

Distribution and Exposure were presented for the population with median follow up of 2 months and for the whole population. Of the 37,796 subjects in the group with median follow up of 2 months who were randomized in the study before 9 October 2020, 90 participants (0.2%) were excluded from the safety population (89 did not receive study intervention and 1 did not provide informed consent).

		BNT162b2 N = 18904	Placebo N = 18892
		N (%)	N (%)
Median follow up 2 months (at least one month after dose 2)	Randomized	18904 (100%)	18892 (100%)
	Vaccinated with Dose 1	18858 (99.8%)	18849 (99.8%)
	Vaccinated with Dose 2	18553 (98.1)	18534 (98.1%)
HIV positive		59	61
Follow up ≥ 2months after dose 2		9531 (50.5%)	9536 (50.6%)
Follow up ≥ 10 to < 12 weeks after dose 2		2853 (15.1%)	2809 (14.9%)
Follow up ≥ 12 to < 14 weeks after dose 2		382 (2.0%)	398 (2.1%)

For Dose 1, three participants randomized to the placebo group received BNT162b2, and two participants randomized to the BNT162b2 group received placebo. For Dose 2, four participants randomized to the placebo group received BNT162b2, and five participants randomized to the BNT162b2 group received placebo.

The majority of participants received Dose 2 between 19 to 23 days after Dose 1 in the BNT162b2 (93.1%) and placebo (92.9%) groups.

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. Note that HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition but did not have safety data available to contribute to the safety analyses at the time of the data cut-off.

In total 1145 individuals of the safety population were SARS-CoV-2 seropositive at baseline.

A high exposure rate of 99.8% to the first dose was reached in both vaccine and control arm and a small number of individuals were withdrawn after the first dose, leading to a high rate of exposure to the second dose in both study arms (98.2% and 98.1%). Reasons for withdrawals (1.0% and 1.4%, respectively) were in most cases withdrawals by the participant, or loss to follow-up.

There were no clinically meaningful differences in the safety population by age group, baseline SARS-CoV-2 status, ethnicity, race, or sex.

Table 14 Safety Population, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis

Baseline SARS-CoV-2 Status		Vaccine Group (as Administered)		
		BNT162b2 (30 µg) n ^a	Placebo n ^a	Total n ^a (%)
Positive	Randomized ^b			1148
	Vaccinated	557	588	1145 (99.7)
	Safety population	557	588	1145 (99.7)
	HIV-positive	12	8	20 (1.7)
	Excluded from safety population			3 (0.3)
	Reason for exclusion			
	Subject did not receive study vaccine			3 (0.3)
Negative	Randomized ^b			35764
	Vaccinated	17885	17858	35743 (99.9)
	Safety population	17884	17858	35742 (99.9)
	HIV-positive	43	50	93 (0.3)
	Excluded from safety population			22 (0.1)
	Reason for exclusion			
	Subject did not receive study vaccine			21 (0.1)
	Did not provide informed consent			1 (0.0)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
 Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
 Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
 a. n = Number of subjects with the specified characteristic, or the total sample.
 b. This value is the denominator for the percentage calculations.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 18NOV2020 (07:27)
 (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
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The disposition, exposure and withdrawal profile of the whole study population was comparable to the group that was randomised before 9 October 2020 with median follow up of 2 months.

Among the 37,706 subjects with a median follow-up of 2 months, 50.6% had ≥ 2 months duration of follow-up after Dose 2 and 91.6% had a duration of follow-up time of ≥ 1 month after Dose 2. Around 3000 individuals have already a follow of at least 10 weeks after dose 2. Updates, including additional safety data as well as assessment of the differences in safety profile in the longer follow-up compared to the initial safety dataset, if any, shall be provided when more mature data will be available.

Six-months post Dose 2 follow-up data from the first ~6000 subjects are expected by the end of February 2021 and this will allow a relevant discussion on the safety profile versus the initial dataset.

Based on the population with a median follow up of 2 months, demographic characteristics are considered well balanced between vaccine and placebo arm. Most included subjects were white (83%), with a median age of 52 years. A balanced distribution is seen regarding gender (51% male, 49%

female). The younger and older age groups were 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Of note, 35% of individuals were obese in both study arms. Across both treatment groups, 20.7% had any comorbidity.

The number of subjects with any Charlson co-morbidity diagnoses was balanced in both study arms (20%). Most prevalent were the diagnoses diabetes mellitus (7.8%) and COPD (7.8%) followed by subjects showing any type of malignant disease (3.9% in vaccine and 3.5% in placebo group). Other diagnoses were abundant with $\leq 1\%$ in both study arms (population with a median follow up of 2 months). In the population with a follow-up ≥ 2 months, Charlson co-morbidity diagnoses was similar.

The demographic distribution was somewhat different when comparing seropositive and seronegative individuals, observing a median age of 43 years in seropositive and of 52 years in seronegative individuals. Furthermore, the seropositive group covered a higher proportion of obese individuals (42.2% versus 34.7%). Demographic characteristics in the whole population were comparable to those seen in the population with a median follow up time of 2 months.

2.6.2. Reactogenicity

Reactogenicity was evaluated in a subset of the Phase 2/3 study of 8,183 subjects (BNT162b2 n=4093; placebo n=4090) from both age groups (16 to 55 and >55 years of age) that received BNT162b2 or vaccine according to the proposed dosing regimen. Of note, the number of subjects aged 16-17 years included in this subset was limited (n=8; BNT162b2 n=5; placebo n=3). After each dose, the subjects reported any local reactions, systemic events, including antipyretic/pain medication usage for 7 days, by using an e-diary (cut-off date 14 Nov 20).

Local reactions

The most commonly reported local reaction among the subject that received BNT162b2 was pain at the injection site, which occurred slightly more common among subjects 16-55 years (N=2291 [83.1%] post Dose 1; N=2098 [77.8%] post Dose 2) compared to those >55 years of age (N=1802 [71.1%] post Dose 1; N=1660 [66.1%] post Dose 2). In the placebo group, pain at the injection site after Doses 1 and 2 was reported at a lower frequency (16-55 [14.0% and 11.7%]; >55 [9.3% vs 7.7%]).

There was no difference in frequency of redness and swelling at injection site after the two doses of BNT162b2. Redness occurred in about 5-7% in both age groups (16-55 [4.5% after Dose 1, 5.9% after Dose 2]; >55 [4.7% after Dose 1, 7.2% after Dose 2]). Swelling was reported also in about 5-7% of the subjects in both age groups (16-55 [5.8% after Dose 1, 6.3% after Dose 2]; >55 [6.5% after Dose 1, 7.5% after Dose 2]). In the placebo group, redness and swelling were reported infrequently in both age groups ($\leq 1.2\%$).

Overall, the majority of local reactions were mild or moderate in severity, no Grade 4 reactions were reported. Severe local reactions ($\leq 0.7\%$) were reported infrequently in the BNT162b2 group after either dose and was more commonly reported in the younger group. Across age groups, local reactions for the BNT162b2 group after either dose had a median onset between 1-3 days (Day 1 was the day of vaccination), with a median duration of 1-2 days.

No clinically meaningful differences in local reactions were observed by baseline SARS-CoV-2 status subgroups. However, since the baseline SARS-CoV-2 positive subgroup included very few participants (vaccinated n=154; placebo n=164), these results should be interpreted with caution.

Systemic reactions

Table 15 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group 16-55 Years – Reactogenicity Subset for Phase 2/3 Analysis– Safety Population

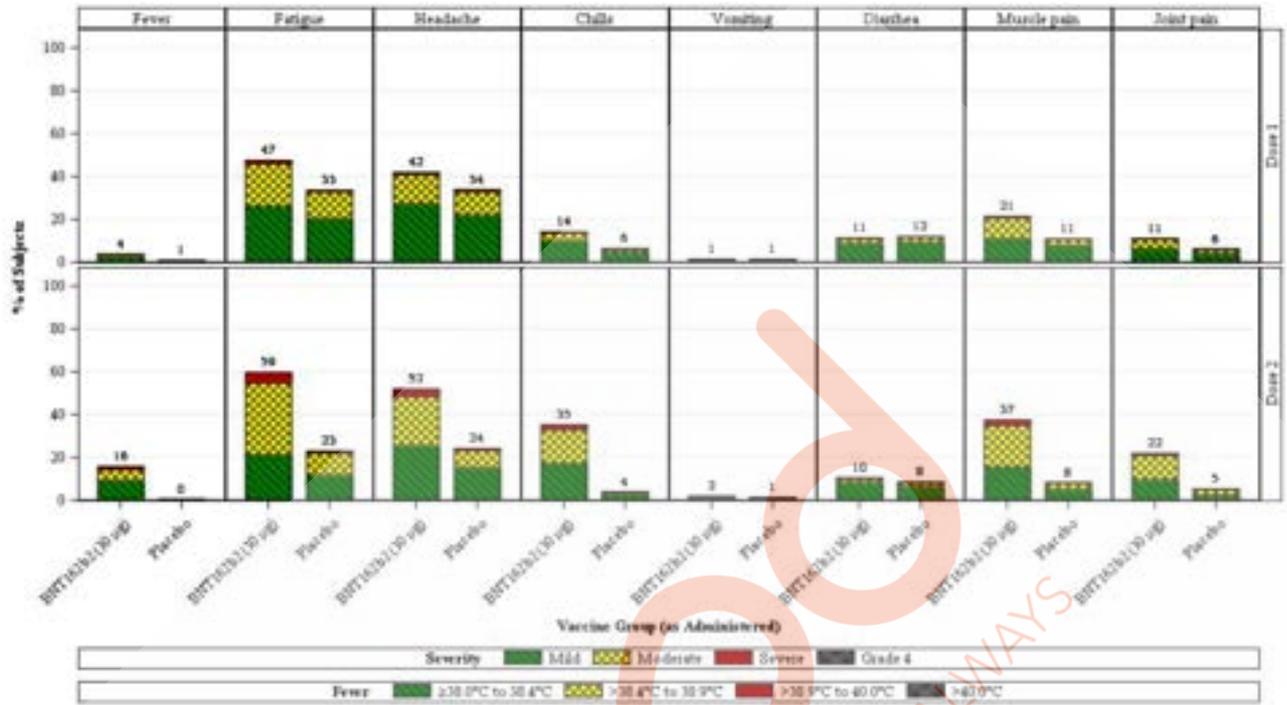
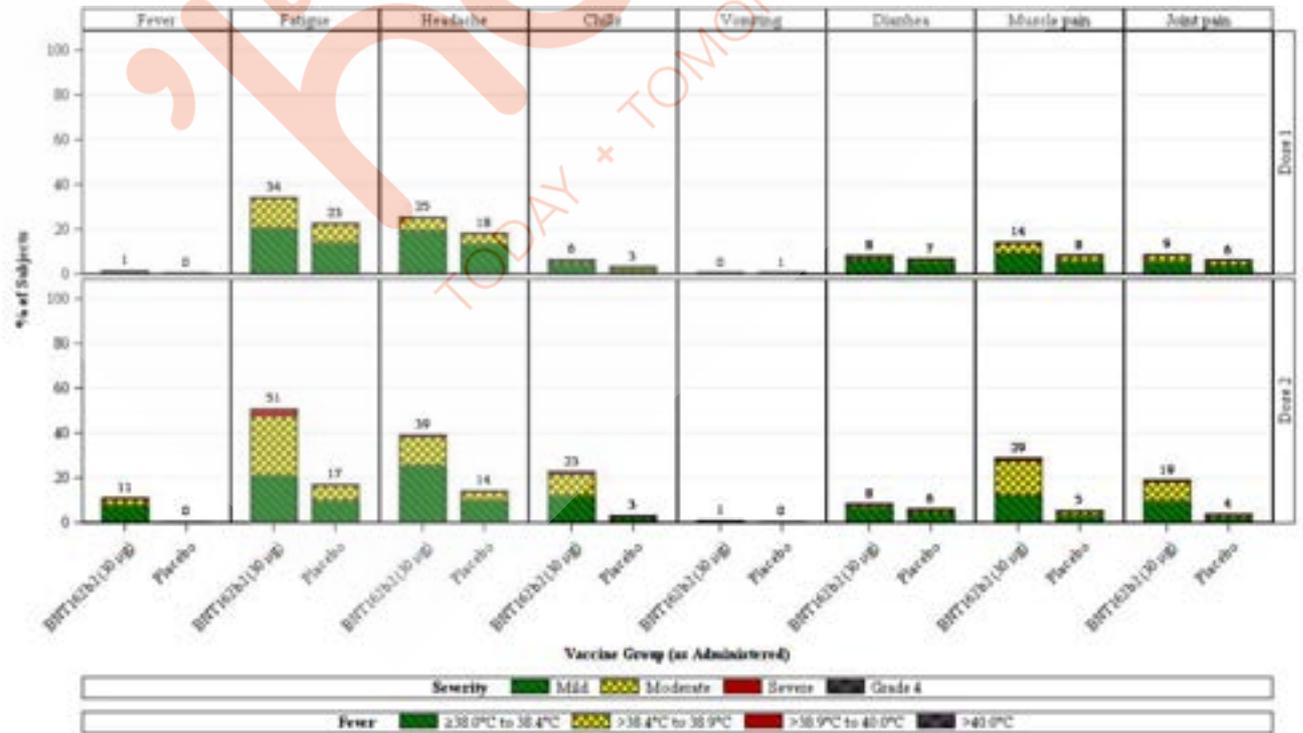


Table 16 Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group >55 Years – Reactogenicity Subset for Phase 2/3 Analysis–Safety Population



Systemic events were generally reported more frequently in the BNT162b2 group than in the placebo group, for both age groups and doses. Across age groups, median onset day for all systemic events after either dose of BNT162b2 was 2-3 days, with a median duration of 1 day.

Systemic events were generally increased in frequency and severity in the younger age group compared with the older age group, with frequencies and severity increasing with number of doses (Dose 1 vs Dose 2). Vomiting and diarrhoea were exceptions, with vomiting reported similarly infrequently in both age groups and diarrhoea reported at similar incidences after each dose. Systemic events in the younger group compared with the older group, with frequencies increasing with number of doses (Dose 1 vs Dose 2), were: fatigue, headache, muscle pain, chills, joint pain and, fever.

Following both Dose 1 and Dose 2, use of antipyretic/pain medication was slightly less frequent in the older age group (19.9% vs 37.7%) than in the younger age group (27.8% vs 45.0%). Of note, medication use increased in both age groups after Dose 2 as compared with after Dose 1. Use of antipyretic/pain medication was less frequent in the placebo group than in the BNT162b2 group and was similar after Dose 1 and Dose 2 in the younger and older placebo groups (ranging from 9.8% to 22.0%).

No clinically meaningful differences in systemic reactions were observed by baseline SARS-CoV-2 status subgroups, however as mentioned data in baseline SARS-CoV-2 positive subjects are limited.

Overall, the reported reactogenicity is in line with what can be expected from any vaccine. The local and systemic reactions were transient and of short duration, the majority were mild to moderate at intensity and the reactions were milder among older subjects (>55 years).

2.6.3. Adverse events

In the subset of participants randomised before 9 October 2020 with Median 2 Months of Follow-Up After Dose 2 (N= 37,586; from Dose 1 to 1 month after dose 2) and the subset of participants with at least 2 Months of Follow-Up After Dose 2 (N=19,067; from dose 1 to data cut off 14 November 2020), the numbers of overall participants who reported at least 1 AE and at least 1 related AE were higher in the BNT162b2 group as compared with the placebo group. This trend continued to be seen through the data cut-off date for all enrolled participants (N=43,252; from dose 1 to data cut-off 14 November 2020). Overall, AEs reported from Dose 1 to 7 days after Dose 1 and from Dose 2 to 7 days after Dose 2 were largely attributable to reactogenicity events (see above). This observation provides a reasonable explanation for the greater rates of AEs observed overall in the BNT162b2 group (26.7%) compared with the placebo group (12.2%).

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn because of AEs.

Table 17 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to date cutoff date (14 Nov 2020) – Subjects with 2 months follow-up time after dose 2 for Phase 2/3 Analysis – Safety Population

Adverse Event	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N*=9531) n ^b (%)	Placebo (N*=9536) n ^b (%)	Total (N*=19067) n ^b (%)
Any event	2044 (21.4)	1197 (12.6)	3241 (17.0)
Related ^c	1297 (13.6)	343 (3.6)	1640 (8.6)
Severe	105 (1.1)	69 (0.7)	174 (0.9)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any serious adverse event	57 (0.6)	53 (0.6)	110 (0.6)
Related ^c	2 (0.0)	0	2 (0.0)
Severe	32 (0.3)	33 (0.3)	65 (0.3)
Life-threatening	10 (0.1)	11 (0.1)	21 (0.1)
Any adverse event leading to withdrawal	1 (0.0)	0	1 (0.0)
Related ^c	0	0	0
Severe	0	0	0
Life-threatening	1 (0.0)	0	1 (0.0)
Death	1 (0.0)	0	1 (0.0)

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.
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Overall, in participants with 2 months follow up after dose 2, 21.4% / 12.6% (vaccine/placebo) and 13.6%/3.6% experienced at least 1 AE and 1 related AE, respectively. It is noted that the frequency of AEs and related AEs is lower compared to individuals with a median follow up of 2 months (27%/12.5% and 20.8%/5.1%).

The frequency of individuals experiencing AEs were slightly higher in the younger compared to older individuals (29.3% and 23.8% vaccine arm; 13.2% and 11.7% placebo arm). SAEs and deaths were however balanced in both study arms in both age groups.

The frequency of immediate AEs after dose 1 was low in participants with median 2 months of follow-up after Dose 2 (0.4%) and the whole population ($\leq 0.5\%$), belonging mostly to the SOC general disorders and administration site conditions, primarily injection site reactions. No participant reported an immediate allergic reaction to vaccine.

Severe AEs, SAEs, AEs leading to discontinuation, and deaths were reported by $\leq 1.1\%$, 0.6% , 0.0% , and 0.0% , i.e. low and equally distributed in both study arms. No differences vs. the whole population were seen according to age groups.

The rate of AEs and related AEs was slightly higher in the SARS-CoV-2 negative group compared to SARS-CoV-2-positive individuals. Stratification according to serostatus in the safety group median follow up 2 months reveals overall very low numbers of severe AEs, SAEs and deaths.

Table 18 Number (%) of Subjects Reporting at Least 1 Adverse Event from Dose 1 to 1 Month after Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subject for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Positive

Adverse Event	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N ^a =545) n ^b (%)	Placebo (N ^a =580) n ^b (%)
Any event	120 (22.0)	57 (9.8)
Related ^c	90 (16.5)	26 (4.5)
Severe	8 (1.5)	2 (0.3)
Life-threatening	2 (0.4)	0
Any serious adverse event	4 (0.7)	1 (0.2)
Related ^c	0	0
Severe	2 (0.4)	1 (0.2)
Life-threatening	2 (0.4)	0
Any adverse event leading to withdrawal	2 (0.4)	1 (0.2)
Related ^c	0	0
Severe	0	0
Life-threatening	1 (0.2)	0
Death	1 (0.2)	0

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.
Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.
c. Assessed by the investigator as related to investigational product.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
.nda2_unblinded/C4591001 IA P3 2MPD2/adae s091 pd2 bs p3 saf

Table 19 Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2, by Baseline SARS-CoV-2 Status - ~38000 Subjects for Phase 2/3 Analysis – Safety Population Baseline SARS-CoV-2 Status: Negative

Adverse Event	Vaccine Group (as Administered)	
	BNT162b2 (30 µg) (N ^a =17841) n ^b (%)	Placebo (N ^a =17808) n ^b (%)
Any event	4837 (27.1)	2253 (12.7)
Related ^c	3742 (21.0)	911 (5.1)
Severe	205 (1.1)	105 (0.6)
Life-threatening	16 (0.1)	20 (0.1)
Any serious adverse event	97 (0.5)	80 (0.4)
Related ^c	3 (0.0)	0
Severe	54 (0.3)	47 (0.3)
Life-threatening	16 (0.1)	19 (0.1)
Any adverse event leading to withdrawal	31 (0.2)	24 (0.1)
Related ^c	13 (0.1)	7 (0.0)
Severe	13 (0.1)	7 (0.0)
Life-threatening	1 (0.0)	4 (0.0)
Death	0	2 (0.0)

Note: Subjects whose baseline SARS-CoV-2 status cannot be determined because of missing N-binding antibody or NAAT at Visit 1 were not included in the analysis.

Note: Positive = positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19. Negative = negative N-binding antibody result at Visit 1, negative NAAT result at Visit 1, and no medical history of COVID-19.

a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.

b. n = Number of subjects reporting at least 1 occurrence of the specified event category. For "any event", n = the number of subjects reporting at least 1 occurrence of any event.

c. Assessed by the investigator as related to investigational product.

PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adae Table Generation: 17NOV2020 (16:29)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File:
./nda2_unblinded/C4591001_IA_P3_2MPD2/adae_s091_pd2_bs_p3_saf

There were 19,067 participants with at least 2 months follow-up time after Dose 2, and similar to the 37,586 participants randomised before 9 October 2020 with a median of 2 months of safety follow up after Dose 2, most AEs reported after Dose 1 up to the safety data cut-off date were reactogenicity, in SOCs of:

- general disorders and administration site conditions (11.9% BNT162b2 vs 2.9% placebo)
- musculoskeletal and connective tissue disorders (5.5% BNT162b2 vs 2.1% placebo)
- nervous system disorders (4.2% BNT162b2 vs 2.1% placebo)
- infections and infestations (1.9% BNT162b2 vs 1.6% placebo)
- gastrointestinal disorders (2.6% BNT162b2 vs 1.8% placebo).

In the younger versus older BNT162b2 age groups, AE SOCs were:

- general disorders and administration site conditions (13.1% vs 10.4%)
- musculoskeletal and connective tissue disorders (6.0% vs 4.9%)

- nervous system disorders (4.8% vs 3.5%)
- infections and infestations (1.9% vs 1.9%)
- gastrointestinal disorders (2.7% vs 2.5%)

Most often occurring events by PT comprised vaccine typical reactions such as injection site pain, fever, fatigue as well as myalgia and arthralgia. Lymphadenopathy and nausea occurred respectively in 0.4% and 0.6% more cases in the vaccine compared to placebo arm.

Related AEs belonged overall to the same SOCs as described above, i.e. general disorders and administration site conditions (3426 cases, 20.8%), musculoskeletal reactions (1148 cases, 6.1%), and nervous system disorders (979 cases, 5.2%) and occurred overall more often in the vaccine than in the placebo arm (median follow up 2 months). Severe AEs occurred more often in the vaccine arm (1.2% vs. 0.6%) in the subset with a median follow up time of 2 months, reflecting a similar SOC pattern.

The following specific observations are made based on PTs:

Numerical disbalances are observed for several hypersensitivity terms ((drug)hypersensitivity/immunisation events; 5/3 cases \geq 2 months group, 13/6 cases whole population, 6/1 cases deemed related in the whole population, 4 cases deemed severe (whole population), in the SOC immune system disorders).

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study, 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and, among those, two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. The participant who received BNT162b2 had a history of allergy to tree pollen. This participant reported Drug hypersensitivity and Urticaria on the day of Dose 1. Both AEs were of moderate severity and lasted one day. The participant did not receive Dose 2 of the vaccine. The participant who received placebo had an allergy to shellfish and iodine. This participant reported Allergy to vaccine and Pharyngeal swelling 1 day after Dose 1. Both events were of moderate severity and lasted 13 days and 10 days, respectively. This participant did not receive Dose 2 of study intervention.

In the \sim 38,000 study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine.

Four cases of facial paralysis were observed in the vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole population). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days had no previous history of Bell's palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole population)). However, none of the cases considered related to study drug treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm, which were however balanced in frequency between vaccine and placebo arm.

An imbalance in PT connected to sleep disturbances was noted in the whole population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus the placebo arm).

A slight imbalance of hyperhidrosis/night sweats was noted in the whole population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole population).

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole population).

Stratification according to age did not reveal meaningful differences in the types of AEs.

A stratification according to serostatus was performed in individuals with a follow up of at least one month (median FUP 2 months) and ≥ 2 months. Most abundant SOCs are similar to the SOCs identified in the general population with ≥ 2 months follow-up. No additional safety concerns are detected when stratifying according to serostatus.

2.6.4. Serious adverse event/deaths/other significant events

SAEs

This section presents the SAEs reported up to the data cut-off (14-nov-20).

Among the 19,067 subjects (BNT162b2 n=9531; placebo n= 9536) with ≥ 2 months of follow-up post Dose 2, small percentages of subjects in the 30 μg BNT162b2 group (56 [0.6%]) and the placebo group (53 [0.6%]) reported any SAEs. Subjects in both the BNT162b2 group and placebo group, respectively, reported SAEs at similar rates for the observed SOCs. A similar frequency was observed for the entire study population and no clinically meaningful differences in SAEs were observed by age, baseline SARS-CoV-2 status, ethnicity, race or sex subgroups.

Among all included subjects (BNT162b2 n=21720; placebo n=21728) three SAEs were reported in the SOC immune system disorders. One SAE of anaphylactic reaction (related to bee sting) and one drug hypersensitivity (related to treatment with doxycycline) was reported in the BNT162b2 group. In addition, one SAE of anaphylactic shock (related to an ant bite) was reported in the placebo group.

In the subset of individuals aged 16-17 years old, one SAE (facial bone fracture) was reported.

After the cut-off date and up to 5-Dec-20, additional 22 SAEs have been reported (blinded data).

SAEs related to study intervention

Up to the cut-off date, four of the SAEs in the BNT162b2 group and none in the placebo group were assessed by the investigator as related to study intervention. One event of lymphadenopathy and one event of shoulder injury due to incorrect administration were considered related to BNT162b2.

It is not agreed that the event of ventricular arrhythmia and the event of pain in the lower back/extremities/and radicular paraesthesia have been convincingly demonstrated to be related to study intervention, since the subjects had underlying conditions that could have caused the two SAEs, there is little biological plausibility, and the overall numbers of reported events do not allow for a causal inference.

Death

Six events of death (2 in the BNT162b2 group and 4 in the placebo group) were reported in the Phase 2/3 study up to the cut-off date of 14-Nov-20. None of the deaths were considered related to study intervention, which is agreed since other pre-existing diseases were more likely to have caused death than the vaccine. After the cut-off date and up to 5-Dec-20, one additional event of death due to aortic rupture were reported (data blinded).

2.6.5. Laboratory findings

Laboratory results are available for the two Phase 1 studies, but not for the Phase 2/3 trials. This is considered acceptable. Except for minor transient decrease in lymphocyte count observed for some of the subjects, no abnormal lab results were reported from the Phase 1 studies.

2.6.6. Safety in special populations

No clinically meaningful differences in AEs were observed by age, country (mostly Argentina, Brazil, USA), ethnicity (Hispanic/Latino, Non-Hispanic/Non-Latino), gender and race (White, Black or African American, all other races) subgroups.

Pregnancy

At the time of the data cut-off in the Phase 2/3 study (14 Nov 2020), a total of 23 participants had reported pregnancies in the safety database, including 9 participants who withdrew from the vaccination period of the study due to pregnancy. These participants are being followed for pregnancy outcomes. Thus, data on pregnancy are very limited at this stage.

Elderly

The Phase 2/3 study included >40% of subjects >55 years of age. In general, reactogenicity and AE rate were slightly lower in older compared to younger individuals (stratified according to median age 55 years). No differences in AE frequency were detected among subjects >70 years of age compared to the older age group >55 year. Thus, no specific safety concern is anticipated for the elderly.

Immunocompromised individuals

Per protocol, participants with chronic stable HIV infection were defined as HIV disease with a documented viral load <50 copies/mL and CD4 count >200 cells/mm³ within 6 months before enrolment, and on stable antiretroviral therapy for at least 6 months. Stratification by CD4 count, efficacy and immunogenicity data are not available at this time but will be provided post-authorisation.

Safety data are available for 196 participants with stable HIV infection. The most frequent AEs in the BNT162b2 group were reported in the General Disorders and Administrative Site Conditions SOC including injection site pain, pyrexia, chills, fatigue, injection site erythema, and injection site swelling.

Assessment of paediatric data on clinical safety

Paediatric individuals age 16 to 17 years of age are included in the Phase 2/3 study that constitutes the safety database in this assessment. The population of subjects aged 16-17 years are limited (n=283). No additional or new AEs were observed compared to adults).

There were no participants in the 16 to 17 years of age group with ≥ 2 months of safety follow-up at the time of the data cut-off (14 November 2020). The longest duration of follow-up in this age group, at the time of the data cut-off, was 30 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study.

The reactogenicity subset of ~ 8000 participants ($n=4093$ BNT162b2; $n=4090$ placebo) contributing e-diary data included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age ($N=100$; $n=49$ BNT162b2; $n= 51$ placebo, as recruited in the Phase 2/3 study under protocol amendment 7) include reactogenicity data (local reactions and systemic events) collected via e-diary up to the safety cut-off date of 14 November 2020. The reported adverse events were primarily reactogenicity events with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

In the reactogenicity subset including individuals aged 12-15 years and the 8 individuals aged 16-17 years, the most frequently reported systemic reaction in both treatment groups were fatigue (59.2% in the BNT162b2 group and 25.5% in the placebo group), followed by headache (57.1% BNT162b2, 43.1% placebo). Fever $\geq 38^{\circ}\text{C}$ was reported for 26.5% more participants who received BNT162b2 over placebo; two (4.1%) of these participants reported severe fever ($>38.9^{\circ}\text{C}$ to 40.0°C).

2.6.7. Safety related to drug-drug interactions and other interactions

Interaction studies with other vaccines have not been performed, which is acceptable given the need to use the vaccine in an emergency situation. The Applicant will conduct a study post-authorisation as indicated in the RMP (see section 2.7).

2.6.8. Discontinuation due to adverse events

Among all 43,448 enrolled participants included in the safety database up to the data cut-off date, few participants in the BNT162b2 group (0.2%) and in the placebo group (0.1%) were withdrawn from the study because of AEs. The results were similar to the AEs leading to withdrawal in the group randomised before 9 October 2020 with median follow up of 2 months. Among 19,067 participants with at least 2 months of follow-up time post Dose 2, 1 participant in the BNT162b2 group and no participants in the placebo group had an AE leading to withdrawal from the study.

No participants in the 16 to 17 years of age group experienced an AE leading to withdrawal. Among all 43,448 participants, no clinically meaningful differences in AEs leading to withdrawal were observed by age or other subgroups.

2.6.9. Post marketing experience

Post-marketing data are not yet available as the vaccine has not been approved in any country at the time of the data cut-off (14-Nov-20). After the cut-off date, it is noted that several countries have recently authorised the vaccine for emergency use (e.g. UK, Canada, US). Two cases of anaphylactoid reaction out of 138,000 persons vaccinated have been reported in individuals carrying Epipen after initiation of vaccination in one country, which resolved with standard therapy. One case of anaphylaxis was reported in another country (unknown denominator) in a subject without known history of

allergies, which required ICU and was then resolved. Post-marketing safety data are expected with the next monthly summary safety report.

2.6.10. Discussion on clinical safety

The safety database for BNT162b2 constitutes of two Phase 1 studies (BNT162-01³ and C4591001⁴) and one Phase 2/3 study (C4591001) which is still ongoing. The cut-off date for safety data included in this assessment is 14 November 2020.

Up to the cut-off date ~44,000 subjects had been recruited and received at least one dose of either BNT162b2 (n=21,720) or placebo (n=21,728). The core safety database of this assessment constitutes of ~19,000 participants who have been followed ≥ 2 months after the 2nd dose of BNT162b2 (n=9531) or placebo (n=9536). The Applicant has also presented data from a subset of ~38,000 subjects randomised before 9 October 2020 with a median follow-up period of 2 months after Dose 2 of BNT162b2 (n=18,860) or placebo (n=18,846).

Demographic characteristics are considered well balanced between vaccine and placebo arm (median follow up 2 months). Subjects were mostly white (83%) and had a median age of 52 years. The younger and older age groups included 57.8% and 42.2% of participants, respectively. Within each age group, most demographic characteristics were similar in the BNT162b2 and placebo groups. Gender was balanced (51% male). Of note, 35% of individuals were obese in study arms. The demographic distribution was different between seropositive and seronegative individuals, with a median age of 43 years in seropositive and of 52 years in seronegative subjects. Furthermore, the seropositive group covered a higher rate of obese individuals (42.2% versus 34.7%). Demographic characteristics in all participants were roughly comparable to those with median follow up of 2 months.

Charlson co-morbidity diagnoses were balanced in both study arms (20%). Most prevalent co-morbidities were diabetes (7.8%), COPD (7.8%) and malignant disease (3.9% in the vaccine arm and 3.5% in the placebo arm). Other diagnoses accounted for $\leq 1\%$ of subjects in both study arms (median follow up of 2 months).

In the Phase 2/3 study reactogenicity was evaluated in a subset of 8,183 subjects who received BNT162b2 (n=4093) or placebo (n=4090) according to the proposed dosing regimen. The number of subjects aged 16-17 years included in the reactogenicity subset was small (n=8; BNT162b2 n=5; placebo n=3). After each dose, all subjects were asked to report any local reactions, systemic events, and antipyretic/pain medication usage for 7 days, by using an e-diary.

Pain at the injection site was the most common local reaction reported in the vaccine group, slightly more frequently reported among subjects 16-55 years (~80%) compared to >55 years (~70%). In the placebo group 8-14% reported pain at injection site. In the vaccine group redness and swelling were overall reported at a frequency of 5-7% in both age groups (vs. placebo 0-1%). Use of antipyretic/pain medication was more common after Dose 2 than after Dose 1 in both age groups, and overall slightly lower among subjects >55 years regardless of the dose (younger group: 28% after dose 1 vs 45% after dose 2; older group: 20% vs 38%). The use of antipyretic/pain medication was less common in the placebo group (younger group: 34% after dose 1 vs 23% after dose 2; older group: 23% vs 18%).

Among the systemic reactions, headache and fatigue were the most common events, and the frequency was higher after Dose 2 compared to Dose 1 (16-55 YOA [47% vs 59%]; >55 YOA [34% vs 51%]). Fever also occurred more frequently after Dose 2 (16-55 YOA [4% vs 16%]; >55 YOA [1% vs

³ Phase I: End of study 28 days after Dose 2.

⁴ Phase I: participants enrolled in Phase1 in groups that do not proceed to Phase 2/3 (i.e. other doses than 30 μ g) may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

11%]). None of the subjects >55 YOA in the placebo group reported events of fever and 1% of the subjects aged 16-55 years reported fever after the first dose.

Overall, the local and systemic reactions were transient and of short duration (resolved within few days after vaccination), the majority were of mild to moderate intensity, and milder and of slightly lower frequency among older subjects (>55 years of age).

In the group of 19,067 participants with 2 months follow up after dose 2, 21.4% and 12.6% (vaccine vs placebo) of the subjects reported at least one AE. 13.6%/3.6% reported at least 1 related AE. Rates were lower compared to the whole enrolled trial population (26.7% (vaccine) and 12.2% (placebo)).

AEs in subjects with a follow up of at least 2 months belonged most often to the SOCs "General disorders and administration site conditions" (11.9% vs 2.9%), "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%), occurring more often in the vaccine than in the placebo arm. PTs comprised most often vaccine typical reactions, i.e. injection site pain, redness and swelling, fever, chills, fatigue, headache as well as myalgia and arthralgia and malaise. Nausea also occurred more often in the vaccine arm (79 cases, i.e. 0.8%, in vaccine vs. 21 cases, i.e. 0.2%, in placebo). Lymphadenopathy was seen in 0.4% subjects in the vaccine arm (38 cases) vs. 0% in the placebo arm (3 cases).

Severe AEs were reported by a small number of subjects ($\leq 1.1\%$) and equally distributed between the study arms. No differences were seen between age groups. Frequencies are comparable in the whole enrolled trial population and when stratifying according to serostatus.

Numerical imbalances are observed for several hypersensitivity/immunisation reaction preferred terms (5/3 cases in the ≥ 2 months follow up subset, 13/6 cases in the whole enrolled trial population subset, 4 cases deemed severe (whole enrolled trial population), in the SOC immune system disorders).

Lymphadenopathy, nausea, and hypersensitivity are reported more often with the vaccine arm. For these items there is a reasonable possibility of a causal relation to vaccination and they are as such included in the SmPC section 4.8.

Subjects were excluded from the Phase 2/3 study if they had a history of severe adverse reaction associated with a vaccine or to any component of the BNT162b2 vaccine. The protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies.

In the Phase 2/3 study 11,673 subjects had a medical history of allergic condition (n=5839 BNT162b2; n=5834 placebo), and among those two cases of allergic AEs (1 in each treatment group) occurred, which were deemed related to study treatment by the investigator. In the $\sim 38,000$ study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. There are incoming reports of anaphylactoid reactions from ongoing vaccination campaigns. A warning is included in the SmPC addressing the need of adequate emergency material in place at the vaccination site, which is common practice with any vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

Four cases of peripheral facial paralysis were observed in vaccine arm (facial paralysis [n=4 BNT162b2; n=0 placebo] facial paresis [n=0 BNT162b2; n=1 placebo] in total 4/1 whole enrolled trial population, however the case of paresis was not considered for this calculation). Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1, which suggest a possible association with the vaccination. The two subjects with a time to onset of 3 and 9 nine days

had no previous history of Bell's palsy, both subjects improved with prednisolone and the events were also deemed related to study intervention by the study physician. Taken together, this was considered to indicate there is a reasonable possibility of a causal relation to the vaccine, and to justify inclusion of peripheral facial paralysis (Bell's palsy) in the SmPC 4.8 with a frequency as 'rare'.

An imbalance in PT connected to sleep disturbances was noted in the whole enrolled trial population, which was driven by 25 more cases of insomnia-related events (insomnia/sleep disorder/abnormal dreams in the BNT162b2 group versus in the placebo arm). The occurrence of insomnia may plausibly be due to e.g. local/systemic reactogenicity that may occur after vaccination. The CHMP agreed to include insomnia in section 4.8. of the SmPC.

A slight imbalance of hyperhidrosis/night sweats was noted in the whole enrolled trial population (n=26/15 BNT162b2 group versus 8/3 in the placebo arm). Hyperhidrosis as a medical term indicates a condition that differs from the sweating associated with episodes of fever. The numerical relation here is not supported by biological plausibility.

Injection site pruritus was reported in 31 subjects in the BNT162b2 group compared to 6 subjects in the placebo arm (whole enrolled trial population). These events may be plausibly associated to the injection of BNT162b2 and should therefore be included in the SmPC section 4.8.

Pain in the extremity was reported in 183 subjects in the BNT162b2 group and in 34 subjects in the placebo group (whole enrolled trial population). In addition to pain at injection site, which was commonly reported, pain in the extremity is also considered plausibly related to the vaccination and should therefore be included in the SmPC section 4.8.

Numerical imbalances in AEs for appendicitis and biliary events are observed (8/4 and 14/5 cases (whole enrolled trial population)), however these are considered not related to study treatment.

Cases of (osteo/peri) arthritis (15/15, vaccine/placebo) and psoriasis (1/1, vaccine/placebo) have been observed in the vaccine arm. These were numerically balanced in frequency between vaccine and placebo arm. Autoimmune events will be monitored post-authorisation as described in the RMP.

SAEs occurred at a low frequency in both BNT162b2 and the placebo group (0.6%, 56 cases in vaccine vs. 53 cases in placebo) in subjects with ≥ 2 months of follow-up post Dose 2, and a similar frequency was observed in the total study population. One SAE of lymphadenopathy and one SAE of shoulder injury were considered related to study intervention. No cases of related SAEs were reported in the adolescent group (only one case of facial bone fracture). Six events of death (2 in the BNT162b2 group and 4 in the placebo group) have been reported in the entire study population, all deemed unrelated to the vaccine.

The rate of subjects discontinuing participation in the study due to AEs was low in both study arms (0.2%/0.1%).

The subgroup of seropositive subjects is limited in size (n=545 BNT162b2; n=580 Placebo). A stratification according to serostatus for AE investigation was specifically performed in individuals with a follow up of at least one month (median Follow up 2 months) and ≥ 2 months. Most reported SOCs are similar to those identified in the ≥ 2 months population. AE rate in seropositive individuals was lower (22%) compared to seronegative individuals (27%) and no specific safety concern is detected in this subpopulation.

23 participants reported pregnancies in the safety database, nine of them were withdrawn from the study due to the pregnancy status. These participants will be followed up for pregnancy outcomes.

The Applicant has not provided a specific analysis of elderly individuals > 70 years included in the development program. In general, reactogenicity and AE rate were slightly lower in older compared to

younger individuals (stratified according to median age 55 years). Thus, no specific safety concern is anticipated for the elderly.

Data on immunocompromised individuals are limited, which was raised as missing information in the RMP and will be further followed up. 196 participants with stable HIV infection were included in the trial and reported AEs that were mostly reactogenicity-related with no SAEs. No specific safety concern is detected in this subpopulation.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics as applicable.

Assessment of paediatric data on clinical safety

The longest duration of follow-up in the 16-17 years of age group, at the time of the data cut-off, was 39 days after Dose 2. The adverse event profile for this adolescent age group did not show meaningful differences vs. the young adult group (18 to 55 years of age) in the study, albeit is numerically lower (11.6%/4.8%, vaccine/placebo).

The reactogenicity subset included a total of 8 participants in the 16 to 17 years of age group (including participants in both the BNT162b2 group and the placebo group).

Available safety data for participants 12 to 15 years of age (N=100; n=49 BNT162b2; n= 51 placebo, as recruited in the Phase 2/3 study under protocol amendment 7) show reactogenicity events (local reactions and systemic events) with no serious adverse events. The local reactogenicity profile seems comparable with the young adult population, with however a higher systemic reactogenicity as compared to young adults.

Overall, the safety of BNT162b2 in individuals 16-17 years of age is extrapolated from young adults in general.

Additional safety data needed in the context of a conditional MA

The final clinical study report for study C4591001 will be submitted no later than December 2023 and is subject to a specific obligation laid down in the MA.

2.6.11. Conclusions on the clinical safety

The safety evaluation is based on one ongoing Phase 2/3 study that at the time of data cut-off (14-Nov-20) included 43,448 subjects who received either two doses of BNT162b2 30µg (n=21 720) or placebo (n=21 728). Overall, the reported reactogenicity profile are in line with any authorised vaccine. In addition, the frequency of reported AEs and SAEs were low. The emerging safety profile is presently considered favourable. Long term safety data, interaction with other vaccines, data on use in pregnancy and other subgroups (e.g. frail subjects, or subjects with pre-existing autoimmune diseases) are missing at this stage.

The lack of long-term follow up renders the data provided non-comprehensive. Therefore, the delivery of the final C4951001 study report, including a 2-year follow up of the studied population, is classified as a specific obligation in the context of a conditional marketing authorisation.

The plan for the generation of further safety data post authorisation is described in the section below.

2.7. Risk Management Plan

Safety Specification

Summary of safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use during pregnancy and while breast feeding Use in immunocompromised patients Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long term safety data

Risks considered important for inclusion of the summary of safety concerns

The review of available safety data, including post-marketing data emerging from use in the UK and US, the experience with biological products and other vaccines leads to the conclusion that anaphylaxis is an important identified risk for Comirnaty. This safety concern will be followed up via routine pharmacovigilance activities and in the planned and ongoing safety studies and reported in the monthly summary safety reports and PSURs.

Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease) should be taken into account. The Applicant has included VAED/VAERD as an important potential risk and will further investigate it in the ongoing pivotal study and a post-authorisation safety study.

Missing information

Since pregnant and breast-feeding women were excluded from the study, no information is available for those populations. It is agreed to include use during pregnancy and while breastfeeding as missing information in the RMP.

At the data cut-off of 14 Nov-20, 10-14 weeks safety data are available. Thus, long-term safety is included as missing information and will be characterised as part of the continuation of the pivotal clinical trial and the PASS.

Interaction with other vaccines, has not been evaluated in clinical trials and may be of interest to prescribers. As elderly individuals will be one target group for vaccination, and they often may need vaccination with other vaccines such as influenza and pneumococcus vaccines, further data is

requested. The Applicant commits to conduct a study of the co-administration of Comirnaty with inactivated quadrivalent influenza vaccine.

Data from use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders), is limited, and it is desirable to gather further data in these groups. Therefore, use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) has been included as missing information in the RMP. Furthermore, information is limited on the use in patients with autoimmune or inflammatory disorders, as well as in immunocompromised patients. Thus, these groups are also included as missing information. Such missing information will be collected in the post-authorisation safety studies.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine, and it is considered acceptable to not include those events in the list of safety specifications.

Pharmacovigilance Plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond the receipt and review and submission of ADRs include:

- A **web-based AE reporting portal** will be available for vaccine providers (e.g. pharmacists, nurses, physicians and others who administer vaccines) and recipients, to assist with anticipated high volume of reports (based on expectations of a large target population for vaccination). The portal will capture key adverse event data in the initial interaction and will provide automated intake into the Pfizer safety database via E2B for safety review.
- **Signal detection activities** for the lifecycle of vaccines consist of individual AE assessment at case receipt, regular aggregate review of cases for trends and statistically disproportionately reported product-adverse event pairs. Aggregated and statistical reviews of data are conducted utilizing Pfizer's software interactive tools. Safety signal evaluation requires the collection, analysis and assessment of information to evaluate potential causal associations between an event and the product and includes subsequent qualitative or quantitative characterization of the relevant safety risk to determine appropriate continued pharmacovigilance and risk mitigation actions. Signal detection activities for the COVID-19 mRNA vaccine, will occur on a weekly basis. In addition, observed versus expected analyses will be conducted as appropriate as part of routine signal management activity.
- Routine signal detection activities for the COVID-19 mRNA Vaccine will include routine and specific review of AEs consistent with the AESI list provided in the RMP.
- In addition, published **literature** will be reviewed weekly for individual case reports and broader signal detection purposes.
- Regulatory authority **safety alerts monitoring**, to detect and further investigate potential signals being raised on other areas outside of EU.
- A specific adverse reaction **follow-up questionnaire** intended to capture clinical details about the nature and severity of COVID-19 illness particularly in relation to potential cases of vaccine lack of effect or VAED.

- In addition to routine 6-monthly PSUR production, monthly summary safety reports will be compiled and submitted to EMA, to support timely and continuous benefit risk evaluations during the pandemic. Minimum data to be submitted include:
 - Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately);
 - Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women);
 - Interval and cumulative number of reports per HLT and SOC;
 - Summary of the designated medical events;
 - Reports per EU country;
 - Exposure data (including age-stratified);
 - Changes to reference safety information in the interval, and current CCDS;
 - Ongoing and closed signals in the interval;
 - AESI reports – numbers and relevant cases;
 - Fatal reports – numbers and relevant cases;
 - Risk/benefit considerations.
- The submission of monthly reports complements the submission of PSURs (requested initially every six months). The need and frequency of submission of the summary safety reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 submissions).
- Joint adverse event and product complaint (including available batch/lot information) trending reviews will be conducted routinely by the Applicant.

The proposed routine pharmacovigilance activities are considered appropriate for the safety profile of the product and the pandemic circumstances.

Traceability

Full traceability from manufacturing to vaccination administration site is crucial to ensure maintenance of the cold-chain as well as for pharmacovigilance purposes should assessment of a safety signal need to be performed by batch/lot.

The Applicant's proposal to ensure traceability include:

- SmPC 4.4 labelling to raise HCP awareness regarding the need to clearly record the name and batch of the vaccine to improve traceability;
- a tracking device on every vaccine shipping container that provides real-time monitoring of GPS location and temperature 24 hours per day, 7 days per week;
- vaccine carton labelling also containing a 2-D barcode which has the batch/lot and expiry embedded within
- additional tools for vaccinators to record manufacturer and lot/batch information at the time of vaccination including a Traceability and Vaccination Reminder Card and peel-off labels (stickers with brand name and lot/batch numbers), acknowledging that each Member State will decide if and how the tools will be used, in accordance with the national provisions for pharmacovigilance.

Each shipment to a vaccination site should be accompanied with a sufficient number of corresponding vaccinee traceability and vaccination reminder cards; the lot/batch numbers will be for the first batches distributed copied manually by the vaccinators, with the Applicant's commitment that by 31 January 2021 all batches shipped will be accompanied at the receipt point in the Member States by sufficient peel-off labels to facilitate the recording of brand name and lot/batch number both in the vaccinators' records and the vaccinee traceability and vaccination reminder cards, where the Member States will require it.

The Traceability and Vaccination Reminder will include:

- Space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine, and keep it thereafter;
- QR code that links to additional information;
- Adverse event reporting information.

Additional pharmacovigilance activities

The Applicant proposes the following 11 studies, of which 1 global, 3 in Europe only, 2 in Europe and US, and 3 in US only; the countries where 2 studies will be conducted are not available at this time. There are 6 interventional studies (C4591001, C4591015, BNT162-01 Cohort 13, C4591018, 1 study in high risk adults and 1 study addressing co-administration with another vaccine) and 5 non-Interventional studies (4 safety and 1 effectiveness):

Study (study short name, and title)	Summary of Objectives	Safety concerns addressed	Milestone	Due dates
Category 2				
C4591001 <i>Ongoing</i>	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19, in particular for severe COVID-19, may suggest the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in patients with co-morbidities (C4591001 subset) Long term safety data.	CSR submission upon regulatory request:	Any time
			CSR submission 6 months post Dose 2:	31-Dec-2021
			Final CSR submission with supplemental follow-up:	31-Aug-2023
Category 3				
C4591011	Assessment of occurrence of safety events of interest, including severe or	Anaphylaxis	Interim reports submission:	30-Jun-2021

<i>Planned</i>	atypical COVID-19 in a cohort of people within the Department of Defense Healthcare System.	<p>AESI-based safety events of interest including vaccine associated enhanced disease</p> <p>Use in pregnancy</p> <p>Use in immunocompromised patients</p> <p>Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)</p> <p>Use in patients with autoimmune or inflammatory disorders</p> <p>Long-term safety data.</p>		31-Dec-2021
				30-Jun-2022
				31-Dec-2022
			Final CSR submission:	31-Dec-2023
C4591012 <i>Planned</i>	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	<p>Anaphylaxis</p> <p>AESI-based safety events of interest including vaccine associated enhanced disease</p> <p>Use in immunocompromised patients</p> <p>Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)</p> <p>Use in patients with autoimmune or inflammatory disorders</p> <p>Long-term safety data.</p>	Interim reports submission:	30-Jun-2021
				31-Dec-2021
				30-Jun-2022
				31-Dec-2022
				31-Dec-2023
			Final CSR submission:	31-Dec-2023
C4591010 <i>Planned</i>	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine.	<p>Anaphylaxis</p> <p>AESI-based safety events of interest</p> <p>Use in pregnancy</p> <p>Long-term safety data.</p>	Final draft protocol submission for EMA review:	31-Jan-2021
			Final CSR submission:	31-Mar-2024

C4591015 <i>Planned</i>	Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine Safety and immunogenicity of COVID-19 mRNA vaccine in pregnant women	Use in pregnancy and while breast feeding.	Protocol draft submission:	28-Feb-2021
			Final CSR submission:	30-Apr-2023
C4591014 <i>Planned</i>	Estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified	-	Protocol draft submission:	31-Mar-2021
			Final CSR submission:	30-Jun-2023
BNT162-01 Cohort 13 <i>Ongoing</i>	To assess potentially protective immune responses in immunocompromised adults	Use in immunocompromised patients.	IA submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022
C4591018 <i>Planned</i>	Safety, immunogenicity over 12 months. Description of COVID-19 cases. RA activity by Clinical Disease Activity Index. N-antigen antibodies for detection of asymptomatic infection.	Use in immunocompromised patients Use in patient with autoimmune or inflammatory disorders.	Protocol submission:	28-Feb-2021
			IA submission:	31-Dec-2021
Safety and immunogenicity in high risk adults <i>Planned</i>	Safety, immunogenicity over 12 months in frail elderly, immunocompromised, autoimmune and other high-risk individuals. Description of COVID-19 cases. N-antigen antibodies for detection of asymptomatic infection.	Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders).	Protocol submission:	30-Jun-2021
			Final CSR submission:	31-Dec-2022
ACCESS/VAC4EU <i>Planned</i>	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine.	Anaphylaxis AESI-based safety events of interest including vaccine associated enhanced disease Use in pregnancy Use in immunocompromised patients Use in frail patients with co-morbidities (e.g, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders	Protocol submission:	28-Feb-2021
			Final CSR submission:	31-Jan-2024

		Long term safety data.		
Co-administration study with seasonal influenza vaccine <i>Planned</i>	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.	Interaction with other vaccines.	Protocol submission:	30-Sep-2021
			Final CSR submission:	31-Dec-2022

Non-Interventional Post Approval Safety Studies (4)

The Applicant proposes 4 complementary studies of real-world safety of COVID-19 mRNA vaccine that use multiple data sources and study designs.

Study C4591010 will be conducted in the EU using primary data collection to monitor a cohort of vaccinees and evaluate risk of safety events of interest reflecting the AESI list. A draft protocol C4591010 has been provided.

Additionally, Pfizer, on behalf of the Applicant, will sponsor one or more PASS using secondary electronic health records data sources in Europe based on a master surveillance protocol developed through the ACCESS project.

Two additional studies will be conducted using US data:

- 1 study using secondary data from EHR of active military and their families (C4591011),
- 1 study using secondary data from EHR of patients included in the Veterans Healthcare Administration system (C4591012).

The draft protocols for the proposed safety studies in the US (C4591011 and C4591012) have been provided.

Interventional studies (6)

The Applicant proposes 6 interventional studies, of which 2 are ongoing and 4 are planned.

- **Study C4591001** is an ongoing Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. At the time of the data cut-off date in Study C4591001 (14 November 2020), a total of 21,720 participants received at least one dose of the candidate vaccine.
- **Study BNT162-01 Cohort 13** is an ongoing multi-site (Germany), Phase I/II, 2-part, dose escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in 30 immunocompromised adults.
- **Study C4591015** is a planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID 19 mRNA vaccine.
- **Study C4591018** is a planned study of BNT162b2 in 100 adults receiving a stable dose of immunomodulators for the treatment of stable rheumatoid arthritis (RA), in two cohorts (50 tofacitinib, 50 TNF inhibitors). Subjects will be studied for safety, immunogenicity by neutralizing antibody titer, and evidence of asymptomatic infection by N-antigen antibodies.

- A planned **Phase II safety and immunogenicity study** (Safety and immunogenicity in high risk adults) in up to 150 immunocompromised adults (with a range of primary immunocompromising conditions and/or receiving immunocompromising treatments).
- **Co-administration study with seasonal influenza vaccine** study investigating the safety and immunogenicity of Comirnaty and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

Non-Interventional PASS in Pregnancy

The Applicant's proposed strategy to assess vaccination during pregnancy will be implemented in 2 stages. It is anticipated that initial use in pregnancy will be very limited; therefore, initially this information will derive from the 4 of the real-world safety studies (C4591010, C4591011, and ACCESS/VAC4EU), described in the preceding section. Study C4591012 is focused on patients in the Veterans Health Administration system and is not expected to capture many pregnancies given the demographics of the source population.

The findings from studies' interim analysis (where planned) will inform a strategy to assess pregnancy outcomes as vaccination in pregnancy expands. The Applicant will consider established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. The applicant's commitment and considerations are noted to evaluate pregnancy outcomes in a PASS using established EU pregnancy research recommendations such as CONSIGN (COVID-19 infectiOn aNd medicineS In pregnancy) when developing any pregnancy related study objectives. Further feasibility analyses are awaited with RMP updates post-approval.

Non-Interventional Post-Approval Effectiveness study (1)

The Applicant will conduct at least one non-interventional study (test negative design) of individuals presenting to the hospital or emergency room with symptoms of potential COVID-19 illness in a real-world setting (C4591014). The effectiveness of COVID-19 mRNA vaccine will be estimated against laboratory confirmed COVID 19 illness requiring admission to the Emergency Department (ED) or hospital where SARS-CoV-2 is identified. These studies will allow to determine the effectiveness of Pfizer's vaccine in a real-world setting and against severe disease, and in specific racial, ethnic, and age groups. The studies proposed below are under evaluation as potential commitments; studies are presented by geographical area (US and EU).

Overall conclusions on the Pharmacovigilance Plan

The proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

None proposed.

Risk minimisation measures

Routine Risk Minimisation Measures

Potential Medication Errors

The Applicant included a discussion on potential medication errors which is endorsed:

Large scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to: reconstitution and administration, vaccination scheme, storage conditions, errors associated with a multi-dose vial, and once other COVID-19 vaccines are available, confusion with other COVID-19 vaccines. These potential medication errors are mitigated through the information in the SmPC and further materials for healthcare providers which will be made available to the Member States to be integrated in the national campaign for communication, as needed.

- SmPC (section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of the COVID-19 mRNA vaccine.
- A poster with step-by-step instruction for vaccine storage, dose planning and preparation, and administration is available, which can be conspicuously displayed in settings where vaccine is to be administered for ongoing reference.
- Brochures for safe handling of the vaccine and dry ice will accompany vaccine shipments.
- Medical information call centres will be available for healthcare providers to obtain information on use of the vaccine.
- Traceability and Vaccination Reminder card will be provided with the pre-printed manufacturer name, dates of vaccination, batch/lot as a mitigation effort for potential confusion between vaccines.
- Peel-off labels with lot/batch number

These available resources will inform healthcare providers on the proper preparation and administration of the vaccine and reduce the potential for medication errors in the context of a mass vaccination campaign. Additionally, the patient information leaflet and, in those MSs where applicable, a Traceability and Vaccination Reminder card informs patients of the vaccine received so that a series is completed with the same product.

Summary of additional risk minimisation measures

None proposed.

The Applicant stated that Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. This is acceptable.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Anaphylaxis	<u>Routine risk minimisation measures:</u> SmPC sections 4.4. and 4.8. <u>Additional risk minimisation measures:</u> <u>None.</u>	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> DCA is intended to facilitate the capture of clinical details about potential anaphylactic reactions in individuals who have received the COVID-19 mRNA vaccine <u>Additional pharmacovigilance activities:</u> Studies (Final CSR Due Date): <ul style="list-style-type: none"> • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Important Potential Risks		
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	<u>Routine risk minimisation measures:</u> None. <u>Additional risk minimisation measures:</u> No risk minimisation measures.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> DCA is intended to facilitate the capture of clinical details about the nature and severity of COVID-19 illness in individuals who have received the COVID-19 mRNA vaccine and is anticipated to provide insight into potential cases of vaccine lack of effect or VAED <u>Additional pharmacovigilance activities:</u> Studies (Final CSR Due Date) <ul style="list-style-type: none"> • C4591001 (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Missing information		
Use in pregnancy and while breast feeding	<u>Routine risk minimisation measures:</u> SmPC section 4.6; PL section 2.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	<p><u>Additional risk minimisation measures:</u></p> <p>No risk minimisation measures.</p>	<p><u>Additional pharmacovigilance activities:</u></p> <p>Studies (Final CSR Due Date)</p> <ul style="list-style-type: none"> • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591015 (30-Apr-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in immunocompromised patients	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC sections 4.4 and 5.1.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No risk minimisation measures.</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>None.</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Studies (Final CSR or IA Due Date)</p> <ul style="list-style-type: none"> • BNT162-01 Cohort 13 (IA: 30-Sep-2021, CSR: 31-Dec-2022) • C4591018 (IA: 31-Dec-2021) • C4591011 (31-Dec-2023) • C4591012_(31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).
Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC section 5.1.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No risk minimisation measures.</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>None.</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>Studies (Final CSR Due Date submission)</p> <ul style="list-style-type: none"> • C4591001 subset (31-Aug-2023) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024) • Safety and immunogenicity in high risk adults (31-Dec-2022).

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with autoimmune or inflammatory disorders	<u>Routine risk minimisation measures:</u> None. <u>Additional risk minimisation measures:</u> No risk minimisation measures.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None. <u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • C4591018 (31-Dec-2021) • ACCESS/VAC4EU (31-Jan-2024).
Interaction with other vaccines	<u>Routine risk minimisation measures:</u> SmPC section 4.5. <u>Additional risk minimisation measures:</u> No risk minimisation measures.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None. <u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> • Co-administration study with seasonal influenza vaccine (31-Dec-2022).
Long term safety data	<u>Routine risk minimisation measures:</u> None. <u>Additional risk minimisation measures:</u> No risk minimisation measures.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None. <u>Additional pharmacovigilance activities:</u> Studies (Final CSR Due Date or IA CSR submission) <ul style="list-style-type: none"> • C4591001 (31-Aug-2023) • C4591010 (31-Mar-2024) • C4591011 (31-Dec-2023) • C4591012 (31-Dec-2023) • ACCESS/VAC4EU (31-Jan-2024).

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Summary of the risk management plan

The public summary of the RMP is acceptable.

Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan **version 1.0** is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. Furthermore, During the duration of the COVID-19 pandemic situation, the MAH shall submit summary safety reports submitted to EMA, including spontaneously reported data and data from compassionate use and expanded access programs. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.9.2. Labelling exemptions

The following exemptions from labelling and serialization requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the *Questions and Answers on labelling flexibilities for COVID-19 vaccines* (EMA/689080/2020 rev.1, from 16 December 2020)⁵ document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

Labelling exemptions

US packaging specific derogations (valid for December '20 and January '21)

All EU Members States (MSs), as well as Norway and Iceland, have agreed to grant a temporary

⁵ Available at https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid19-vaccines_en.pdf, last consulted on 21 December 2021.

exemption to allow the placing in the EU market of the US packaging, under the following conditions:

- a. The validity is only temporary and the MAH shall switch to the EU labelling requirements by February '21;
- b. The US pack will have included a Quick Response (QR) code which the vaccine recipient could scan and gain access to the package leaflet (PL) in his/her national language;
- c. The MAH shall supply a separate printed PL in the national language(s) of those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine.

EU packaging specific derogations (from February '21 onwards)

- a. Outer and immediate labelling will be provided in English only.

The MAH shall provide outer and immediate labelling in all EU languages by 2nd Q 2022. This exemption is justified on the deep-frozen storage/shipping requirements and the necessity to label batches ahead of time. Production of different vaccine packs in different languages will significantly reduce the supply chain efficiency. The multiple changes on packaging lines will result in significant time and capacity losses and would slow down the rapid deployment of COVID-19 vaccines. Moreover, English only labelling will better help to manage a shortage situation in one country by using immediately the supply from another country.

- b. A printed package leaflet will be provided in the national language(s) for those MSs that require so, i.e. Belgium, Bulgaria, Croatia, Czech Republic, France and Greece. All other MSs, that have granted a temporary exemption for an EN only PL, will receive 5 printed copies of the EN PL with each shipment of the vaccine. In addition, a QR code printed on the outer label and the PL will provide access to the package leaflet in the national language(s).

The MAH shall provide a printed package leaflet in all EU languages by 2nd Q 2022.

The MAH shall engage with the National Competent Authorities (other than the 6 mentioned above) to discuss and speed up the provision of PLs in the respective national language(s) of the MSs concerned. The MAH shall also contact MSs directly to agree on the exact numbers of PLs to be distributed, again in line with the published Q&A on labelling flexibilities.

- c. The Blue Box will be omitted for the initial batches. The MAH shall provide the Blue Box via a QR code at a later stage following agreement on exact timing of implementation with the National Competent Authorities in each MS.

- d. The inclusion of the EU Marketing Authorisation number in the labelling will be implemented with the switch from US packaging to EU compliant packs in February 2021.

Exemption from the obligation of serialisation

US packaging specific derogations (valid for December '20 and January '21)

- a. It is acceptable that the US pack will be placed in the EU market without serialisation according to the EU FMD requirements. Only the Global Trade Item Number (GTIN) will be common for US & EU and this will be printed on the US pack.

EU packaging specific derogations (from February until March '21)

- All EU Member States have accepted a temporary derogation from serialisation for the EU pack from February until the end of March 2021.

- The MAH shall provide two progress reports on the serialisation: a first by 1st of February '21 and a second by 1st of March '21 referring to details on the progress achieved in terms of ensuring compliance, e.g. proof of acquiring the relevant equipment, the date for the validation, the proof of contract to connect to the European Medicines Verification Organisation.

- The MAH shall provide additional mitigating measures, e.g. immediate reporting of any stolen product during the period of exemption, reporting of any counterfeit or falsified vaccine in the EU or third countries in the legal supply or internet, reconciliation of product distributed and used in the respective territory.

2.9.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- The Summary of Product Characteristics
- The Package Leaflet
- Safe Handling Guidelines for Dry Ice
- Shipping and Handling Guidelines Brochure
- Preparation and Administration Video
- Storage and Handling Video
- Returning the Thermal Shipping Container video
- How to prepare and Administer Poster
- Traceability and vaccination reminder card
- Returning the thermal Shipping Container brochure
- Dry Ice Replenishment Brochure
- Link to Adverse Event Reaction Reporting

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation (EC) No 726/2004, Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is an infectious disease caused by a newly discovered coronavirus, SARS-CoV-2, which appeared in the Wuhan province in China in 2019 and has spread world-wide during 2020 ever since, causing WHO to declare a pandemic on 11 March 2020. The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to Severe Acute Respiratory Syndrome (SARS). The pandemic is ongoing despite unprecedented efforts to control the outbreak. According to ECDC histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

As of 1 December 2020, there have been >63 million globally confirmed COVID-19 cases and >1.4 million deaths, with 191 countries/regions affected.

At the time of this marketing application submission, confirmed cases and mortality continue to rise globally. The ongoing pandemic remains a significant challenge to public health and economic stability worldwide.

Comirnaty is intended for active immunisation against SARS-CoV-2, thereby preventing COVID-19.

3.1.2. Available therapies and unmet medical need

There is currently no approved vaccine in the EU available to prevent COVID-19. Several development programs are ongoing globally and currently other applications are under evaluation by regulatory authorities worldwide. There is a very high global demand for vaccines to help contain the pandemic and decrease morbidity and mortality in at risk groups.

3.1.3. Main clinical studies

The clinical development consists of one FIH phase 1 study (BNT162-01) in younger and older adults (18-55 years and 56-85 years) comparing 4 vaccine candidates, and one pivotal clinical study, C4591001 (or BNT162-02).

The pivotal study is a phase 1/2/3 placebo-controlled, randomised, observer-blind, dose finding, multicentre study performed in the US (start date 4 May 2020), Argentina, Brazil, Turkey, Germany, and South Africa, to evaluate the safety, immunogenicity and efficacy of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 in healthy adults. The phase 1 part of the study was designed for dose evaluation of 2 vaccines: BNT162b1 and BNT162b2 in younger (18-55 years) and older (65-85 years) adults. The Phase 2 part was designed to confirm safety and immunogenicity of the selected vaccine, BNT162b2, in the first 360 subjects enrolled in the Phase 2/3 part of the study.

The Phase 2/3 part of the study was designed to enrol up to 43,998 subjects (randomised 1:1 to BNT162b2 or placebo) to receive BNT162b2 at the dose of 30 µg, given as 2 IM injections 21 day apart (within 19 to 42 days), for an efficacy assessment in addition to safety and exploratory immunogenicity assessments.

The primary endpoint was symptomatic COVID-19 incidence per 1000 person-years of follow-up based on centrally or locally confirmed nucleic acid amplification test (NAAT) in subjects without serological or virological evidence of SARS-CoV-2 infection before and during vaccination regimen (cases confirmed ≥ 7 days after Dose 2), and in subjects with and without evidence of SARS-CoV-2 infection before and during vaccination regimen. The study was event-driven, i.e. the final efficacy analysis was to be triggered by 162 cases; in practice 170 cases were reached.

3.2. Favourable effects

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9) in subjects ≥ 16 years of age without prior evidence of SARS-CoV-2 infection and 94.6% (95% CI 89.6, 97.6) in all subjects regardless of prior evidence of SARS-CoV-2 infection (primary endpoint). This outcome met the pre-specified success criteria.

Vaccine efficacy after dose 1 to before dose 2 was 52.4% (95% CI 29.5, 68.4). Vaccine efficacy from 10 days after dose 1 to before dose 2 was estimated to be 86.7% (95% CI 68.6, 95).

The efficacy analyses in the all-available efficacy population (including participants who had protocol violations), showed consistent results with those in the primary analysis population. The efficacy analyses using CDC defined symptoms to identify a COVID-19 case gave similar efficacy results as the primary endpoints.

The VE in each demographic subgroup analysed, as defined by age (including subjects > 65 years), sex, race, ethnicity, and country and in individuals with comorbidities including obesity, diabetes, hypertension and cardiopulmonary diseases was $> 90\%$. In the obese population, VE was 95.4% (CI 95% 86.0%, 99.1%).

VE among 65-74-year-olds was 92.9% (CI 95% 53.1%, 99.8%). VE among > 75 -year-olds was 100% (CI 95% -13.1%, 100.0) with 0 cases in the vaccine group and 5 cases in the placebo group. VE among > 65 years and at risk of severe COVID-19 was 91.7% (95% 44.2%, 99.8%).

Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19, but the number of cases after second dose was very low, 1 case in the vaccine group and 4 cases in placebo group. Counting cases from after dose 1, there were 1 case in the vaccine group and 9 cases in the placebo group.

Phase 1 and phase 2 immunogenicity data from both the pivotal study C4591001 and supportive study BNT162-01 have shown robust humoral responses after vaccination with 2 doses of BNT162b2 at 30 μg in both younger (18-55 years) and older adults (age groups 56-85 years and 65-85 years), and both in terms of neutralising antibodies and IgG-antigen binding antibodies. The second dose given 21 days post-dose 1 induced a marked boosting effect in both younger and older adults. Responses were generally faster and higher in younger adults than in older adults. The levels of neutralizing antibodies titres were moderate 21 days after dose 1. The peak of neutralizing antibodies titres was reached 14 days post-dose 2 in older adults versus 7 days post-dose 2 in younger adults. Immune responses were maintained up to 1-month post-dose 2 in both age groups based on available data.

Study BNT162-01 provides evidence for T cell-mediated immune response, with antigen-induced IFN γ expression demonstrating a Th1 CD4+ and CD8+ phenotype following the second dose of vaccine. For the 30 μg dose cohort vaccinated with BNT162b2, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults.

The immunogenicity results are only considered supportive at this stage, as no correlate of protection has been established. The immune responses support the need for two doses, as neutralising antibody

levels increased substantially following the second dose compared to the first dose. Cell mediated immune responses were demonstrated in very few subjects in phase 1 but confirm a Th1 dominated cytokine pattern.

3.3. Uncertainties and limitations about favourable effects

Based on the available limited data, no reliable conclusion on the efficacy of the vaccine against severe COVID-19 can be drawn from 7 days after the second dose (secondary endpoint). The estimated efficacy against severe COVID-19 occurring at least 7 days after dose 2 was 66.4%, with a large and negative lower bound CI (95% CI: -124.8%; 96.3%). Only a limited number of events occurred at the cut-off date of analysis (1 and 4 cases in the vaccine and placebo groups respectively). The posterior probability for the true vaccine efficacy $\geq 30\%$ (74.29%) did not meet the pre-specified success criterion. Consequently, the efficacy against the severe disease across subgroups, notably certain populations at high-risk of severe COVID-19 cannot be estimated (elderly and subjects with comorbidities).

Efficacy against asymptomatic infection is not available but, notwithstanding all the limitations, will be assessed through seroconversion of N-binding antibodies in BNT162b2 and placebo recipients who did not experience COVID-19.

The pivotal study was not designed to assess the effect of the vaccine against transmission of SARS-CoV-2 from subjects who would be infected after vaccination. The efficacy of the vaccine in preventing SARS-CoV-2 shedding and transmission, in particular from individuals with asymptomatic infection, can only be evaluated post-authorisation in epidemiological or specific clinical studies.

Duration of protection has currently been followed up for approximately 100 days after dose 1. Data on longer term protection are anticipated to the extent that the ongoing phase 3 study can continue as planned with a placebo group. The assessment of efficacy over a period of at least 6 months is expected to determine the need and the appropriate time of a booster dose.

There seems to be at least a partial onset of protection after the first dose, but this remains unconfirmed at this stage.

There are very limited or no data in immunocompromised subjects and in pregnant women. Efficacy in subjects aged 16-17 years is extrapolated from young adults as no cases of disease were reported in this small group at this stage.

Available data do not suffice to establish efficacy in subjects seropositive for SARS-CoV-2 at baseline, and subjects with a known history of COVID-19. However, efficacy is anticipated in this group, to the extent that they are not naturally protected against re-infection, which is presently incompletely characterised.

3.4. Unfavourable effects

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies (BNT162-01 and C4591001) that included 21,744 participants that have received at least one dose of Comirnaty.

In Study C4591001, a total of 21,720 participants 16 years of age or older received at least 1 dose of Comirnaty and a total of 21,728 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of Comirnaty.

At the time of the analysis of Study C4591001, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older. Reactogenicity was evaluated in a subset of 8183 subjects (n=4093 vaccinated; n=4090 placebo) up to 7 days after each dose.

Regarding reactogenicity, the most frequent adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%). All reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. The frequency of headache, fatigue and fever was higher after Dose 2 in both age groups.

Regarding AEs, at least one AE was reported in 21% of the vaccinated subjects and in 13% of the placebo arm. The frequency of severe AEs was low (<1%) in both study arms. The most frequently reported SOC were "General disorders and administration site conditions (11.9% vs 2.9%)", "musculoskeletal reactions" (5.5% vs 2.1%), and "nervous system disorders" (4.2% vs 2.1%). PTs comprised mainly of vaccine typical reactions such as injection site pain, headache, fever, fatigue, malaise as well as myalgia and arthralgia.

For subjects with a follow-up of ≥ 2 months, SAE were reported at a low frequency (0.5-0.6%) in both the vaccine and the placebo group, with no clinically meaningful differences by age, baseline serostatus, ethnicity, race or sex. Lymphadenopathy and nausea were reported to occur more often in the vaccine group compared to the placebo group in the whole enrolled trial population (respectively 0.4% and 0.6% higher rate than placebo). Numerical imbalances in reporting were observed for insomnia, injection site pruritus and pain in extremity. Since these are supported by a biologically plausible relation to vaccination, these AEs are reflected in the SmPC.

Acute peripheral paralysis was reported in 4 vs. 0 cases (vaccine vs placebo) in the whole study population, of which 2 cases were deemed related to study treatment (see section 2.6.10). For acute peripheral paralysis, there is a reasonable possibility of a causal relation to vaccination and should therefore be included in the SmPC.

In the $\sim 38,000$ study participants with a median of 2 months of safety follow-up after Dose 2, none reported an immediate AE (occurring within 30 minutes after dosing) that was indicative of an allergic reaction to vaccine. Three reports of anaphylaxis were identified during vaccination campaigns by the time this report was written.

Few cases of hypersensitivity/immunisation reaction events have been observed with the vaccine (13 vs 6 cases) in the whole study population. Hypersensitivity should be annotated in the SmPC, section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

Long term safety data is not available at this stage, however the Phase 2/3 study will follow the included subjects up to 2 years post vaccination, so these data are expected post-authorisation.

AEs were slightly lower in subjects seropositive to SARS-CoV-2 at baseline (22% vs. 27% in seronegatives), however the number of such subjects was limited (vaccinated n=558; placebo n=590).

Data on immunocompromised individuals is limited, as only 196 participants with stable HIV infection were included in the study. No specific safety concern was detected.

Data from exposure during pregnancy is very limited. Up to the cut-off date 23 pregnancies have been reported in the Phase 2/3 trial and will be followed up for outcome.

Multiple long-term pharmacoepidemiology safety studies are planned to be conducted in order to confirm the safety profile in the already studied population as well as in a broader population including pregnant, immunocompromised and very elderly subjects.

There is no data available on interaction with other vaccines given in co-administration.

In the Phase 2/3 study, the total number of included subjects aged 16-17 years was smaller compared to other age groups (n=138 BNT162b; n=145 placebo), however no safety concerns were identified.

Uncertainties remain regarding causality association of acute peripheral paralysis to vaccination due to the limited number of cases, which are consistent with background rates. Nevertheless, facial paralysis will be included as an adverse event of special interest (AESI) for pharmacovigilance monitoring and in the active surveillance study protocols.

While apart from facial paralysis, whose aetiology is currently unknown, no possible autoimmune adverse events were identified as causally related to vaccination, rare events of this nature cannot be excluded based on the size of the available data set.

There is a theoretical risk, based on non-clinical data with MERS and SARS vaccines, of vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), however no cases were identified in clinical studies with COVID-19 vaccines, including Comirnaty, and the characterisation of the immune response does not indicate a risk profile in this regard (Th1 skewed).

This vaccine contains two new components (cationic lipid ALC-0315 and PEGylated lipid ALC-0159) in the LNP, for which there is limited experience. Some uncertainties remain regarding the ALC-0315 long half-life. Regarding PEG related toxicity which is known to depend on the dose, dose frequency, duration of treatment and molecular weight of the PEG protein, immunogenicity is not expected to be an issue due to the low molecular weight of this PEG (<2KDa). The scientific data available at this stage do not raise noticeable concerns regarding immunogenicity or immunotoxicity of the PEG, but current evidence is not definitive.

3.6. Effects Table

Table 20 Effects Table for Comirnaty intended for active immunisation to prevent COVID-19 caused by against SARS-CoV-2 in individuals 16 years of age and older (data cut-off: 14 Nov 2020)

Effect	Short Description	Unit	BNT162b2 (30 µg)	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Vaccine efficacy	First COVID-19 occurrence from 7	% (95% CI)	95.0 (90.0, 97.9)			

Effect	Short Description	Unit	BNT162b2 (30 µg)	Placebo	Uncertainties / Strength of evidence	References		
	days after Dose 2, without prior SARS-CoV-2, overall	Cases/ Number of subjects at risk for the endpoint	8/ 17411	162/ 17511	Robust data with similar efficacy confirmed in all age sub-groups (16-64YOA, >65YOA, 65-74YOA, >75YOA)	Evaluable efficacy population (7 days post dose 2) - Study C495100		
	Patients aged ≥65	% (95% CI)	94.7 (66.7, 99.9)					
		Cases/ Number of subjects at risk for the endpoint	1/3848	19/3880				
Unfavourable Effects								
Lymphadenopathy		% (denominator)	0.3% (n=21720)	0% (N=21728)	Small number of cases, short duration of follow-up	All enrolled Phase 2/3 participants		
Facial paralysis		Number of cases	4	1				
Hypersensitivity/immunisation reaction		Number of cases	13	6				
			Post dose 1	Post dose 2	Post dose 1	Post dose 2	Transient events, majority mild to moderate intensity	Reactogenicity subset of study C495100
Pain at injection site	16-55 years		83%	79%	14%	12%		
	>55 years		71%	66%	9%	8%		
Headache	16-55 years	%	42%	52%	34%	24%		
	>55 years		25%	39%	18%	14%		
Fatigue	16-55 years		25%	39%	25%	39%		
	>55 years		34%	51%	23%	17%		

Abbreviations:

COVID-19: Coronavirus disease, SARS-CoV-2: Severe Acute Respiratory Syndrome, CI: Confidence Interval

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, substantial efficacy in preventing symptomatic COVID-19 infection has been demonstrated, as well as an acceptable safety profile in a large phase 3 study. Uncertainties relate to the

characterization of active substance and finished product. Given the comparable immunogenicity from 10 to 30µg doses, an impact on efficacy of the acceptance of somewhat lower levels of intact mRNA in the commercial product is not considered likely. Furthermore, based on low levels and biological plausibility, an impact of mRNA impurities on safety is deemed unlikely (see section 3.7.3).

Due to the limited extent of safety follow-up, the delivery of final data from the full 2-year follow up in the pivotal clinical trial are considered important to confirm the current knowledge.

With regards to the balance of efficacy and safety benefits and risks, it is overwhelmingly positive for subjects at risk of severe COVID-19, including the elderly and those with comorbid conditions, which are known to increase the risk of complication and death due to infection.

Uncertainties concerning the pharmaceutical characterization of the commercial product are compatible with a positive benefit/risk balance. This pertains not only to adults but, by extrapolation, to individuals 16-17 years of age.

Data are limited in individuals seropositive against SARS-CoV-2 at baseline. Available data however do not indicate any specific safety concerns, and efficacy is anticipated also in this subset.

There are no data on use in pregnant women, but a protective effect is anticipated. In the light of the reassuring data from the DART study, noting that pregnancy as such is a risk factor for severe COVID-19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis.

Based on biological plausibility no risk in breastfeeding is anticipated.

While there was no indication of an excess risk of severe allergic reactions such as anaphylaxis in the clinical study program, three post marketing cases, of which 2 in patients carrying adrenaline pens and one in a person with no known history of allergies, have been reported during vaccination campaigns, and all resolved with standard treatment. Hypersensitivity to the active substance or to any of the excipients is a contraindication. However, there is presently no substantial evidence of a negative benefit/risk balance in a subject with severe allergy to substances absent in the vaccine. For all subjects, the vaccine should be administered in settings where resuscitation facilities are available, as specified in the SmPC and in line with other vaccines. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.

There are no efficacy data in immunocompromised individuals. Such patients may not be protected as well as immunocompetent individuals by vaccination. While there are limited safety data too in the immunocompromised subjects (a broad and disparate category), no particular safety issues are anticipated, and the benefit/risk balance of vaccination of such subjects is deemed positive, also in light of the underlying excess risk of COVID-19.

Studies to monitor potential safety concerns (autoimmune disorders, VAED) are planned.

3.7.2. Balance of benefits and risks

Overall, the available data are supportive of a positive B/R in the proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

Given the emergency situation, it is considered that the identified uncertainties can be addressed post-authorisation in the context of a conditional MA, including further characterisation of the active substance and finished product, the continuation of the pivotal study as long as possible, and post-approval effectiveness studies and routine disease surveillance.

Conditional marketing authorisation

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine (Process 1). The commercial batches are produced using a different process (Process 2), and the comparability of these processes relies on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are limited in relation to critical quality attributes and impurities.

Data demonstrates the presence of truncated/modified forms of mRNA at somewhat higher levels in the batches manufactured with the commercial process as compared to material used in clinical trials. These forms are not sufficiently characterised, and although the limited data provided for protein expression does not fully address uncertainties relating to the risk of translating proteins/peptides other than the intended spike protein, the amount of any such proteins, is expected to be too low to elicit an immune response of biological relevance.

Indeed, considering the low dose of mRNA (30 µg), the impurities are not considered a safety issue based on general toxicological principles. However, when present in the cell it cannot be excluded that different proteins than the intact full-length spike will be expressed. The risk of unwanted immunological events is considered low based on the following observations and considerations:

- Such impurities were present in the vaccine used in the Phase 3 clinical trials with an acceptable safety profile. Although the lack of characterisation hinders a full comparability evaluation there is no indication that there would be important qualitative differences in the nature of these impurities.
- The high levels of these impurities reflect the instability of RNA resulting in generation of RNA fragments both in the transcription step and thereafter. Based on electrophoretic data it appears that there is a diverse set of fragments. Although not confirmed, it is unlikely that these RNA molecules to a large extent would be mRNA molecules with intact 5'-cap and 3'-polyA able to be translated into a specific protein or peptide.
- The level of any individual fragment of mRNA species would anyway be magnitudes lower than the level of the intact mRNA and this would be mirrored by the level of protein expression. The spike protein is a highly immunogenic protein and immunodominance would also ascertain that the immune response to the truncated proteins would be non-significant.

Also, lipid related impurities were observed in recently produced finished product batches. Based on the low dose (30 µg mRNA) it is considered that the amounts of these impurities are too low to be of toxicological significance.

Regarding the proposed control strategy for active substance and finished product, questions were raised both with regard to the suitability of the test methods used and the acceptance criteria for some tests.

Considering the above and the current public health emergency, the characterisation of the active substance and finished product are considered acceptable, and the proposed specifications for RNA integrity and 5'-Cap are considered to be scientifically justified and acceptable. Nevertheless, additional data to complete the characterisation of the active substance and finished product, and considering clinical experience, are considered important to confirm the adequacy of these specifications, and these data should be provided post-approval as specific obligations to the MA.

Therefore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

Studies are underway to complete the characterisation of the active substance and finished product, and additional clinical data from batches currently in use in ongoing clinical studies, are considered important to confirm the clinical qualification of these specifications. Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment by the CHMP in order to complete all proposed specific obligations. Based on the Applicant's plans and documentation, it is expected that data to fulfil all quality SOs will be submitted gradually between March and July 2021.

Furthermore, the applicant will continue the ongoing pivotal Phase 3 randomized, placebo-controlled, observer-blind study C4591001 to obtain 2-year long-term data and to ensure sufficient follow-up in order to confirm the efficacy and safety of Comirnaty.

- Unmet medical needs will be addressed

There is no approved or widely available COVID-19 vaccine, and COVID-19 remains associated with substantial morbidity and mortality. While care for patients who have COVID-19 has improved over time and with clinical experience, no medications to cure COVID-19 are available and there remains an urgent need for a prophylactic vaccine during the ongoing pandemic.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Convincing efficacy evidence including the elderly and those with comorbid conditions has been provided and long-term effectiveness and safety data will be provided post-authorisation. Taking all this into account, it would not be considered appropriate to withhold a highly beneficial vaccine considering the severity of COVID-19 disease and the current global pandemic situation, since the demonstrated benefits in the current emergency setting clearly outweigh the uncertainties of the available data as outlined above.

3.8. Conclusions

The overall benefit/risk balance of Comirnaty is positive.

As available data are non-comprehensive, granting of a conditional marketing authorisation is relevant, and in line with provisions of Article 14-a of Regulation (EC) No 726/2004 it is supported.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Comirnaty is favourable in the following indication:

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions and specific obligations:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 August 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 August 2021 at the latest, in line with the agreed plan for this transfer of testing. Progress reports have to be submitted on 31 March 2021 and included in the annual renewal application.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021. Interim reports: 31 March 2021
In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021. Interim reports: March 2021
In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021. Interim reports: January 2021, April 2021.
In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Bibliography of References - Ivermectin for the Treatment of COVID-19

Primary data							
Type of study	Bibliography	Country	Cohort	Dosage	Comment		
Case-control	Behera et al. Role of ivermectin in the prevention of SARS-CoV-2 infection among healthcare workers in India: A matched case-control study. <i>PLoS ONE</i> 2021; 16(2): e0247163. doi: 10.1371/journal.pone.0247163	India	186	15mg for 40–60 kg; 18mg for 60–80 kg; 24mg for > 80 kg;24			6
	Elaftly et al. Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (IVANS-NRIZ study) on the clearance of mild COVID-19. <i>J Med Virol</i> . 2021. doi: 10.1002/jmv.26880.	Egypt	113	200-300µg/kg for 60-90kg; 300-400 µg/kg for 90-120kg; 500µg/kg for >120kg			16
	Hellwig & Maia. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin. <i>Int J Antimicrob Agents</i> , 2021; 57(1): 106248. doi: 10.1016/j.ijantimicag.2020.106248					Negative	
	Rajter et al. Use of Ivermectin is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019: The Ivermectin in COVID Nineteen Study. <i>Chest</i> . 2021; 159(1):85-92. doi: 10.1016/j.chest.2020.10.009	USA	280				3
	Elgazzar et al. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. <i>Research Square</i> . 2020 [Preprint]. doi: 10.21203/rs.3.rs-100956/v2	Egypt	600				2
	Spoorthi & Sasank. Utility of Ivermectin and Doxycycline combination for the treatment of SARS-CoV-2. <i>Int Arc Integr Med</i> . 2020; 7(10): 177-182, 2020.	India	100				8
	Arevalo et al. Ivermectin reduces coronavirus infection in vivo: a mouse experimental model. <i>bioRxiv</i> . 2020. 11.02.363242; doi: https://doi.org/10.1101/2020.11.02.363242					Mechanism	9
	Arouche et al. Molecular Docking of Azithromycin, Ritonavir, Lopinavir, Osetamivir, Ivermectin and Heparin Interacting with Coronavirus Disease 2019 Main and Severe Acute Respiratory Syndrome Coronavirus-2 3C-Like Proteases.						44
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	Caly et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. <i>Antiviral Research</i> . 2020; 178:104787. doi:10.1016/j.antiviral.2020.104787.					Mechanism of action	
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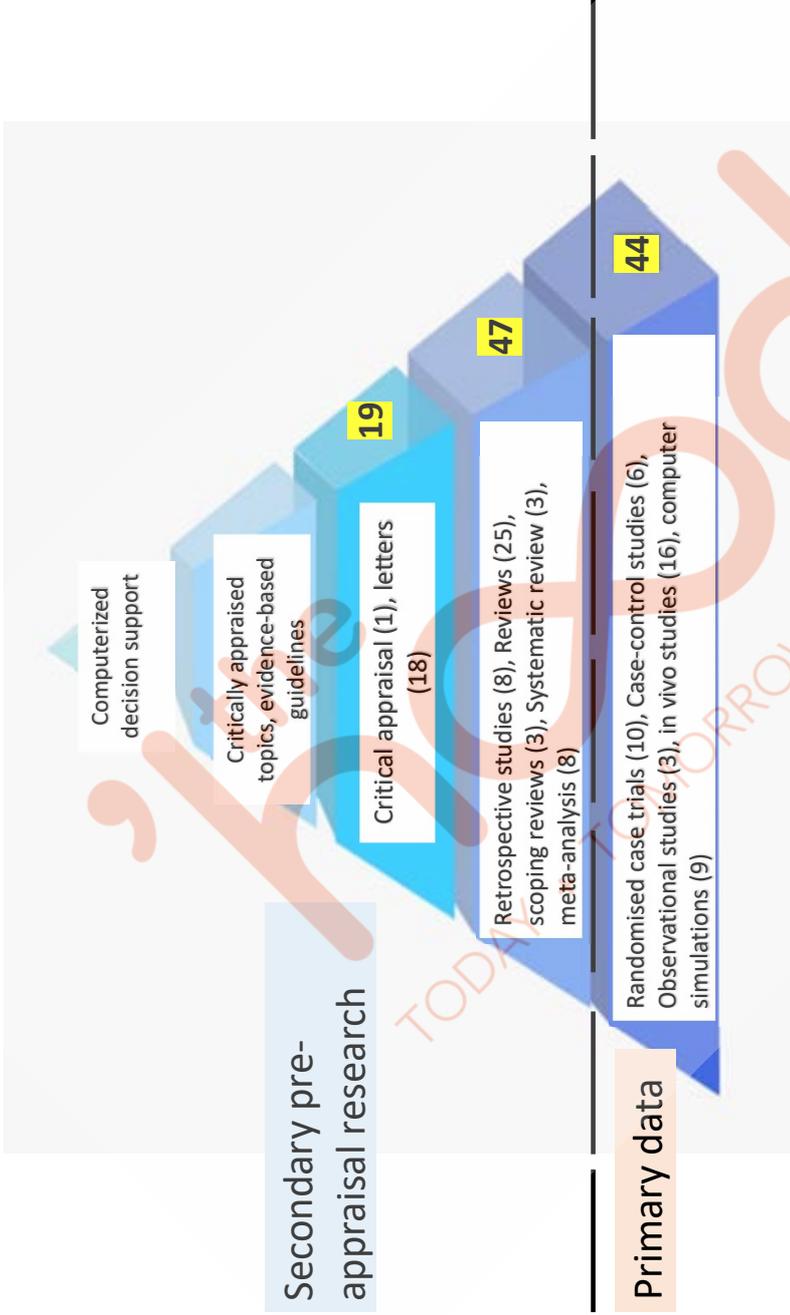
Type of study	Secondary data					Focus
	Bibliography	Country	Cohort	Dosage		
Retrospective study	Chamie-Quintero et al. Sharp Reductions in COVID-19 Case Fatalities and Excess Deaths in Peru in Close Conjunction, State-By-State, with Ivermectin Treatments, 2021. [Preprint]. Doi: 10.2139/ssrn.3765018	Peru	25 states			
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	Hirsch & Héctor. Ivermectin as Prophylaxis Against COVID-19 Retrospective Cases Evaluation. Microbiol Infect Dis. 2020; 4(4): 1-8.	Argentina	162	0.2 mg/kg		
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Retrospective studies	8
Scoping reviews	3
Systematic reviews	3
Meta analysis	8
Critical appraisal	1
Reviews	25
Letters	18
Total	66

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Scoping reviews						Negative
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Systematic reviews	Gómez-Ríos et al. Research on repurposed antivirals currently available in Colombia as treatment alternatives for COVID-19. <i>Ingeniería y Competitividad</i> , 23(1). 10290. enero-julio2021. doi: 10.25100/yc.2311.10290					
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	Padhy et al. Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis. <i>J Pharm Pharm Sci</i> . 2020;23:462-469. doi: 10.18433/jpps31457.					
Critical appraisal	Sharun et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. <i>Ann Clin Microbiol Antimicrob</i> (2020) 19:23. doi: 10.1186/s12941-020-00368-w					
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Appendix 4

Open Letter to the President of the University of Guelph



Friday September 17, 2021

University of Guelph
50 Stone Rd. E.
Guelph, ON,
N1E 2G1

Dear Dr. Charlotte A.B. Yates, President and Vice-Chancellor,

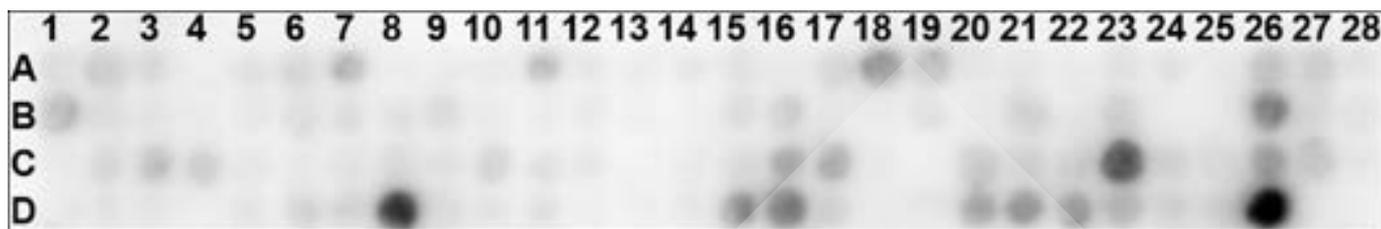
I will forewarn you that this is a lengthy letter. However, it only represents a fraction of the information that I would like to be able to share with you. I have found it necessary to write this so you can fully understand my perspective. With my life and that of my family, many friends and treasured colleagues being destroyed under your watch, I figure the least you can do is read and consider this very carefully. It is incredible to note that many, if not most, of my on-campus detractors have judged me without reading any of my scientific arguments or talking to me about them.

The COVID-19 Vaccine Mandate at the University of Guelph

You issued a mandate that everyone within the University of Guelph community must receive a COVID-19 vaccine. I have spent most of my lifetime learning to be a very deep and critical thinker and to follow the weight of scientific evidence. I am a well-recognized expert in vaccinology. As per my extensive funding, research, publication, and teaching records, I am a vaccine lover and an innovator in this field. I promote highly effective vaccines that have undergone extensive, rigorous, and proper safety testing as the most efficient type of medicines that exist. Vaccines that meet these criteria have prevented a vast amount of mortality and morbidities around the world. However, **I could not be in stronger disagreement with you forcing the current COVID-19 vaccines upon everyone** who is part of our campus community. I respect the challenges that a university president faces when trying to manage a large and dynamic academic institution. However, your roots are as a scholar. As a publicly funded institution of advanced learning, it is incumbent on us to demonstrate an ability to view the world around us in a constructively critical fashion such that we can improve the lives of others. We should be able to do this free of political or financial pressures and without bias or prejudice or fear of censorship and harassment. As a viral immunologist that has been working on the front lines of the scientific and medical community throughout the duration of the declared COVID-19 pandemic, I feel compelled to speak on behalf of the many who will not, due to extreme fear of retribution. We now live in a time when it is common practice for people to demand and expect to receive confidential medical information from others. I will not be coerced into disclosing my private medical information. However, for the sake of highlighting some of the absurdities of COVID-19 vaccine mandates I choose, of my own free will, to freely disclose some of my medical information here...

Those with Naturally Acquired Immunity Don't Need to be Vaccinated and are at Greater Risk of Harm if Vaccinated

I participated in a clinical trial that has been running for approximately 1.5 years. The purpose is to develop a very sensitive and comprehensive test of immunity against SARS-CoV-2; in large part to inform the development of better COVID-19 vaccines (<https://insight.jci.org/articles/view/146316>). My personal results prove that I have naturally acquired immunity against SARS-CoV-2. With this test, spots indicate a positive result for antibodies against a particular part of the virus. Darker spots correlate with more antibodies. Antibody responses correlate with the induction of memory B cells. Antibodies will wane over time, but B cells can survive for many years and rapidly produce massive quantities of antibodies upon re-exposure to a pathogen. On the following page are my results, along with a map of which part of the virus each spot represents...



Peptide Identification on CCJ SARS-CoV-2 SPOT peptide arrays

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28			
A	Spike S1				Spike S1 RBD				Spike S1				Spike S2																		
B	Spike S2								Nucleocapsid								Memb.														
C	Nsp2		Nsp3						Nsp1	Nsp2		Nsp3		Nsp4		Nsp5	Nsp8+9														
D	Nsp10 +11	Nsp12			Nsp13		Nsp14		Nsp15			Nsp16	Orf3	Orf4	IgG																

The dark spot at position D26 is the positive control and indicates that the assay worked. My results demonstrate that I have broad immunity against multiple components of SARS-CoV-2, including the spike protein. Importantly, spot B26 shows that I have antibodies against the membrane protein. This protein is not highly conserved across coronaviruses. As such, it provides evidence that I was infected with SARS-CoV-2. Note that I was sick only once since the pandemic was declared. It was a moderately severe respiratory infection that took ~four weeks to recover from. The SARS-CoV-2 PCR test was negative, despite being run at an unreasonably high number of cycles. This suggests that I was one of the many for whom SARS-CoV-2 has proven to be of low pathogenicity or not even a pathogen (*i.e.* no associated disease). There is a plethora of scientific literature demonstrating that naturally acquired immunity against SARS-CoV-2 is likely superior to that conferred by vaccination only. Indeed, it is much broader, which means that emerging variants of SARS-CoV-2 will have more difficulty evading it as compared to the very narrow immunity conferred by the vaccines. Importantly, the duration of immunity (*i.e.* how long a person is protected) has proven to be far longer than that generated by the current vaccines. The duration of immunity for the mRNA-based COVID-19 vaccines appears to be a horrifically short ~4.5 months. I actually wrote a lay article back in February 2021 to explain why a vaccine of this nature would fail to be able to achieve global herd immunity on its own (<https://theconversation.com/5-factors-that-could-dictate-the-success-or-failure-of-the-covid-19-vaccine-rollout-152856>). This is why places like Canada, the USA, and Israel have found it necessary to roll out third doses. And now there is talk (and a commitment in Israel) to roll out fourth doses (yes, that's four doses within one year). The World Health Organization recognized the value of natural immunity quite some time ago. Unfortunately, in Canada and at the University of Guelph, we have failed to recognize that the immune system works as it was designed to. Its ability to respond is not limited solely to vaccines. Here are some references to support this: https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Natural_immunity-2021.1; <https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiab295/6293992>; <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7803150/>. As someone who develops vaccines, I can tell you that it is difficult to make a vaccine that will perform as poorly as the current COVID-19 vaccines. Indeed, most vaccines given in childhood never require a booster shot later in life. The take-home message here is that people like me, who have naturally acquired immunity, do not need to be vaccinated. Nor is it needed to protect those around the person who already has immunity. Worse, research from three independent groups has now demonstrated that those with naturally acquired immunity experience more severe side-effects from COVID-19 vaccines than those who were immunologically naïve prior to vaccination ([https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370\(21\)00194-2/fulltext](https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00194-2/fulltext); <https://www.medrxiv.org/content/10.1101/2021.04.15.21252192v1>; <https://www.medrxiv.org/content/10.1101/2021.02.26.21252096v1>). In other words, **for those with natural immunity, vaccination is not only unnecessary, but it would put them at enhanced risk of harm. Knowing this, nobody should ever mandate COVID-19 vaccination.** Instead, it would be in the best interest of helping everyone make the most informed health decisions for themselves to make voluntary testing for immunity available.

Testing for Naturally Acquired Immunity was a Viable Option but was Ignored

You and the provost met with me and two other colleagues back in March 2021 and we presented the opportunity for the University of Guelph to show leadership and offer testing for immunity to our campus community in support of a safe return to in-person teaching and learning. You embraced this idea with enthusiasm and promised to move forward with it. This did not materialize so one of my colleagues contacted you. Once again, you agreed it was an excellent idea and that you would move forward with it. Nothing happened. So, my two colleagues and I met with one of our vice-presidents in May 2021. They also thought that making an antibody test available was an excellent idea and promised to work on getting it implemented on campus. Nothing materialized. They were contacted again by one of my colleagues. There was no response. There is no excuse for forcing vaccines on people, especially after having been given the opportunity to implement testing for immunity and refusing to do so.

The University of Guelph won't pay for me to receive a booster vaccine against rabies unless I can demonstrate that my antibodies are below what has been deemed to be a protective titer. This is because it would not be appropriate to give me a vaccine that is not without risk if I don't need it. Also, the university does not want to pay the ~\$850 cost of the vaccination regimen unless I absolutely need it. In short, you will not allow me to receive that booster vaccine without first evaluating me on an annual basis for evidence of immunity (or lack thereof). So why was this principle rejected for the SARS-CoV-2 vaccines, for which there is vastly less reliable safety data available, and none for the long-term? Canada should have been acquiring data about immunity starting a long time ago. It is a particularly poor precedent for a university to reject the concept of acquiring data that could inform safer and more effective COVID-19 policies. Immunity testing would even benefit vaccinated individuals. It is well known that responses to vaccines in outbred populations follows a normal curve and includes individuals that are non-responders (*i.e.* they are left without immunity and are, therefore, unprotected following vaccination) and low-responders (insufficient protection). In fact, this concept has been the focus of an internationally recognized research program on our campus that has brought many accolades and awards to our institution.

You have banned me from campus for at least the next year. I can show proof of immunity against SARS-CoV-2 but you will not allow me to enter buildings. But someone else can show a receipt saying that someone saw two needles go into their arm and you will allow them to enter. You actually have no idea if that person has immunity. There have even been reported cases of people accidentally or even intentionally (*e.g.* a case in Germany) being administered saline instead of the vaccine. **Does it make sense to ban someone who is immune from campus but allow people who are presumed, but not confirmed, to be immune?** This is a scenario that you have created. As a fellow academic, **I am requesting that you provide me with a strong scientific rationale why you are allowing thousands with an unconfirmed immunity status onto our campus, but you are banning people like me who are known to have immunity.** Further, **please explain how you feel it is ethical to force COVID-19 vaccines on people who are uncomfortable with being coerced when you do not know their immunity status.** Despite attempts to halt the spread of SARS-CoV-2 via masking and physical distancing, the reality is that the virus has not complied with these attempts to barricade it. Indeed, it has infected many people across Canada, many of whom may not have even realized it because it is not a dangerous pathogen for them. From the perspective of a medical risk-benefit analysis, this is a no-brainer. A medical procedure that adds no value but carries known and still-to-be-defined risks should never be mandated!

The University Back-Tracked on Advice from its Own Legal Counsel!

I, along with two colleagues, attended a meeting with one of our vice-presidents in May 2021. In that meeting the legal advice that was provided to the University of Guelph was disclosed. We were told this included making COVID-19 vaccines voluntary, that nobody on campus should be made to feel coerced into being vaccinated, and that nobody should feel pressured to disclose their vaccination status. On this basis, I was to serve as one of the on-campus faculty contacts for anyone who experienced any of these issues. **Did Canada's laws change during the summer in a way that rendered this legal advice no longer valid?** Now I am having to spend an inordinate amount of time trying to help the many people whose lives have imploded due to the university's vaccine mandate.

I am a Scientist Who is Knowledgeable and Values Integrity Despite What So-Called 'Fact Checkers' Have Claimed

There are many on our campus who repeatedly put my name out to the public with claims that I disseminate misinformation. Not one of these individuals has ever given me the courtesy of a conversation prior to publicly attacking me. None of them will engage me in public discussions of the science to allow people to judge the legitimacy, or lack thereof, of what I am saying. Censorship on our campus has become as prevalent as it is off-campus. My detractors, rather than showing a deep understanding of the science underlying COVID-19 vaccines, continually refer to the so-called 'fact checks' that have been posted about me. Let me tell you some things about the so-called 'fact checkers'. Firstly, they give scientists and physicians of integrity unreasonably short periods of time to respond to their requests for answers. For example, as I write this letter, I have 13,902 unread messages in my inbox and my voice mail is at maximum capacity. I have yet to see a 'fact check' request prior to its expiry, which remarkably, is often within mere hours of an e-mail being sent. This is an unreasonable expectation from a busy professional. Also, many 'fact checkers' lack sufficient expertise. In some cases, 'fact checker' sites have had to rely on postdoctoral trainees in other countries to write responses.

Most of the harassment against me began after 'fact checkers' cherry-picked one short radio interview that I gave to a lay audience. Some have accused me of only giving half the story in that interview. They were most kind; I was only able to reveal ~0.5% of the story. It is unfair to critique a tiny portion of one's arguments that were presented off-the-cuff to a lay audience with no opportunity for me to respond in real-time. For your information, I **have rebutted every single one of the 'fact checks' that I am aware of** in various public interviews. Let me give you one example that some of our colleagues on our campus have repeatedly misused while harassing me in social media...

One of the many issues that I have raised with the vaccines is that should a reasonable concentration of the free spike protein get into systemic circulation, it could potentially harm the endothelial cells lining our blood vessels. I cited this study: <https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.121.318902>. The authors were contacted, and they claimed I had misinterpreted the study. They said that spike-specific antibodies would mop up any spike proteins in the blood, thereby protecting the blood vessels. They argued that this demonstrated that vaccinating people against the spike protein is a good thing. However, the authors are not immunologists and they failed to recognize the limitations of their own study in drawing these kinds of conclusions. Specifically, they did not recognize that in a naïve individual receiving a mRNA-based COVID-19 vaccine, there are no antibodies; either pre-existing in the host, or in the vaccine formulation. In fact, it will take many days for the antibody response to be induced and for titers to begin reaching substantial concentrations. This leaves a large window of time in which any free spike proteins could exert their biological functions/harm in the body before there are any antibodies to neutralize them. Worse, most of the spike proteins should be expressed by our own cells. In that case, the antibodies will target and kill them in a form of autoimmunity. The authors of the paper forgot that their model was in the context of natural infection, where vaccination would precede exposure to SARS-CoV-2. In that case, I agree that there would be pre-existing antibodies that could neutralize spike proteins of viral origin entering the circulation. This was perceived to be one of the 'strongest' arguments used by others to try to discredit me. The reality is that it is completely incorrect and represents an embarrassing misinterpretation by the authors of the original paper and the many 'fact-checkers' that believed them without question.

Criminal Harassment

You have allowed colleagues to harass me endlessly for many consecutive months. They have lied about me, called me many names, and have even accused me of being responsible for deaths. I submitted a harassment claim and your administrators ruled that it did not meet the bar of civil harassment. In stark contrast, I have been contacted by members of off-campus policing agencies who have told me that it exceeds the minimum bar of criminal harassment. I am sorry, but a faculty member can only take so much bullying and see such a lack of adherence to scientific and bioethical principles before it becomes necessary to speak up. Under your watch, you have allowed my life to be ruined by turning a blind eye to on-campus bullying, ignoring our campus principles of promoting mental

well-being and a workplace in which I can feel safe. In addition to this you have banned me from the campus because I have robust, broadly protective, and long-lasting immunity against SARS-CoV-2 but lack a piece of paper suggesting that it was obtained via two injections. Did you see this front page of one of Canada's major newspapers?...

...remarkably, the on-campus COVID-19 policies you are promoting fuel this kind of pure hatred from people, most of whom have not confirmed their own immunity status, against someone like me who is immune to SARS-CoV-2!!! **Does that make any sense?** My workplace has become a poisoned environment where the bullying, harassment, and hatred against me have been incessant. Are you ever going to put an end to the childish and irrational behaviours being demonstrated by our colleagues? I have received thousands of emails from around the world that indicate the university should be embarrassed and ashamed to allow such childish behaviour from faculty members to go unchecked in front of the public. I have invested a decade of my life into the University of Guelph. I have conducted myself professionally and worked to an exceptionally high standard. I have consistently received excellent ratings for my research, teaching, and service. I have received rave reviews from students for my teaching. I have received prestigious research and teaching awards. I have brought funding to our campus from agencies that had never partnered with the University of Guelph in our institution's history. I have brought in ~\$1 million-worth of equipment to improve our infrastructure, etc., etc. I am a man of integrity and a devoted public servant. I want to make Canada a better place for my family and for my fellow Canadians. We are a public institution. My salary is covered by taxpayers. This declared pandemic involves science that is in my 'wheelhouse'. Since the beginning, I have made myself available to answer questions coming from the public in a fashion that is unbiased and based solidly on the ever-exploding scientific literature. My approach has not changed. Has some of it contradicted the very narrow public health narrative carried by mainstream media? Yes. Does that make it wrong? No. I will stand by my track record. When Health Canada authorized the use of AstraZeneca's vaccine I, along with two colleagues, wrote an open letter requesting that this vaccine not be used, in part on the grounds that it was being investigated for a link to potentially fatal blood clots in many European countries. I was accused at that time by so-called 'fact checkers' of providing misinformation. Less than two months later, Canada suspended the AstraZeneca vaccination program because it was deemed to be too unsafe as a result of causing blood clots that cost the unnecessary loss of lives of Canadians. More recently, I was heavily criticized for raising concerns in a short radio interview about a potential link between the Pfizer BioNTech COVID-19 vaccine and heart inflammation in young people, especially males. This is now a well-recognized problem that has been officially listed as a potential side-effect of the mRNA COVID-19 vaccines. It was also the subject of a recent Public Health Ontario Enhanced Epidemiological Summary Report highlighting the increased risk of myocarditis and pericarditis to young males following COVID-19 mRNA vaccination. As such, I have a proven track record of accurately identifying concerns about the COVID-19 vaccines.



A Lack of Safety Data in Pregnant Females as Another Example of Why Vaccines Should Not be Mandated

I would like to give another disconcerting safety-related example of why a COVID-19 vaccine mandate could be dangerous. We have pregnant individuals or those who would like to become pregnant on campus. There was a highly publicized study in the prestigious *New England Journal of Medicine* that formed the foundation of declaring COVID-19 vaccines safe in pregnant females (<https://www.nejm.org/doi/full/10.1056/nejmoa2104983>). The authors of this study declared that there was no risk of increased miscarriage to vaccinated females. This study resulted in

many policies being instituted to promote vaccination of this demographic, for which the bar for safety should be set extremely high. Did you know that this apparent confirmation of safety had to be rescinded recently because the authors performed an obvious mathematical error? I witnessed several of my colleagues from Canada and other countries bravely push for a review of this paper under withering negative pressures. Once the editor finally agreed to do so, the authors had no choice but to admit that made a mathematical error. Most of the world does not realize this. This admission of using an inappropriate mathematical formula can be found here: <https://www.nejm.org/doi/full/10.1056/NEJMx210016>. This means that **the major rationale for declaring COVID-19 vaccines safe in pregnant females is gone! How can someone force a COVID-19 vaccine on a pregnant female when there are insufficient safety data available to justify it?**

Advocating for the Vulnerable and Those Fearful of Retribution

My concern is not primarily for myself. I am using my case to highlight how wrong your vaccine mandate is. I am more concerned for the more vulnerable on our campus. I hold tenure, and if ever there was a time when this was important, it is now. However, I have had to bear witness to numerous horrible situations for students and staff members. Students have been physically escorted off our campus, sometimes being removed from their residence, sometimes with their parents also being escorted off. Staff members have been escorted off campus and immediately sent home on indefinite leaves without pay, leaving them unable to adequately care for their families. In many of these situations it seemed like the interactions intentionally occurred in very public settings with it being made clear to all onlookers that the person or people were not vaccinated. Parents have been denied attending meetings with their children who are entering the first year of a program. They recognize that adult learners would normally not have their parents accompany them, but we are living in unusual times with excessive and unfair (arguably illegal?) pressures being applied and these parents are entitled to advocate and defend the best interests of their sons and daughters. Many students have deferred a year in the desperate hope that our campus community will not be so draconian next year. Others fought hard to earn their way into very competitive programs and are not being guaranteed re-entry next year. Many faculty members refused to offer on-line learning options for those who did not wish to be vaccinated. On the flip-side, there are also faculty members, like many students and staff, who are completely demoralized. This includes some who were happily vaccinated but are upset by the draconian measures of your COVID-19 policies and/or will be unwilling to receive future booster shots. I can tell you many stories of students and staff members who couldn't resist the pressure to get vaccinated because they were losing vast amounts of sleep and experiencing incredible anxiety and were on the verge of mental and/or physical breakdowns. In some of these cases, they were crying uncontrollably before, during, and after their vaccination, which they only agreed to under great duress. This does not represent informed consent! I have had several members of our campus community contact me with concerns that they may have suffered vaccine-induced injuries ranging from blood clots to chest pain to vision problems to unexpected and unusual vaginal bleeding. Can I prove these were due to the vaccine? No. But can anyone prove they were not? No. And it is notable that these are common events reported in adverse event reporting systems around the world. In all cases, the attending physicians refused to report these events, even though it is supposed to be a current legal requirement to do so. These people obediently got vaccinated and were then abandoned when they became cases that did not help sell the current public health messaging.

A World Where Everyone is Vaccinated Looks Nothing Like Normal

The two-week lockdown that was supposed to lead into learning to live with SARS-CoV-2 has turned into the most mismanaged crisis in the history of our current generations. I ask you to look around with a very critical eye. You just reported that 99% of the campus community is vaccinated. Congratulations, you have far exceeded the stated standard for what is apparently the new goal of 'herd vaccination'. I cannot use the typical term 'herd immunity' here because immunity is not being recognized as legitimate; only inferred immunity based on receiving two needles counts. We were told that achieving herd immunity by vaccination alone was the solution to this declared pandemic. This has been achieved on our campus in spades. I sat in on our town hall meetings with our local medical officer of health who confidently told us that the risk of breakthrough infections in the vaccinated was almost zero. Why, then are people so petrified of the unvaccinated. Look at vaccines for travellers going to exotic locations.

These are vaccines of some quality. Travellers take these vaccines, and not only do they not avoid the prospective pathogen, but they happily travel to the location where it is endemic (*i.e.* they enthusiastically enter the danger zone because they are protected). So, what does our campus look like with almost every person vaccinated? Everyone must remain masked and physically distanced. There is no gathering or loitering allowed in stairwells or any open spaces in buildings or outside. People are still being told which doors to enter and exit, when they can do so, where to stand in line, when to move. Incredibly, time restrictions are even being implemented in some eating areas because some students were deemed to be “snacking too long” with their masks off and, therefore, putting others at risk of death. In short, the on-campus COVID-19 policies are even more draconian than they were last year, but everyone is vaccinated. It doesn't seem like the vaccines are working very well when a fully vaccinated campus cannot ease up on restrictions. But, of course, we already know how poorly these vaccines are performing. Based on fundamental immunological principles, parenteral administration of these vaccines provides robust enough systemic antibody responses to allow these antibodies to spill over into the lower respiratory tract, which is a common point at which pathogens can enter systemic circulation due to the proximity of blood vessels to facilitate gas exchange. However, they do not provide adequate protection to the upper respiratory tract, like natural infection does, or like an intranasal or aerosolized vaccine likely would. As such, people whose immunity has been conferred by a vaccine only are often protected from the most severe forms of COVID-19 due to protection in the lower lungs, but they are also susceptible to proliferation of the virus in the upper airways, which causes them to shed equivalent quantities of SARS-CoV-2 as those who completely lack immunity. Dampened disease with equal shedding equals a phenotype that approaches that of a classic super-spreader; something that we erroneously labeled healthy children as until the overwhelming scientific evidence, which matches our historical understanding, clarified that this was not the case. I have been in meetings where faculty have demanded to know who the unvaccinated students will be in their classes so they can make them sit at the back of the classroom! I can't believe that some of my colleagues are thinking of resorting to the type of segregation policies that heroes like Viola Desmond, Rosa Parks, Martin Luther King Jr., Carrie M. Best, and Lulu Anderson fought so hard against so many years ago.

The Exemption Fiasco

With respect to exemptions for COVID-19 vaccines, the University of Guelph provided a number based on creed or religion but then, remarkably, rescinded these. These previously exempt individuals were required to resubmit applications using a more onerous form; many that had been honoured previously were rejected upon re-submission. Many have been rejected since. Based on the reports I have received from many people these rejections of exemption requests were typically not accompanied by explanations. Nor have many been told, despite asking, who it is that sits on the committee making decisions about these exemptions. I would never be allowed to assign marks to students anonymously, nor without being able to justify them. Yet there seems to be a lack of transparency with exemptions and many of these decisions are destroying people's lives; the outcomes are not trivial. Could you please disclose the names of the people serving on the University of Guelph's committee that reviews exemptions? Also, could this committee please provide to applicants, retroactively, comments to justify their decisions? I have even heard it said in recent meetings that a lot of people are happy to hear that exemptions, including some medical exemptions are being denied. Why are our faculty celebrating refusals of medical exemptions for students?

A Lack of Consultation with the Experts on Vaccines

You have stated on numerous occasions that your COVID-19 policies have only been implemented after extensive consultation with local and regional experts. Interestingly, however, you have refused, for some unknown reason, to consult with any of the senior non-administrative immunologists on your campus. I would like to remind you that vaccinology is a sub-discipline of immunology. Notably, all three of us have offered repeatedly to serve on COVID-19 advisory committees, both on-campus and for our local public health unit, which also lacks advanced training in immunology and virology. The three of us have stayed on top of the cutting-edge scientific findings relevant to COVID-19 and meeting regularly with many national and international collaborative groups of scientists and physicians to debate and discuss what we are learning. I think it is notable that the senior non-administrative

immunologists unanimously agree that COVID-19 vaccines should not be mandated for our campus based on extensive, legitimate scientific and safety reasons.

Mandating COVID-19 Vaccines is Criminal

I am no legal expert but have consulted with many lawyers who have told me that these vaccine mandates break many existing laws. Here is one example copied from the Criminal Code of Canada:

Extortion

- **346 (1)** *Every one commits extortion who, without reasonable justification or excuse and with intent to obtain anything, by **threats, accusations, menaces or violence induces or attempts to induce any person, whether or not he is the person threatened, accused or menaced or to whom violence is shown, to do anything or cause anything to be done.***

In your case, you are demanding that members of our academic community submit to receiving a COVID-19 vaccine against their will (a medical procedure that may very well be unnecessary and carry enhanced risk of harm) or face banishment from the campus. Again, I am not an expert in this area, but I am confident there will be lawyers willing to test this in court. Those responsible for issuing vaccine mandates will need to decide how confident they are that they will not lose these legal battles.

Integrity of Teaching

In this new world where followers of scientific data are vilified, I also worry about my ability to teach with integrity. Unbelievably, the Minister of Health of Canada, Patty Hajdu, told Canadians that vitamin D being a critical and necessary component of the immune system in its ability to clear intracellular pathogens like SARS-CoV-2 is fake news! Do you now that I have taught all my students about the importance of vitamin D (often in the historical context of how it was discovered as being critical for positive outcomes in patients with tuberculosis that were quarantined in sanatoriums). I also teach the concept of herd immunity, with vaccination being a valuable tool to achieve this. I do not teach the concept of 'herd vaccination' while promoting ignorance of natural immunity. There are other basic immunological principles that I teach that have either not been recognized during the pandemic as legitimate scientific principles or they have been altogether contradicted by public health and/or government officials. Will I still be allowed to teach immunology according to the decades of scientific information that I have built my course upon? Or will I be disciplined for teaching immunological facts? There are many attempts to regulate what I can and cannot say these days, so these are serious questions.

Instilling Fear of a Minority Group Breeds Hatred

We live in an era where issues of equity, diversity, and inclusion are supposed to be at the forefront of all discussions at academic institutions. However, you are openly discriminating against and excluding a subset of our community that happens to be highly enriched with people engendered with critical thinking; a quality that we are supposed to be nurturing and promoting. With COVID-19 mandates, an environment has been created on our university campus that promotes hatred, bullying, segregation, and fear of a minority group whose only wrongdoing has been to maintain critical thinking and decision-making that is based on facts and common sense. I have yet to meet an anti-vaxxer on our campus. Everyone I know of is simply against the mismanagement of exceptionally poor-quality COVID-19 vaccines. History tells us that instilling fear of a minority group never ends well. This scenario must be rectified immediately if our campus is ever to return to a safe and secure working and learning environment for all.

Committing to Abolishing the COVID-19 Vaccine Mandate

President Yates, **the favour of a reply is requested.** Not the kind that defers to public health officials, or a committee, or anyone else. Instead, a reply with the scientific rigour expected from a scholarly colleague rebutting each of my comments and addressing each question. Surely, you know the science underpinning COVID-19 vaccines inside and out by now. I strongly suspect that nobody would make a decision that disrupts an entire community and destroys the lives of some of its members without a fully developed rationale that can point to the weight of the peer-reviewed scientific literature to back it up. If it would be easier, I would be happy to have an open and respectful, but public and blunt moderated conversation about your vaccine mandate in front of our campus community; much like in the spirit of old-fashioned, healthy scientific debates. You can have your scientific and medical advisors attend and I will invite an equal number. I am not saying this to be challenging. I honestly think it would be a great way to educate our campus community and expose them to the full spectrum of the science. And, if I am as wrong as my 'fact checkers' say, I would love for them to demonstrate this for my own sake as much as anyone else's. So far, despite hundreds of invitations, not one person has done this in a scenario where I can respond in real-time. You need to understand; all I want is my life back and to be able to recognize my country again. I want to see the lives of the students, staff, and other faculty members that I have seen destroyed **be restored** again. I want to be able to return to my workplace and not be fearful of being hated or exposed to social, mental, and physical bullying. Instead, I want to be able to turn my talents and full attention back to being an academic public servant who can design better ways to treat diseases and help train Canada's next generation of scientific and medical leaders. I simply cannot know all that I have shared in this letter and have suffered as much as I have and be silent about it. My great uncles and family members before them served heroically in the World Wars to ensure Canada would remain a great and free democracy. I think they would be horrified by what they see in Canada today. Indeed, many of my friends who immigrated from Communist countries or countries run by dictatorships are sharing fears about the direction our country is heading; it is reminding them of what they fled from. Further, mandating COVID-19 sets a scary precedent. Did you know that multiplex tests for both SARS-CoV-2 and influenza viruses are on the horizon, along with dual-purpose vaccines that will use the same mRNA-based technology to simultaneously target SARS-CoV-2 and influenza viruses (<https://www.ctvnews.ca/health/coronavirus/moderna-developing-single-dose-covid-19-flu-combo-vaccine-1.5578445>). Rhetorically, will the University of Guelph consider masking, distancing, and/or mandating vaccines for influenza in the future? **Please rescind your COVID-19 vaccine mandate immediately. It is doing more harm than good. Unbelievably, among many other problems, it is even discriminating against those who can prove they are immune to SARS-CoV-2!**

Mandating COVID-19 Vaccines Creates Absurd Situations

In closing, and to highlight the absurdity of mandating COVID-19 vaccines... President Yates, I have proven to you that I am immune to SARS-CoV-2, but you have banned me from the campus and ruined my life because I don't have a piece of paper saying that someone saw two needles go into my shoulder. You have a piece of paper that says that someone saw two needles go into your shoulder, but you have not proven that you are immune to SARS-CoV-2. However, you are allowed on campus and your life can proceed uninterrupted. **How is that fair?**

Respectfully and in the mutual interest of the health and well-being of **all** members of our community,



Dr. Byram W. Bridle, PhD
Associate Professor of Viral Immunology
Department of Pathobiology
University of Guelph

COMIRNATY™ COVID-19 VACCINE

This is the attachment marked BEL-3 referred to in the Affidavit/Declaration of BYRAM BRIDLE Sworn/Affirmed/Declared at AUCKLAND on this 05 day of JANUARY 2022 before me:
Signature [Signature] PO5824

Consumer Medicine Information (CMI) summary

The [full CMI](#) on the next page has more details. If you are worried about receiving this vaccine, speak to your doctor or pharmacist.

1. Why am I being given COMIRNATY?

COMIRNATY is a vaccine given to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults and adolescents from 12 years of age and older. COMIRNATY contains the active ingredient BNT162b2 [mRNA]. For more information, see Section [1. Why am I being given COMIRNATY?](#) in the full CMI.

2. What should I know before I am given COMIRNATY?

You should not be given COMIRNATY if you have had an allergic reaction to any of the ingredients in COMIRNATY. See list at the end of the CMI.

Check with your doctor if you have had: a severe allergic reaction or breathing problems after any other vaccine or after being given COMIRNATY in the past; fainted following any needle injection; a severe illness or infection with high fever; a weakened immune system or are on a medicine that affects your immune system; a bleeding disorder, bruise easily or are on a blood thinning medicine.

As with any vaccine, COMIRNATY may not fully protect all those who receive it and it is not known how long you will be protected.

Talk to your doctor if you have any other medical conditions, take any other medicines, or are pregnant or plan to become pregnant or are breastfeeding.

COMIRNATY should not be given to children under 12 years. For more information, see Section [2. What should I know before I am given COMIRNATY?](#) in the full CMI.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription. Tell your doctor or pharmacist if you have recently received any other vaccine. For more information, see Section [3. What if I am taking other medicines?](#) in the full CMI.

4. How will I be given COMIRNATY?

COMIRNATY will be given as an injection into the muscle of your upper arm by a doctor, nurse or pharmacist. You will be given one dose followed by a second dose at least 21 days later. It is very important that you receive your second dose. A doctor, nurse or pharmacist will observe you for at least 15 minutes after being given COMIRNATY. For more information, see Section [4. How will I be given COMIRNATY?](#) in the full CMI.

5. What should I know while being given COMIRNATY?

Things you should know	<ul style="list-style-type: none">If you receive one dose of COMIRNATY, you should receive a second dose of the same vaccine 21 days later to complete the vaccination schedule.You may not be protected against COVID-19 disease until at least seven days after your second dose.You may not be protected if you only receive one dose, so a second dose is important.
Driving or using machines	<ul style="list-style-type: none">Be careful before you drive or use any machines or tools until you know how COMIRNATY affects you. Some of the side effects of COMIRNATY may temporarily affect your ability to drive or use machines.

For more information, see Section [5. What should I know while being given COMIRNATY?](#) in the full CMI.

6. Are there any side effects?

Very common side effects of COMIRNATY include pain/swelling at injection site, tiredness, headache, muscle pain, chills, joint pain and fever. For more information, including what to do if you have any side effects, see Section [6. Are there any side effects?](#) in the full CMI.

COMIRNATY™ COVID-19 VACCINE

Active ingredient: BNT162b2 [mRNA]

Consumer Medicine Information (CMI)

This leaflet provides important information about using COMIRNATY. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about receiving COMIRNATY.**

Where to find information in this leaflet:

- [1. Why am I being given COMIRNATY?](#)
- [2. What should I know before I am given COMIRNATY?](#)
- [3. What if I am taking other medicines?](#)
- [4. How will I be given COMIRNATY?](#)
- [5. What should I know while being given COMIRNATY?](#)
- [6. Are there any side effects?](#)
- [7. Product details](#)

1. Why am I being given COMIRNATY?

COMIRNATY contains the active ingredient BNT162b2 [mRNA]. COMIRNATY is an mRNA (messenger ribonucleic acid) vaccine.

COMIRNATY is a vaccine given to prevent COVID-19 disease caused by SARS-CoV-2 virus in adults and adolescents from 12 years of age and older.

COMIRNATY works by triggering your immune system to produce antibodies and blood cells that work against the virus, to protect against COVID-19 disease.

2. What should I know before I am given COMIRNATY?

Warnings

COMIRNATY should not be given:

- if you are allergic to BNT162b2 [mRNA] or any of the ingredients listed at the end of this leaflet.

Check with your doctor if you have:

- had a severe allergic reaction or breathing problems after any other vaccine or after being given COMIRNATY in the past.
- fainted following any needle injection.
- a severe illness or infection with high fever. However, you can have your vaccination if you have a mild fever or upper airway infection like a cold.
- a weakened immune system, such as due to HIV infection or are on a medicine that affects your immune system.

- a bleeding disorder, bruise easily or are on a blood thinning medicine.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section [6. Are there any side effects?](#)

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported after vaccination with COMIRNATY. The cases have mostly occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger men. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

You may develop a temporary, stress-related response associated with the process of receiving your injection. This may include dizziness, fainting, sweating, increased heart rate and/or anxiety.

As with any vaccine, COMIRNATY may not fully protect all those who receive it and it is not known how long you will be protected.

Pregnancy and breastfeeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this vaccine.

Children and adolescents

COMIRNATY should not be given to children under 12 years.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Tell your doctor or pharmacist if you have recently received any other vaccine.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect, or are affected by, COMIRNATY.

4. How will I be given COMIRNATY?

- COMIRNATY will be given as an injection into the muscle of your upper arm by a doctor, nurse or pharmacist.
- You will be given one dose followed by a second dose at least 21 days later. If you miss the second dose, ask your doctor for advice.

- A doctor, nurse or pharmacist will observe you for at least 15 minutes after being given COMIRNATY.

5. What should I know while being given COMIRNATY?

Things you should know

- If you receive one dose of COMIRNATY, you should receive a second dose of the same vaccine at least 21 days later to complete the vaccination schedule.
- You may not be protected against COVID-19 disease until at least seven days after your second dose.
- You may not be protected if you only receive one dose, so a second dose is important.

Driving or using machines

Be careful before you drive or use any machines or tools until you know how COMIRNATY affects you.

Some of the side effects of COMIRNATY may temporarily affect your ability to drive or use machines.

Storage of the vaccine

COMIRNATY is stored at -90 °C to -60 °C. It must be kept in the original package in order to protect from light.

A doctor, nurse or pharmacist will prepare the injection for you before you are given it.

Getting rid of any unwanted vaccine

A doctor, nurse or pharmacist will dispose of any unused vaccine.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.

See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Very common side effects

Very common side effects	What to do
<ul style="list-style-type: none"> • pain/swelling at injection site • tiredness • headache • muscle pain • chills • joint pain • fever 	<p>Speak to your doctor if you have any of these very common side effects and they worry you.</p>

Common side effects

Common side effects	What to do
<ul style="list-style-type: none"> • redness at injection site • nausea • 	<p>Speak to your doctor if you have any of these common side effects and they worry you.</p>

Uncommon side effects

Uncommon side effects	What to do
<ul style="list-style-type: none"> • enlarged lymph nodes • feeling unwell • insomnia • decreased appetite • excessive sweating • night sweats • physical weakness and/or lack of energy • 	<p>Speak to your doctor if you have any of these side effects and they worry you.</p>

Rare side effects

Rare side effects	What to do
<ul style="list-style-type: none"> • temporary one-sided facial drooping • 	<p>Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice this side effect.</p>

Other side effects (frequency unknown)

Other side effects (frequency unknown)	What to do
<ul style="list-style-type: none"> • severe allergic reaction • allergic reactions such as rash, itching, hives or swelling of the face • inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in chest pain, breathlessness and/or palpitations 	<p>Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice this serious side effect.</p>
<ul style="list-style-type: none"> • diarrhoea • vomiting • pain in arm 	<p>Speak to your doctor if you have any of these side effects and they worry you.</p>

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

7. Product details

What COMIRNATY contains

Active ingredient (main ingredient)	<ul style="list-style-type: none">• BNT162b2 [mRNA]
Other ingredients (inactive ingredients)	<ul style="list-style-type: none">• ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)• 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)• Distearoylphosphatidylcholine (DSPC)• Cholesterol• Potassium chloride• Monobasic potassium phosphate• Sodium chloride• Dibasic sodium phosphate dihydrate• Sucrose• Water for injections

Do not receive this vaccine if you are allergic to any of these ingredients.

What COMIRNATY looks like

COMIRNATY is a white to off-white suspension provided in a multidose clear glass vial.

After dilution, each vial contains 6 doses of vaccine.

Who distributes COMIRNATY

Pfizer New Zealand Limited

PO Box 3998

Auckland

Toll Free Number: 0800 736 363

This leaflet was prepared in July 2021.

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Pfizer New Zealand Limited
Level 1, Suite 1.4, Building B
8 Nugent Street, Grafton, Auckland 1023
PO Box 3998, Shortland Street, Auckland, New Zealand 1140
Tel: 09 354 3065 Fax: 09 374 7630

EXHIBIT NOTE	
This is the attachment marked	B21-4 referred to in the
Affidavit/Declaration of	BYRAM BRIDLE
Sworn/Affirmed/Declared at	DUNEDIN
this	25 day of JANUARY 2020 before me:
Signature	<i>[Signature]</i> P05824

Pfizer New Zealand Limited

14 February 2021

Dear Healthcare Professional,

Supply of COMIRNATY COVID-19 Vaccine in New Zealand

Pfizer New Zealand Limited has commenced supply of COMIRNATY COVID-19 VACCINE 0.5 mg/mL concentrated suspension for injection. COMIRNATY is indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older. The use of this vaccine should be in accordance with official recommendations.

As the national COVID-19 immunisation plan is being implemented as quickly as possible, it is appropriate that important practical information regarding this vaccine is understood.

Identification and labelling

Pfizer's COVID-19 vaccine is supplied as a concentrated suspension in a 2 mL, multi-dose glass vial with a purple, flip-off cap. The vaccine will be supplied in trays containing 195 vials, or other packaging configurations depending upon the agreement with the New Zealand government.

Due to the nature of the pandemic, production and supply of the vaccine is being managed in a just-in-time model, which means that it is possible to receive the vaccine packaged in a number of different artworks. Given the name of the vaccine and the name of the active ingredient have changed over time, it is possible that the following names may appear on labels, inserts and other associated packaging components:

Product name:

Pfizer-BioNTech COVID-19 Vaccine
COVID-19 Vaccine
COVID-19 mRNA Vaccine
COMIRNATY

Active ingredient (generic) name:

BNT162b2 [mRNA]

Irrespective of the pack livery, all are equivalent, in that they refer to the same product with the same formulation.

Example product labelling is attached to this letter. Please be aware of the following:

1. **'Pfizer-BioNTech COVID-19 Vaccine'** (see Attachment 1):

- The labels will also state that they are for use under Emergency Use Authorization. This statement has been included to meet the requirements of the US Food and Drug Administration (FDA) but is not relevant or applicable to the vaccine's use in New Zealand.
- The labels will state that the vaccine **MUST BE DILUTED BEFORE USE** with sterile 0.9% Sodium Chloride Injection, USP. However, any pharmacopeial grade of sterile 0.9% sodium chloride can be used for dilution of this vaccine.
- The use of the name 'BNT 162b2 (SARS-COV-2-mRNA vaccine) 5-dose vial' in the fact sheet is not applicable to NZ. Vaccine supplied in NZ will be referred to differently, as explained above).
- The vials instruct to record the Date and Time of **dilution**, this is aligned with the instructions in the Medsafe-approved Data Sheet.

2. **Product supplied with the tradename 'COMIRNATY'** (see Attachment 2):

- Instructions on the vials require the Date and Time that the vial contents should be **discarded** to be recorded on the vial. This is different to the instructions in the Medsafe approved Data Sheet, which instruct to record the Date and Time of dilution.

Number of doses per vial

This is a multidose vial and must be diluted with 1.8 mL 0.9% saline solution before use. Instructions for dilution are contained in the Medsafe approved Data Sheet available at www.medsafe.govt.nz/profs/Datasheet/c/comirnatyinj.pdf. One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution. 1 dose (0.3 mL) contains 30 micrograms of BNT162b2 [mRNA] (embedded in lipid nanoparticles).

Whilst some stock is labelled as containing 5 doses when diluted, 6 doses may be withdrawn from each vial, **if the appropriate combination of low dead-volume needles and/or syringes is used**. This information is reflected in the Medsafe-approved Data Sheet. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose. If the amount of vaccine remaining in the vial cannot provide a full 0.3 mL dose, discard the vial and any excess volume. **DO NOT** pool excess vaccine from multiple vials.

Each box of the vaccine may contain either the US fact sheet or the EU fact sheet as a package insert. For the purpose of use in New Zealand, please refer to the Medsafe-approved Data Sheet for COMIRNATY that is available on the Medsafe website.

Storage requirements for the frozen, thawed and diluted vaccine

Adherence to the storage and handling guidance relating to the vaccine is critical to ensuring its quality and efficacy. As all of the storage guidance may not be present on the labels supplied, please ensure that the following guidance is followed when storing the vaccine. This guidance is also provided in the Medsafe-approved Data Sheet and the resources provided by Pfizer.

Frozen vaccine

The vaccine is shipped frozen to New Zealand, and must be stored in a freezer at -90°C to -60°C. The vaccine should be kept in the original package in order to protect it from light. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Refer to sections 6.3 and 6.4 of the Data Sheet for additional information on handling the frozen vial trays.

Thawed vaccine

The vaccine must be thawed prior to dilution. Frozen vials should be transferred to an environment of 2°C to 8°C to thaw; a 195 vial pack may take 3 hours to thaw. Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 30°C for immediate use.

Once removed from the freezer, the unopened vaccine can be stored for up to 5 days at 2°C to 8°C, and up to 2 hours at temperatures up to 30 °C, prior to use. Thawed vials can be handled in room light conditions. Once thawed, COMIRNATY should not be re-frozen.

Depending upon your location, you could receive the vials pre-thawed at 2°C to 8°C. Vials that have been pre-thawed at a site approved by the New Zealand Ministry of Health will be repackaged in new cartons containing 5 or 15 vials per carton, and will be labelled with the thawed expiry date (5 days from the date of thawing). **If you receive the vaccine pre-thawed, please note the expiry date that is marked on the carton label, as this represents the date that the vaccine must be diluted and administered by.**

Diluted vaccine

For diluted medicinal product, chemical and physical in-use stability has been demonstrated for 6 hours at 2°C to 30°C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

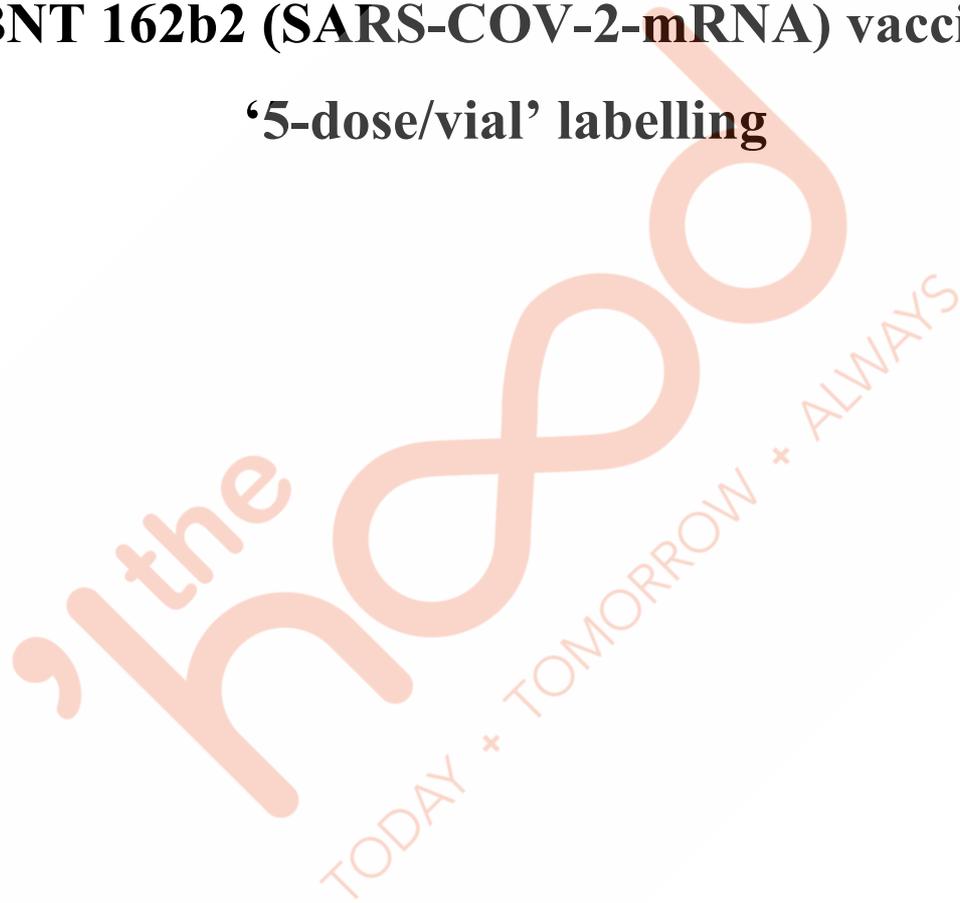
For additional information regarding Pfizer's COVID-19 vaccine, refer to the COMIRNATY Data Sheet on the Medsafe website www.medsafe.govt.nz/profs/Datasheet/c/comirnatyinj.pdf, or contact Pfizer by phone (0800 736 363) or e-mail medicalaffairs.anz@pfizer.com



Scott Williams
Vaccines Medical Director New Zealand, Australia and Korea

Attachment 1

BNT 162b2 (SARS-COV-2-mRNA) vaccine '5-dose/vial' labelling



NO COPY

Pfizer-BioNTech
COVID-19 Vaccine
Suspension for Intramuscular Injection
195 Multiple Dose Vials
(after dilution each vial contains 5 doses of 0.3 mL)

STORAGE:
Prior to dilution, store at -80°C to -60°C (-112°F to -76°F).
Store in this carton to protect from light.

DOSAGE AND ADMINISTRATION:
After dilution, each vial contains 5 doses of 0.3 mL.
See FDA-authorized Fact Sheet for dosage, preparation and administration information.

MUST BE DILUTED BEFORE USE.
Dilute with sterile 0.9% Sodium Chloride Injection, USP (not supplied).
After dilution, store the vaccine at 2°C to 30°C (35°F to 86°F).
Use within 6 hours of dilution.
Discard any unused vaccine or any vaccine frozen after dilution.
Contains no preservatives.

Rx only

NDC 59267-1000-2

Manufactured by
Pfizer Inc
New York, NY 10017
Manufactured for
BioNTech
Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany
For Use under Emergency
Use Authorization.

359267100023
EPO UPC @ 100%



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NO COPY, NO INK,

EXP:

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Pfizer-BioNTech COVID-19 Vaccine
Suspension for Intramuscular Injection
195 Multiple Dose Vials
(after dilution each vial contains 5 doses of 0.3 mL)

STORAGE: Prior to dilution, store at -80°C to -60°C (-112°F to -76°F).
Store in this carton to protect from light.

DOSAGE AND ADMINISTRATION:
After dilution, each vial contains 5 doses of 0.3 mL.
See FDA-authorized Fact Sheet for dosage, preparation and administration information.

MUST BE DILUTED BEFORE USE.
Dilute with sterile 0.9% Sodium Chloride Injection, USP (not supplied).
After dilution, store the vaccine at 2°C to 30°C (35°F to 86°F).
Use within 6 hours of dilution.
Discard any unused vaccine or any vaccine frozen after dilution.
Contains no preservatives.

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PAA156052

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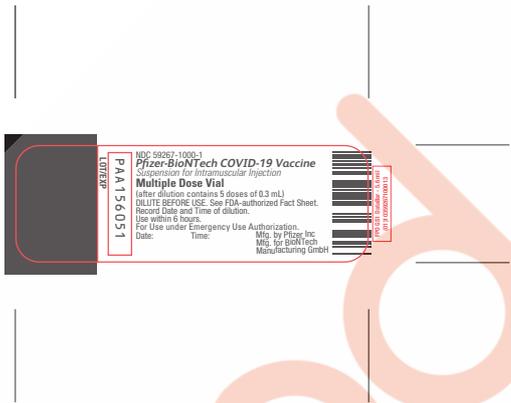
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the hoodnz

TODAY + TOMORROW + ALWAYS

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Mgr D. M. Guerin	Rev 4	GA	PR	GS / ART REV (LCA)	GS / ART REV (FA)
GS J. Wood			CHANGES OK	CHANGES OK	CHANGES OK
GA T. Nowak					



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 TODAY + TOMORROW + ALWAYS

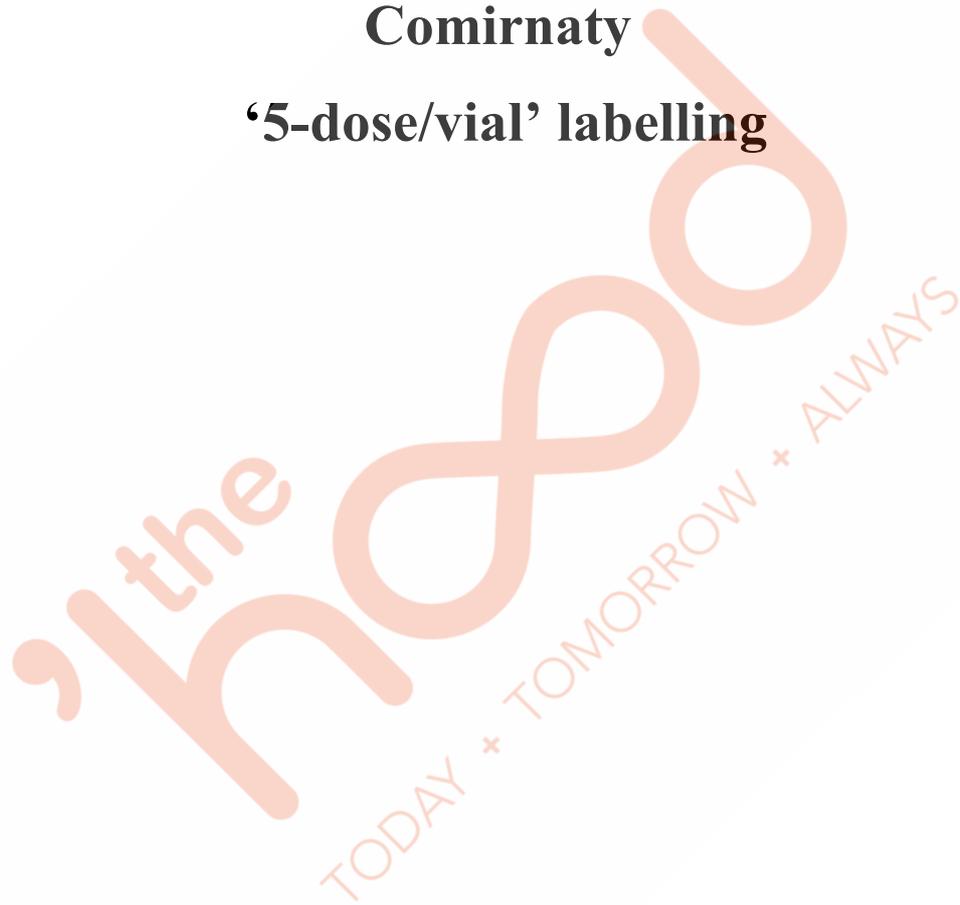
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Mgr	D. M. Guerin	Rev	GA	PR	GS / ART REV (LCA)	GS / ART REV (FA)
GS	J. Wood	4		CHANGES	CHANGES	CHANGES
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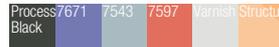
Attachment 2

Comirnaty '5-dose/vial' labelling



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Concentrate for dispersion for injection
COVID-19 mRNA Vaccine
 Intramuscular use after dilution
195 multidose vials
 (After dilution, each vial contains 5 doses of 0.3 mL.)

Storage: Prior to dilution, store at -90°C to -60°C in the original package in order to protect from light. After dilution, store the vaccine at 2°C to 30°C and use within 6 hours. Discard any unused vaccine.

Dilute before use: Dilute each vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection.
 Read the package leaflet before use.

Excipients: ALC-0315, ALC-0159, DSPC, cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate, sucrose, water for injections.

BIONTECH | 

BioNTech Manufacturing GmbH
 An der Goldgrube 12
 55131 Mainz, Germany

Scan QR code for more information



EU/1/20/1528

COMIRNATY™

Concentrate for dispersion for injection
COVID-19 mRNA Vaccine
 Intramuscular use after dilution
195 multidose vials
 Prior to dilution, store at -90°C to -60°C.

PC: 04260703260002
 Lot/EXP/SN

OVERPRINT AREA

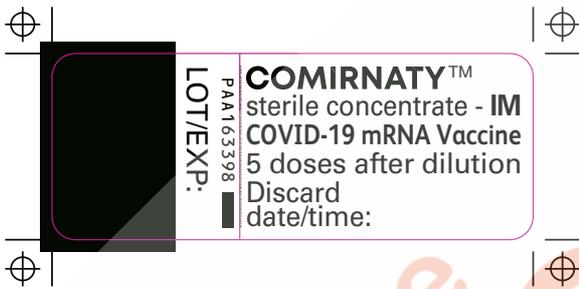
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PAA164513

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date:26-Nov-20 16:24:39



itemnr.: PAA163398

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<i>date/initials:</i> 25-Nov-20/SPEN			
<i>country:</i> EU			
<i>sourcecode:</i>			

EXHIBIT NOTE	
This is the attachment marked <u>B21-5</u> referred to in the Affidavit/Declaration of <u>BYEAM BEIDLE</u>	
Sworn/Affirmed/Declared at <u>Auckland, GÜELPH, ONT</u>	
this <u>25</u> day of <u>JANUARY</u> 20 <u>22</u> before me:	
Signature: <u>[Signature]</u> P05826	

**FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING
(VACCINATION PROVIDERS)**

**EMERGENCY USE AUTHORIZATION (EUA) OF
THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS
DISEASE 2019 (COVID-19)**

**FOR 12 YEARS OF AGE AND OLDER
DILUTE BEFORE USE**

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, for active immunization to prevent COVID-19 in individuals 5 years of age and older.

There are 2 formulations of Pfizer-BioNTech COVID-19 Vaccine authorized for use in individuals 12 years of age and older:

The formulation supplied in a multiple dose vial with a purple cap **MUST BE DILUTED PRIOR TO USE.**

The formulation supplied in a multiple dose vial with a gray cap and label with a gray border **IS NOT DILUTED PRIOR TO USE.**

This Fact Sheet pertains only to Pfizer-BioNTech COVID-19 Vaccine supplied in a multiple dose vial with a purple cap, which is authorized for use in individuals 12 years of age and older and **MUST BE DILUTED PRIOR TO USE.**

Pfizer-BioNTech COVID-19 Vaccine supplied in a multiple dose vial with a purple cap is authorized for use to provide:

- a 2-dose primary series to individuals 12 years of age and older;
- a third primary series dose to individuals 12 years of age and older who have been determined to have certain kinds of immunocompromise;
- a single booster dose to individuals 12 years of age and older who have completed a primary series with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA); and
- a single booster dose to individuals 18 years of age and older who have completed primary vaccination with a different authorized COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

COMIRNATY (COVID-19 Vaccine, mRNA) is an FDA-approved COVID-19 vaccine made by Pfizer for BioNTech that is indicated for active immunization to prevent COVID-19 in individuals 16 years of age and older. It is approved for use as a 2-dose primary series for the prevention of COVID-19 in

individuals 16 years of age and older. It is also authorized for emergency use to provide:

- a 2-dose primary series to individuals 12 through 15 years of age;
- a third primary series dose to individuals 12 years of age and older who have been determined to have certain kinds of immunocompromise;
- a single booster dose to individuals 12 years of age and older who have completed a primary series with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA); and
- a single booster dose to individuals 18 years of age and older who have completed primary vaccination with a different authorized COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

The FDA-approved COMIRNATY (COVID-19 Vaccine, mRNA) and the EUA-authorized Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years of age and older when prepared according to their respective instructions for use can be used interchangeably.¹

COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine intended for individuals 12 years of age and older should not be used for individuals 5 through 11 years of age because of the potential for vaccine administration errors, including dosing errors.²

SUMMARY OF INSTRUCTIONS FOR COVID-19 VACCINATION PROVIDERS

Vaccination providers enrolled in the federal COVID-19 Vaccination Program must report all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine. See “MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION” for reporting requirements.

¹ When prepared according to their respective instructions for use, the FDA-approved COMIRNATY (COVID-19 Vaccine, mRNA) and the EUA-authorized Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years of age and older can be used interchangeably without presenting any safety or effectiveness concerns.

² Notwithstanding the age limitations for use of the different formulations and presentations described above, individuals who will turn from 11 years to 12 years of age between their first and second dose in the primary regimen may receive, for either dose, either: (1) the Pfizer-BioNTech COVID-19 Vaccine authorized for use in individuals 5 through 11 years of age (each 0.2 mL dose containing 10 mcg modRNA) (supplied in multidose vials with orange caps); or (2) COMIRNATY (COVID-19 Vaccine, mRNA) or the Pfizer-BioNTech COVID-19 Vaccine authorized for use in individuals 12 years of age and older (each 0.3 mL dose containing 30 mcg modRNA) (supplied in multidose vials with gray caps and multidose vials with purple caps).

The Pfizer-BioNTech COVID-19 Vaccine is a suspension for intramuscular injection.

Primary Series

The Pfizer-BioNTech COVID-19 Vaccine is administered as a primary series of 2 doses (0.3 mL each) 3 weeks apart in individuals 12 years of age or older.

A third primary series dose of the Pfizer-BioNTech COVID-19 Vaccine (0.3 mL) at least 28 days following the second dose is authorized for administration to individuals at least 12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Booster Dose

A single Pfizer-BioNTech COVID-19 Vaccine booster dose (0.3 mL) may be administered at least 5 months after completing a primary series of the Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY to individuals 12 years of age and older.

A single booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be administered to individuals 18 years of age and older as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

See this Fact Sheet for instructions for preparation and administration. This Fact Sheet may have been updated. For the most recent Fact Sheet, please see www.cvdvaccine.com.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine for active immunization against COVID-19, please see www.clinicaltrials.gov.

DESCRIPTION OF COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that appeared in late 2019. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

DOSAGE AND ADMINISTRATION

The storage, preparation, and administration information in this Fact Sheet apply to the Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years of age and older, which is supplied in a multiple dose vial with a purple cap and **MUST BE DILUTED** before use.

Pfizer-BioNTech COVID-19 Vaccine, Multiple Dose Vial with Purple Cap

Age Range	Dilution Information	Doses Per Vial After Dilution	Dose Volume
12 years and older	Dilute with 1.8 mL sterile 0.9% Sodium Chloride Injection, USP prior to use	6	0.3 mL

Storage and Handling

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine multiple dose vials with purple caps arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and preferably store in an ultra-low temperature freezer between -90°C to -60°C (-130°F to -76°F) until the expiry date printed on the label. This information in the package insert supersedes the storage conditions printed on the vial cartons.

Cartons and vials of Pfizer-BioNTech COVID-19 Vaccine supplied in multiple dose vials with purple caps with an expiry date of September 2021 through February 2022 printed on the label may remain in use for 3 months beyond the printed date as long as approved storage conditions between -90°C to -60°C (-130°F to -76°F) have been maintained. Updated expiry dates are shown below.

<u>Printed Expiry Date</u>		<u>Updated Expiry Date</u>
September 2021	→	December 2021
October 2021	→	January 2022
November 2021	→	February 2022
December 2021	→	March 2022
January 2022	→	April 2022
February 2022	→	May 2022

If not stored between -90°C to -60°C (-130°F to -76°F), vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Vials must be kept frozen and protected from light until ready to use. Vials stored at -25°C to -15°C (-13°F to 5°F) for up to

2 weeks may be returned one time to the recommended storage condition of -90°C to -60°C (-130°F to -76°F). Total cumulative time the vials are stored at -25°C to -15°C (-13°F to 5°F) should be tracked and should not exceed 2 weeks.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Transportation of Frozen Vials

If local redistribution is needed and full cartons containing vials cannot be transported at -90°C to -60°C (-130°F to -76°F), vials may be transported at -25°C to -15°C (-13°F to 5°F). Any hours used for transport at -25°C to -15°C (-13°F to 5°F) count against the 2-week limit for storage at -25°C to -15°C (-13°F to 5°F). Frozen vials transported at -25°C to -15°C (-13°F to 5°F) may be returned one time to the recommended storage condition of -90°C to -60°C (-130°F to -76°F).

Thawed Vials Before Dilution

Thawed Under Refrigeration

Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 1 month. A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature

For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions. Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Transportation of Thawed Vials

Available data support transportation of one or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours.

Vials After Dilution

- After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution.
- During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
- Any vaccine remaining in vials must be discarded after 6 hours.
- Do not refreeze.

Dosing and Schedule

Primary Series

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a primary series of 2 doses (0.3 mL each) 3 weeks apart to individuals 12 years of age and older.

A third primary series dose of the Pfizer-BioNTech COVID-19 Vaccine (0.3 mL) at least 28 days following the second dose is authorized for administration to individuals at least 12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Booster Dose

A single Pfizer-BioNTech COVID-19 Vaccine booster dose (0.3 mL) may be administered at least 5 months after completing a primary series of the Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY to individuals 12 years of age and older.

A single booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be administered to individuals 18 years of age and older as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

The FDA-approved COMIRNATY (COVID-19 Vaccine, mRNA) and the EUA-authorized Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years of age and older when prepared according to their respective instructions for use, can be used interchangeably.

COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine intended for individuals 12 years of age and older should not be used for individuals 5 through 11 years of age because of the potential for vaccine administration errors, including dosing errors.

Dose Preparation

Each vial **MUST BE DILUTED** before administering the vaccine.

Prior to Dilution

- The Pfizer-BioNTech COVID-19 Vaccine multiple dose vial with a purple cap contains a volume of 0.45 mL and is supplied as a frozen suspension that does not contain preservative.
- Each vial must be thawed before dilution.
 - Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] (see *Storage and Handling*).
 - Refer to thawing instructions in the panels below.

Dilution

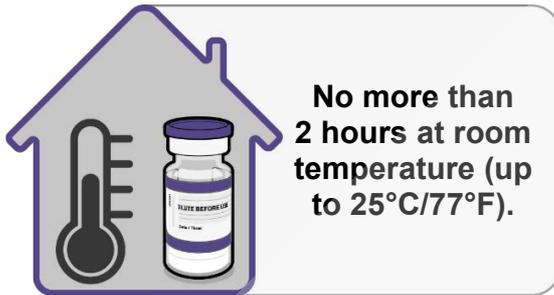
Dilute the vial contents using 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. ONLY use sterile 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent. Do not add more than 1.8 mL of diluent.

After dilution, 1 vial contains 6 doses of 0.3 mL.

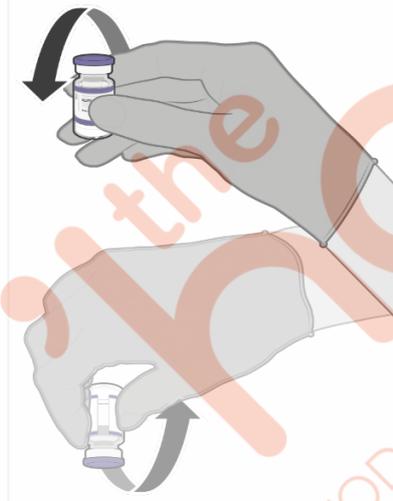
Dilution and Preparation Instructions	
Pfizer-BioNTech COVID-19 Vaccine Vial with Purple Cap – VIAL VERIFICATION	
 <p>✓ Purple plastic cap and purple label border.</p>	Verify that the vial of Pfizer-BioNTech COVID-19 Vaccine has a purple plastic cap. Some vials also may have a purple label border.

Dilution and Preparation Instructions

Pfizer-BioNTech COVID-19 Vaccine Vial with Purple Cap – THAWING PRIOR TO DILUTION



- Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by:
 - Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 1 month.
 - Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes.
- Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.

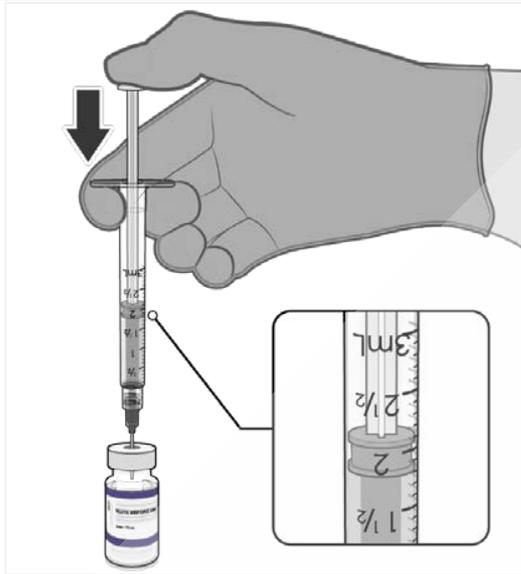


Gently × 10

- Before dilution invert vaccine vial gently 10 times.
- Do not shake.
- Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles.
- Do not use if liquid is discolored or if other particles are observed.

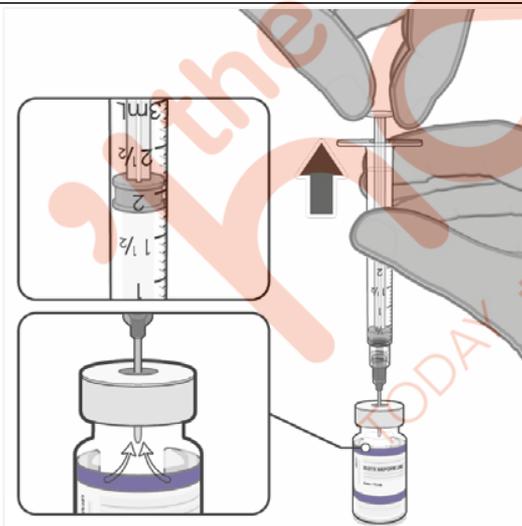
Dilution and Preparation Instructions

Pfizer-BioNTech COVID-19 Vaccine Vial with Purple Cap – DILUTION



Add 1.8 mL of sterile 0.9% sodium chloride injection, USP.

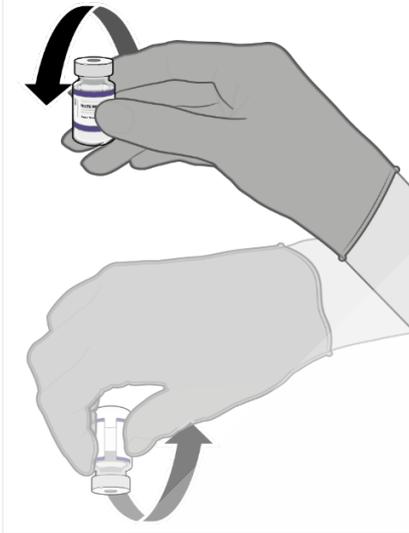
- Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent.
- Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle).
- Cleanse the vaccine vial stopper with a single-use antiseptic swab.
- Add 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP into the vaccine vial.



**Pull back plunger to 1.8 mL to
remove air from vial.**

Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.

Dilution and Preparation Instructions



Gently × 10

- Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix.
- Do not shake.
- Inspect the vaccine in the vial.
- The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.

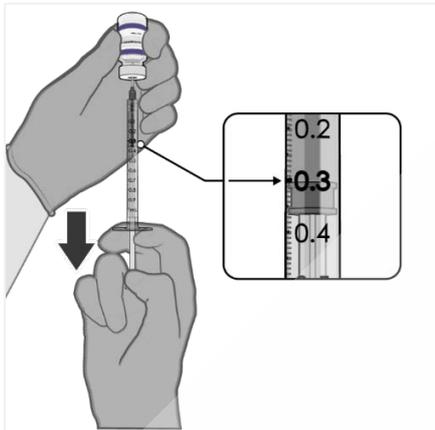


**Record the date and time of dilution.
Use within 6 hours after dilution.**

- Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label.
- Store between 2°C to 25°C (35°F to 77°F).
- Discard any unused vaccine 6 hours after dilution.

Dilution and Preparation Instructions

Pfizer-BioNTech COVID-19 Vaccine Vial with Purple Cap – WITHDRAWAL OF INDIVIDUAL 0.3 mL DOSES



Withdraw 0.3 mL dose of vaccine.

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using a low dead-volume syringe and/or needle.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Administer immediately.

Administration

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine with purple caps contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 6 doses from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and content.
- Do not pool excess vaccine from multiple vials.

Contraindications

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine (see *Full EUA Prescribing Information*).

Warnings

Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention (CDC) guidelines (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html>).

Myocarditis and Pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting.

Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

Limitation of Effectiveness

Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

Adverse Reactions

Adverse Reactions in Clinical Trials

Adverse reactions following administration of the Pfizer-BioNTech COVID-19 Vaccine that have been reported in clinical trials include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, lymphadenopathy, decreased appetite, rash, and pain in extremity (see *Full EUA Prescribing Information*).

Adverse Reactions in Post Authorization Experience

Severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema), diarrhea, vomiting, pain in extremity (arm), and syncope have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine.

Myocarditis and pericarditis have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine.

Use with Other Vaccines

There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

INFORMATION TO PROVIDE TO VACCINE RECIPIENTS/CAREGIVERS

As the vaccination provider, you must communicate to the recipient or their caregiver, information consistent with the “Vaccine Information Fact Sheet for Recipients and Caregivers” (and provide a copy or direct the individual to the website www.cvdvaccine.com to obtain the Vaccine Information Fact Sheet) prior to the individual receiving each dose of the Pfizer-BioNTech COVID-19 Vaccine, including:

- FDA has authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine, which is not an FDA-approved vaccine.
- The recipient or their caregiver has the option to accept or refuse Pfizer-BioNTech COVID-19 Vaccine.
- The significant known and potential risks and benefits of the Pfizer-BioNTech COVID-19 Vaccine, and the extent to which such risks and benefits are unknown.
- Information about available alternative vaccines and the risks and benefits of those alternatives.

For information on clinical trials that are testing the use of the Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19, please see www.clinicaltrials.gov.

Provide a vaccination card to the recipient or their caregiver with the date when the recipient needs to return for the second dose of Pfizer-BioNTech COVID-19 Vaccine.

Provide the v-safe information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in v-safe. V-safe is a new voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. V-safe also provides second-dose reminders if needed and live telephone follow-up by CDC if participants report a significant health impact following COVID-19 vaccination. For more information, visit: www.cdc.gov/vsafe.

MANDATORY REQUIREMENTS FOR PFIZER-BIONTECH COVID-19 VACCINE ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION³

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of Pfizer-BioNTech COVID-19 Vaccine, the following items are required. Use of unapproved Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 under this EUA is limited to the following (all requirements **must** be met):

1. Pfizer-BioNTech COVID-19 Vaccine is authorized for use in individuals 5 years of age and older.
2. The vaccination provider must communicate to the individual receiving the Pfizer-BioNTech COVID-19 Vaccine or their caregiver, information consistent with the “Vaccine Information Fact Sheet for Recipients and Caregivers” prior to the individual receiving Pfizer-BioNTech COVID-19 Vaccine.
3. The vaccination provider must include vaccination information in the state/local jurisdiction’s Immunization Information System (IIS) or other designated system.

³ Vaccination providers administering COMIRNATY (COVID-19 Vaccine, mRNA) must adhere to the same reporting requirements.

4. The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):
 - vaccine administration errors whether or not associated with an adverse event,
 - serious adverse events* (irrespective of attribution to vaccination),
 - cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
 - cases of COVID-19 that result in hospitalization or death.

Complete and submit reports to VAERS online at <https://vaers.hhs.gov/reportevent.html>. For further assistance with reporting to VAERS call 1-800-822-7967. The reports should include the words “Pfizer-BioNTech COVID-19 Vaccine EUA” in the description section of the report.

5. The vaccination provider is responsible for responding to FDA requests for information about vaccine administration errors, adverse events, cases of MIS in adults and children, and cases of COVID-19 that result in hospitalization or death following administration of Pfizer-BioNTech COVID-19 Vaccine to recipients.

* Serious adverse events are defined as:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent 1 of the outcomes listed above.

OTHER ADVERSE EVENT REPORTING TO VAERS AND PFIZER INC.

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

ADDITIONAL INFORMATION

For general questions, visit the website or call the telephone number provided below.

To access the most recent Pfizer-BioNTech COVID-19 Vaccine Fact Sheets, please scan the QR code provided below.

Global website	Telephone number
<p data-bbox="357 651 659 680">www.cvdvaccine.com</p> 	<p data-bbox="979 696 1190 725">1-877-829-2619</p> <p data-bbox="959 745 1211 775">(1-877-VAX-CO19)</p>

AVAILABLE ALTERNATIVES

COMIRNATY (COVID-19 Vaccine, mRNA) is an FDA-approved vaccine to prevent COVID-19 caused by SARS-CoV-2. There may be clinical trials or availability under EUA of other COVID-19 vaccines.

COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine intended for individuals 12 years of age and older should not be used for individuals 5 through 11 years of age because of the potential for vaccine administration errors, including dosing errors.

FEDERAL COVID-19 VACCINATION PROGRAM

This vaccine is being made available for emergency use exclusively through the CDC COVID-19 Vaccination Program (the Vaccination Program). Healthcare providers must enroll as providers in the Vaccination Program and comply with the provider requirements. Vaccination providers may not charge any fee for the vaccine and may not charge the vaccine recipient any out-of-pocket charge for administration. However, vaccination providers may seek appropriate reimbursement from a program or plan that covers COVID-19 vaccine administration fees for the vaccine recipient (private insurance, Medicare, Medicaid, Health Resources & Services Administration [HRSA] COVID-19 Uninsured Program for non-insured recipients). For information regarding provider requirements and enrollment in the CDC COVID-19 Vaccination Program, see <https://www.cdc.gov/vaccines/covid-19/provider-enrollment.html>.

Individuals becoming aware of any potential violations of the CDC COVID-19 Vaccination Program requirements are encouraged to report them to the Office of the Inspector General, U.S. Department of Health and Human Services, at 1-800-HHS-TIPS or <https://TIPS.HHS.GOV>.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, FDA has issued an EUA for the unapproved product, Pfizer-BioNTech COVID-19 Vaccine, and for certain uses of FDA-approved COMIRNATY (COVID-19 Vaccine, mRNA) for active immunization against COVID-19.

FDA issued this EUA, based on Pfizer-BioNTech's request and submitted data.

For the authorized uses, although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine and COMIRNATY (COVID-19 Vaccine, mRNA) may be effective for the prevention of COVID-19 in individuals as specified in the *Full EUA Prescribing Information*.

This EUA for the Pfizer-BioNTech COVID-19 Vaccine and COMIRNATY (COVID-19 Vaccine, mRNA) will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

For additional information about Emergency Use Authorization visit FDA at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

The Countermeasures Injury Compensation Program

The Countermeasures Injury Compensation Program (CICP) is a federal program that has been created to help pay for related costs of medical care and other specific expenses to compensate people injured after use of certain medical countermeasures. Medical countermeasures are specific vaccines, medications, devices, or other items used to prevent, diagnose, or treat the public during a public health emergency or a security threat. For more information about CICP regarding the Pfizer-BioNTech COVID-19 Vaccine used to prevent COVID-19, visit www.hrsa.gov/cicp, email cicp@hrsa.gov, or call: 1-855-266-2427.



Manufactured by
Pfizer Inc., New York, NY 10017

BIONTECH

Manufactured for
BioNTech Manufacturing GmbH
An der Goldgrube 12
55131 Mainz, Germany

LAB-1450-19.1

Revised: 03 January 2022

END SHORT VERSION FACT SHEET
Long Version (Full EUA Prescribing Information) Begins On Next Page

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TODAY * TOMORROW * ALWAYS

**FULL EMERGENCY USE
AUTHORIZATION (EUA) PRESCRIBING
INFORMATION**

PFIZER-BIONTECH COVID-19 VACCINE

**FULL EMERGENCY USE AUTHORIZATION
PRESCRIBING INFORMATION: CONTENTS***

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* Sections or subsections omitted from the full emergency use authorization prescribing information are not listed.

FULL EMERGENCY USE AUTHORIZATION (EUA) PRESCRIBING INFORMATION

1 AUTHORIZED USE

Pfizer-BioNTech COVID-19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 5 years of age and older.

This EUA Prescribing Information pertains only to Pfizer-BioNTech COVID-19 Vaccine supplied in a multiple dose vial with a purple cap, which is authorized for use in individuals 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

The storage, preparation, and administration information in this Prescribing Information apply to the Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years of age and older, which is supplied in a multiple dose vial with a purple cap and MUST BE DILUTED before use.

Pfizer-BioNTech COVID-19 Vaccine, Multiple Dose Vial with Purple Cap

Age Range	Dilution Information	Doses Per Vial After Dilution	Dose Volume
12 years and older	Dilute with 1.8 mL sterile 0.9% Sodium Chloride Injection, USP prior to use	6	0.3 mL

2.1 Preparation for Administration

Dose Preparation

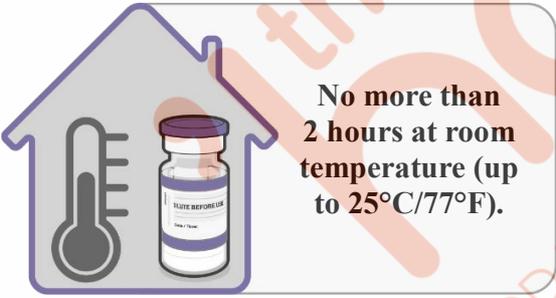
Each vial **MUST BE DILUTED** before administering the vaccine.

Prior to Dilution

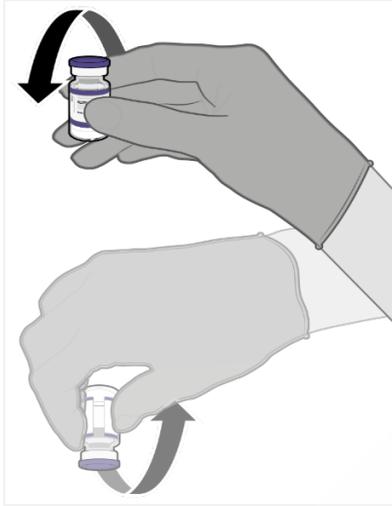
- The Pfizer-BioNTech COVID-19 Vaccine multiple dose vial with a purple cap contains a volume of 0.45 mL and is supplied as a frozen suspension that does not contain preservative.
- Each vial must be thawed before dilution.
- Vials may be thawed in the refrigerator [2°C to 8°C (35°F to 46°F)] or at room temperature [up to 25°C (77°F)] [see *How Supplied/Storage and Handling (19)*].
- Refer to thawing instructions in the panels below.

Dilution

- Dilute the vial contents using 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP (not provided) to form the Pfizer-BioNTech COVID-19 Vaccine. Do not add more than 1.8 mL of diluent.
- ONLY use sterile 0.9% Sodium Chloride Injection, USP as the diluent. This diluent is not packaged with the vaccine and must be sourced separately. Do not use bacteriostatic 0.9% Sodium Chloride Injection or any other diluent.
- After dilution, 1 vial contains 6 doses of 0.3 mL.

Dilution and Preparation Instructions	
Pfizer-BioNTech COVID-19 Vaccine Vial with Purple Cap – VIAL VERIFICATION	
 <p>✓ Purple plastic cap and purple label border.</p>	Verify that the vial of Pfizer-BioNTech COVID-19 Vaccine has a purple plastic cap. Some vials also may have a purple label border on the label.
Pfizer-BioNTech COVID-19 Vaccine Vial with Purple Cap – THAWING PRIOR TO DILUTION	
 <p>No more than 2 hours at room temperature (up to 25°C/77°F).</p>	<ul style="list-style-type: none">• Thaw vial(s) of Pfizer-BioNTech COVID-19 Vaccine before use either by:<ul style="list-style-type: none">○ Allowing vial(s) to thaw in the refrigerator [2°C to 8°C (35°F to 46°F)]. A carton of vials may take up to 3 hours to thaw, and thawed vials can be stored in the refrigerator for up to 1 month.○ Allowing vial(s) to sit at room temperature [up to 25°C (77°F)] for 30 minutes.• Using either thawing method, vials must reach room temperature before dilution and must be diluted within 2 hours.

Dilution and Preparation Instructions



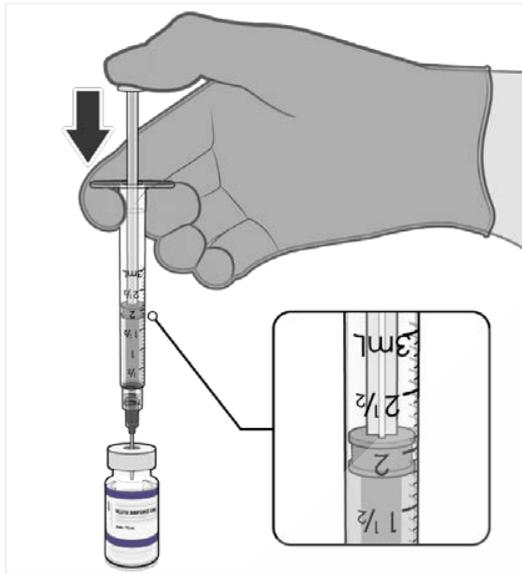
Gently × 10

- Before dilution invert vaccine vial gently 10 times.
- Do not shake.
- Inspect the liquid in the vial prior to dilution. The liquid is a white to off-white suspension and may contain white to off-white opaque amorphous particles.
- Do not use if liquid is discolored or if other particles are observed.

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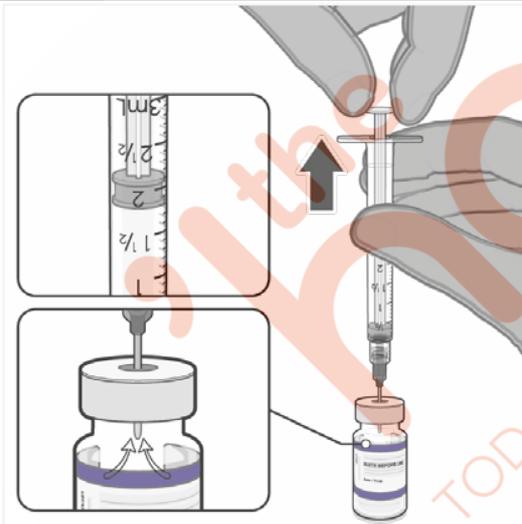
Dilution and Preparation Instructions

Pfizer-BioNTech COVID-19 Vaccine Vial with Purple Cap – DILUTION



Add 1.8 mL of sterile 0.9% sodium chloride injection, USP.

- Obtain sterile 0.9% Sodium Chloride Injection, USP. Use only this as the diluent.
- Using aseptic technique, withdraw 1.8 mL of diluent into a transfer syringe (21-gauge or narrower needle).
- Cleanse the vaccine vial stopper with a single-use antiseptic swab.
- Add 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP into the vaccine vial.



Pull back plunger to 1.8 mL to remove air from vial.

Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.

Dilution and Preparation Instructions



Gently × 10

- Gently invert the vial containing the Pfizer-BioNTech COVID-19 Vaccine 10 times to mix.
- Do not shake.
- Inspect the vaccine in the vial.
- The vaccine will be an off-white suspension. Do not use if vaccine is discolored or contains particulate matter.

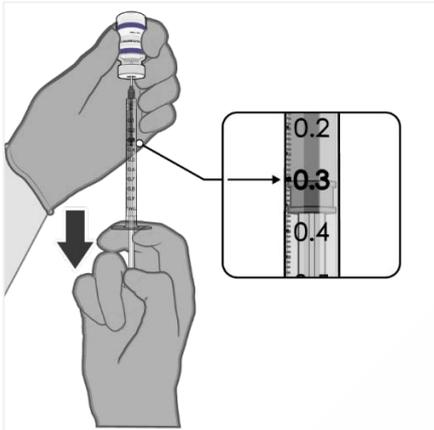


**Record the date and time of dilution.
Use within 6 hours after dilution.**

- Record the date and time of dilution on the Pfizer-BioNTech COVID-19 Vaccine vial label.
- Store between 2°C to 25°C (35°F to 77°F).
- Discard any unused vaccine 6 hours after dilution.

Dilution and Preparation Instructions

Pfizer-BioNTech COVID-19 Vaccine Vial with Purple Cap – WITHDRAWAL OF INDIVIDUAL 0.3 mL DOSES



Withdraw 0.3 mL dose of vaccine.

- Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the Pfizer-BioNTech COVID-19 Vaccine preferentially using a low dead-volume syringe and/or needle.
- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Administer immediately.

2.2 Administration Information

Visually inspect each dose in the dosing syringe prior to administration. The vaccine will be an off-white suspension. During the visual inspection,

- verify the final dosing volume of 0.3 mL.
- confirm there are no particulates and that no discoloration is observed.
- do not administer if vaccine is discolored or contains particulate matter.

Administer the Pfizer-BioNTech COVID-19 Vaccine intramuscularly.

After dilution, vials of Pfizer-BioNTech COVID-19 Vaccine with purple caps contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract 6 doses from a single vial.

Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

2.3 Vaccination Schedule

Primary Series

The Pfizer-BioNTech COVID-19 Vaccine is administered intramuscularly as a primary series of 2 doses (0.3 mL each) 3 weeks apart in individuals 12 years of age and older.

A third primary series dose of the Pfizer-BioNTech COVID-19 Vaccine (0.3 mL) at least 28 days following the second dose is authorized for administration to individuals at least 12 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Booster Dose

A single Pfizer-BioNTech COVID-19 Vaccine booster dose (0.3 mL) may be administered at least 5 months after completing a primary series of the Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY to individuals 12 years of age and older.

A single booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be administered to individuals 18 years of age and older as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

The FDA-approved COMIRNATY (COVID-19 Vaccine, mRNA) and the EUA-authorized Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years of age and older when prepared according to their respective instructions for use, can be used interchangeably.

COMIRNATY (COVID-19 Vaccine, mRNA) and the Pfizer-BioNTech COVID-19 Vaccine intended for individuals 12 years of age and older should not be used for individuals 5 through 11 years of age because of the potential for vaccine administration errors, including dosing errors.

3 DOSAGE FORMS AND STRENGTHS

Pfizer-BioNTech COVID-19 Vaccine is a suspension for injection.

After preparation, each dose of the Pfizer-BioNTech COVID-19 Vaccine supplied in vials with purple caps is 0.3 mL for individuals 12 years of age and older [*see Dosage and Administration (2.1)*].

4 CONTRAINDICATIONS

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine [*see Description (13)*].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine.

Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention (CDC) guidelines

(<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html>).

5.2 Myocarditis and Pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

5.3 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting.

5.4 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine.

5.5 Limitation of Effectiveness

The Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients.

6 OVERALL SAFETY SUMMARY

It is MANDATORY for vaccination providers to report to the Vaccine Adverse Event Reporting System (VAERS) all vaccine administration errors, all serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and hospitalized or fatal cases of COVID-19 following vaccination with the Pfizer-BioNTech COVID-19 Vaccine.⁴ To the extent feasible, provide a copy of the VAERS form to Pfizer Inc. Please see the REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS section for details on reporting to VAERS and Pfizer Inc.

⁴ Vaccination providers administering COMIRNATY (COVID-19 Vaccine, mRNA) must adhere to the same reporting requirements.

Primary Series

In clinical studies of participants 16 years of age and older who received Pfizer-BioNTech COVID-19 Vaccine containing 30 mcg of a nucleoside-modified messenger RNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 (30 mcg modRNA), adverse reactions following administration of the primary series included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%).

In a clinical study in adolescents 12 through 15 years of age who received Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA), adverse reactions following administration of the primary series included pain at the injection site (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), lymphadenopathy (0.8%), and nausea (0.4%).

Booster Dose

In a clinical study of participants 18 through 55 years of age, adverse reactions following administration of a booster dose were pain at the injection site (83.0%), fatigue (63.7%), headache (48.4%), muscle pain (39.1%), chills (29.1%), joint pain (25.3%), lymphadenopathy (5.2%), nausea (0.7%), decreased appetite (0.3%), rash (0.3%), and pain in extremity (0.3%).

Post Authorization Experience

Severe allergic reactions, including anaphylaxis, have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine.

Myocarditis and pericarditis have been reported following administration of the Pfizer-BioNTech COVID-19 Vaccine.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Primary Series

The safety of the primary series Pfizer-BioNTech COVID-19 Vaccine was evaluated in participants 12 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America.

Study BNT162-01 (Study 1) was a Phase 1/2, 2-part, dose-escalation trial that enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) is a Phase 1/2/3, multicenter, multinational, randomized, saline placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection (Phase 1) and efficacy (Phase 2/3) study that has enrolled approximately 46,000 participants, 12 years of age or older. Of these, approximately 43,448 participants [21,720 Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2; 21,728 placebo] in Phase 2/3 are 16 years of age or older (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively) and

2,260 adolescents are 12 through 15 years of age (1,131 and 1,129 in the vaccine and placebo groups, respectively).

In Study 2, all participants 12 through 15 years of age, and 16 years of age and older in the reactogenicity subset, were monitored for solicited local and systemic reactions and use of antipyretic medication after each vaccination in an electronic diary. Participants are being monitored for unsolicited adverse events, including serious adverse events, throughout the study [from Dose 1 through 1 month (all unsolicited adverse events) or 6 months (serious adverse events) after the last vaccination]. Tables 1 through 6 present the frequency and severity of solicited local and systemic reactions, respectively, within 7 days following each dose of Pfizer-BioNTech COVID 19 Vaccine and placebo.

Participants 16 Years of Age and Older

At the time of the analysis of Study 2 for the EUA, 37,586 [18,801 Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) and 18,785 placebo] participants 16 years of age or older had been followed for a median of 2 months after the second dose.

The safety evaluation in Study 2 is ongoing. The safety population includes participants 16 years of age and older enrolled by October 9, 2020, and includes safety data accrued through November 14, 2020.

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among participants who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the total participants who received either the Pfizer-BioNTech COVID-19 Vaccine or placebo, 50.6% were male and 49.4% were female, 83.1% were White, 9.1% were Black or African American, 28.0% were Hispanic/Latino, 4.3% were Asian, and 0.5% were American Indian/Alaska Native.

Solicited Local and Systemic Adverse Reactions

Across both age groups, 18 through 55 years of age and 56 years of age and older, the mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for swelling 2.3 days (range 1 to 34 days) for participants in the Pfizer-BioNTech COVID-19 Vaccine group.

Solicited reactogenicity data in 16 and 17 year-old participants are limited.

Table 1: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18 Through 55 Years of Age[‡] – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=2291 n^b (%)	Placebo Dose 1 N^a=2298 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=2098 n^b (%)	Placebo Dose 2 N^a=2103 n^b (%)
Redness^c				
Any (>2 cm)	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2)	10 (0.5)	0 (0.0)

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=2291 n^b (%)	Placebo Dose 1 N^a=2298 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=2098 n^b (%)	Placebo Dose 2 N^a=2103 n^b (%)
Swelling^c				
Any (>2 cm)	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0.0)
Pain at the injection site^d				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

‡ Eight participants were between 16 and 17 years of age.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

Table 2: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 18 Through 55 Years of Age[‡] – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=2291 n^b (%)	Placebo Dose 1 N^a=2298 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=2098 n^b (%)	Placebo Dose 2 N^a=2103 n^b (%)
Fever				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
≥38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)
Fatigue^c				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	467 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Headache^c				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321 (15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=2291 n^b (%)	Placebo Dose 1 N^a=2298 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=2098 n^b (%)	Placebo Dose 2 N^a=2103 n^b (%)
Chills^c				
Any	321 (14.0)	146 (6.4)	737 (35.1)	79 (3.8)
Mild	230 (10.0)	111 (4.8)	359 (17.1)	65 (3.1)
Moderate	82 (3.6)	33 (1.4)	333 (15.9)	14 (0.7)
Severe	9 (0.4)	2 (0.1)	45 (2.1)	0 (0.0)
Vomiting^d				
Any	28 (1.2)	28 (1.2)	40 (1.9)	25 (1.2)
Mild	24 (1.0)	22 (1.0)	28 (1.3)	16 (0.8)
Moderate	4 (0.2)	5 (0.2)	8 (0.4)	9 (0.4)
Severe	0 (0.0)	1 (0.0)	4 (0.2)	0 (0.0)
Diarrhea^e				
Any	255 (11.1)	270 (11.7)	219 (10.4)	177 (8.4)
Mild	206 (9.0)	217 (9.4)	179 (8.5)	144 (6.8)
Moderate	46 (2.0)	52 (2.3)	36 (1.7)	32 (1.5)
Severe	3 (0.1)	1 (0.0)	4 (0.2)	1 (0.0)
New or worsened muscle pain^c				
Any	487 (21.3)	249 (10.8)	783 (37.3)	173 (8.2)
Mild	256 (11.2)	175 (7.6)	326 (15.5)	111 (5.3)
Moderate	218 (9.5)	72 (3.1)	410 (19.5)	59 (2.8)
Severe	13 (0.6)	2 (0.1)	47 (2.2)	3 (0.1)
New or worsened joint pain^c				
Any	251 (11.0)	138 (6.0)	459 (21.9)	109 (5.2)
Mild	147 (6.4)	95 (4.1)	205 (9.8)	54 (2.6)
Moderate	99 (4.3)	43 (1.9)	234 (11.2)	51 (2.4)
Severe	5 (0.2)	0 (0.0)	20 (1.0)	4 (0.2)
Use of antipyretic or pain medication^f	638 (27.8)	332 (14.4)	945 (45.0)	266 (12.6)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

‡ Eight participants were between 16 and 17 years of age.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

Table 3: Study 2 – Frequency and Percentages of Participants with Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=1802 n^b (%)	Placebo Dose 1 N^a=1792 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=1660 n^b (%)	Placebo Dose 2 N^a=1646 n^b (%)
Redness^c				
Any (>2 cm)	85 (4.7)	19 (1.1)	120 (7.2)	12 (0.7)
Mild	55 (3.1)	12 (0.7)	59 (3.6)	8 (0.5)
Moderate	27 (1.5)	5 (0.3)	53 (3.2)	3 (0.2)
Severe	3 (0.2)	2 (0.1)	8 (0.5)	1 (0.1)
Swelling^c				
Any (>2 cm)	118 (6.5)	21 (1.2)	124 (7.5)	11 (0.7)
Mild	71 (3.9)	10 (0.6)	68 (4.1)	5 (0.3)
Moderate	45 (2.5)	11 (0.6)	53 (3.2)	5 (0.3)
Severe	2 (0.1)	0 (0.0)	3 (0.2)	1 (0.1)
Pain at the injection site^d				
Any (>2 cm)	1282 (71.1)	166 (9.3)	1098 (66.1)	127 (7.7)
Mild	1008 (55.9)	160 (8.9)	792 (47.7)	125 (7.6)
Moderate	270 (15.0)	6 (0.3)	298 (18.0)	2 (0.1)
Severe	4 (0.2)	0 (0.0)	8 (0.5)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

Table 4: Study 2 – Frequency and Percentages of Participants with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Participants 56 Years of Age and Older – Reactogenicity Subset of the Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=1802 n^b (%)	Placebo Dose 1 N^a=1792 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=1660 n^b (%)	Placebo Dose 2 N^a=1646 n^b (%)
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue^c				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=1802 n^b (%)	Placebo Dose 1 N^a=1792 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=1660 n^b (%)	Placebo Dose 2 N^a=1646 n^b (%)
Headache^c				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Chills^c				
Any	113 (6.3)	57 (3.2)	377 (22.7)	46 (2.8)
Mild	87 (4.8)	40 (2.2)	199 (12.0)	35 (2.1)
Moderate	26 (1.4)	16 (0.9)	161 (9.7)	11 (0.7)
Severe	0 (0.0)	1 (0.1)	17 (1.0)	0 (0.0)
Vomiting^d				
Any	9 (0.5)	9 (0.5)	11 (0.7)	5 (0.3)
Mild	8 (0.4)	9 (0.5)	9 (0.5)	5 (0.3)
Moderate	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Diarrhea^e				
Any	147 (8.2)	118 (6.6)	137 (8.3)	99 (6.0)
Mild	118 (6.5)	100 (5.6)	114 (6.9)	73 (4.4)
Moderate	26 (1.4)	17 (0.9)	21 (1.3)	22 (1.3)
Severe	3 (0.2)	1 (0.1)	2 (0.1)	4 (0.2)
New or worsened muscle pain^c				
Any	251 (13.9)	149 (8.3)	477 (28.7)	87 (5.3)
Mild	168 (9.3)	100 (5.6)	202 (12.2)	57 (3.5)
Moderate	82 (4.6)	46 (2.6)	259 (15.6)	29 (1.8)
Severe	1 (0.1)	3 (0.2)	16 (1.0)	1 (0.1)
New or worsened joint pain^c				
Any	155 (8.6)	109 (6.1)	313 (18.9)	61 (3.7)
Mild	101 (5.6)	68 (3.8)	161 (9.7)	35 (2.1)
Moderate	52 (2.9)	40 (2.2)	145 (8.7)	25 (1.5)
Severe	2 (0.1)	1 (0.1)	7 (0.4)	1 (0.1)
Use of antipyretic or pain medication	358 (19.9)	213 (11.9)	625 (37.7)	161 (9.8)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

From an independent report (*Kamar N, Abravanel F, Marion O, et al. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med*), in 99 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) 97±8 months previously who received a third

vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported in recipients who were followed for 1 month following post Dose 3.

Unsolicited Adverse Events

Serious Adverse Events

In Study 2, among participants 16 through 55 years of age who had received at least 1 dose of vaccine or placebo (Pfizer-BioNTech COVID-19 Vaccine = 10,841; placebo = 10,851), serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.3% of placebo recipients. In a similar analysis, in participants 56 years of age and older (Pfizer-BioNTech COVID-19 Vaccine = 7,960, placebo = 7,934), serious adverse events were reported by 0.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.6% of placebo recipients who received at least 1 dose of Pfizer-BioNTech COVID-19 Vaccine or placebo, respectively. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2.

Appendicitis was reported as a serious adverse event for 12 participants, and numerically higher in the vaccine group, 8 vaccine participants and 4 placebo participants. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

In Study 2 in which 10,841 participants 16 through 55 years of age received Pfizer-BioNTech COVID-19 Vaccine and 10,851 participants received placebo, non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported in 29.3% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 13.2% of participants in the placebo group, for participants who received at least 1 dose. Overall in a similar analysis in which 7960 participants 56 years of age and older received Pfizer-BioNTech COVID-19 Vaccine, non-serious adverse events within 30 days were reported in 23.8% of participants who received Pfizer-BioNTech COVID-19 Vaccine and 11.7% of participants in the placebo group, for participants who received at least 1 dose. In these analyses, 91.6% of study participants had at least 30 days of follow-up after Dose 2.

The higher frequency of reported unsolicited non-serious adverse events among Pfizer-BioNTech COVID-19 Vaccine recipients compared to placebo recipients was primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination that are consistent with adverse reactions solicited among participants in the reactogenicity subset and presented in Tables 3 and 4. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy were imbalanced with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (64) vs. the placebo group (6), which is plausibly related to vaccination. Throughout the safety follow-up period to date, Bell's palsy (facial paralysis) was reported by 4 participants in the Pfizer-BioNTech COVID-19 Vaccine group. Onset of facial paralysis was Day 37 after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of Bell's palsy were reported in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Adolescents 12 Through 15 Years of Age

In an analysis of Study 2, based on data up to the cutoff date of March 13, 2021, 2,260 adolescents (1,131 Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA); 1,129 placebo) were 12 through 15 years of age. Of these, 1,308 (660 Pfizer-BioNTech COVID-19 Vaccine and 648 placebo) adolescents have been followed for at least 2 months after the second dose. The safety evaluation in Study 2 is ongoing.

Demographic characteristics in Study 2 were generally similar with regard to age, gender, race, and ethnicity among adolescents who received Pfizer-BioNTech COVID-19 Vaccine and those who received placebo. Overall, among the adolescents who received the Pfizer-BioNTech COVID-19 Vaccine, 50.1% were male and 49.9% were female, 85.9% were White, 4.6% were Black or African American, 11.7% were Hispanic/Latino, 6.4% were Asian, and 0.4% were American Indian/Alaska Native.

Solicited Local and Systemic Adverse Reactions

The mean duration of pain at the injection site after Dose 1 was 2.4 days (range 1 to 10 days), for redness 2.4 days (range 1 to 16 days), and for swelling 1.9 days (range 1 to 5 days) for adolescents in the Pfizer-BioNTech COVID-19 Vaccine group.

Table 5: Study 2 – Frequency and Percentages of Adolescents With Solicited Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Adolescents 12 Through 15 Years of Age – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=1127 n^b (%)	Placebo Dose 1 N^a=1127 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=1097 n^b (%)	Placebo Dose 2 N^a=1078 n^b (%)
Redness^c				
Any (>2 cm)	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling^c				
Any (>2 cm)	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain at the injection site^d				
Any	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)
Severe	11 (1.0)	0 (0.0)	7 (0.6)	0 (0.0)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after vaccination.

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: >2.0 to ≤5.0 cm; Moderate: >5.0 to ≤10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

Table 6: Study 2 – Frequency and Percentages of Adolescents with Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After Each Dose – Adolescents 12 Through 15 Years of Age – Safety Population*

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=1127 n^b (%)	Placebo Dose 1 N^a=1127 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=1097 n^b (%)	Placebo Dose 2 N^a=1078 n^b (%)
Fever				
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)
≥38.0°C to 38.4°C	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)
>38.4°C to 38.9°C	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)
>38.9°C to 40.0°C	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue^c				
Any	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)
Headache^c				
Any	623 (55.3)	396 (35.1)	708 (64.5)	263 (24.4)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	169 (15.7)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)
Chills^c				
Any	311 (27.6)	109 (9.7)	455 (41.5)	73 (6.8)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	52 (4.8)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0 (0.0)
Vomiting^d				
Any	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)
Moderate	0 (0.0)	2 (0.2)	4 (0.4)	1 (0.1)
Severe	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea^e				
Any	90 (8.0)	82 (7.3)	65 (5.9)	43 (4.0)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	38 (3.5)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New or worsened muscle pain^c				
Any	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)
Severe	2 (0.2)	0 (0.0)	6 (0.5)	2 (0.2)

	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 1 N^a=1127 n^b (%)	Placebo Dose 1 N^a=1127 n^b (%)	Pfizer-BioNTech COVID-19 Vaccine[†] Dose 2 N^a=1097 n^b (%)	Placebo Dose 2 N^a=1078 n^b (%)
New or worsened joint pain^c				
Any	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)
Severe	1 (0.1)	0 (0.0)	4 (0.4)	0 (0.0)
Use of antipyretic or pain medication^f	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after each dose.

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

* Randomized participants in the safety analysis population who received at least 1 dose of the study intervention.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

Unsolicited Adverse Events

In the following analyses of Study 2 in adolescents 12 through 15 years of age (1,131 of whom received Pfizer-BioNTech COVID-19 Vaccine and 1,129 of whom received placebo), 98.3% of study participants had at least 30 days of follow-up after Dose 2.

Serious Adverse Events

Serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 0.1% of placebo recipients. There were no notable patterns or numerical imbalances between treatment groups for specific categories of serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Non-Serious Adverse Events

Non-serious adverse events from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 5.8% of Pfizer-BioNTech COVID-19 Vaccine recipients and by 5.8% of placebo recipients. From Dose 1 through 30 days after Dose 2, reports of lymphadenopathy plausibly related to the study intervention were imbalanced, with notably more cases in the Pfizer-BioNTech COVID-19 Vaccine group (7) vs. the placebo group (1). There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to Pfizer-BioNTech COVID-19 Vaccine.

Booster Dose Following a Primary Series of Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA)

A subset of Study 2 Phase 2/3 participants of 306 adults 18 through 55 years of age received a booster dose of Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) approximately 6 months (range of 4.8 to 8.0 months) after completing the primary series. Additionally, a total of 23 Study 2 Phase 1 participants (11 participants 18 through 55 years of age and 12 participants 65 through 85 years of age) received a booster dose of

Pfizer-BioNTech COVID-19 Vaccine approximately 8 months (range 7.9 to 8.8 months) after completing the primary series. Safety monitoring after the booster dose was the same as that in the reactogenicity subset who received the primary series.

Among the 306 Phase 2/3 participants, the median age was 42 years (range 19 through 55 years of age), 45.8% were male and 54.2% were female, 81.4% were White, 27.8% were Hispanic/Latino, 9.2% were Black or African American, 5.2% were Asian, and 0.7% were American Indian/Alaska Native. Among the 12 Phase 1 participants 65 through 85 years of age, the median age was 69 years (range 65 through 75 years of age), 6 were male and all were White and Not Hispanic/Latino. Following the booster dose, the median follow-up time was 2.6 months (range 2.1 to 2.9 months) for Phase 1 participants and 2.6 months (range 1.1 to 2.8 months) for Phase 2/3 participants.

Solicited Local and Systemic Adverse Reactions

Table 7 and Table 8 present the frequency and severity of reported solicited local and systemic reactions, respectively, within 7 days of a booster dose of Pfizer-BioNTech COVID-19 Vaccine for Phase 2/3 participants 18 through 55 years of age.

In participants who received a booster dose, the mean duration of pain at the injection site after the booster dose was 2.6 days (range 1 to 8 days), for redness 2.2 days (range 1 to 15 days), and for swelling 2.2 days (range 1 to 8 days).

Table 7: Study 2 – Frequency and Percentages of Participants With Solicited Local Reactions, By Maximum Severity, Within 7 Days After the Booster Dose of Pfizer-BioNTech COVID-19 Vaccine – Participants 18 through 55 Years of Age*

Solicited Local Reaction	Pfizer-BioNTech COVID-19 Vaccine[†]
	Booster Dose N^a = 289 n^b (%)
Redness^c	
Any (>2 cm)	17 (5.9)
Mild	10 (3.5)
Moderate	7 (2.4)
Severe	0
Swelling^c	
Any (>2 cm)	23 (8.0)
Mild	13 (4.5)
Moderate	9 (3.1)
Severe	1 (0.3)
Pain at the injection site^d	
Any	240 (83.0)
Mild	174 (60.2)
Moderate	65 (22.5)
Severe	1 (0.3)

Note: Reactions were collected in the electronic diary (e-diary) from Day 1 to Day 7 after the booster dose.

Note: No Grade 4 solicited local reactions were reported.

* A subset of Phase 2/3 participants 18 through 55 years of age who received a booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) approximately 6 months after completing the primary series.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

b. n = Number of participants with the specified reaction.

Solicited Local Reaction	Pfizer-BioNTech COVID-19 Vaccine[†] Booster Dose N^a = 289 n^b (%)
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c. Mild: >2.0 to 5.0 cm; Moderate: >5.0 to 10.0 cm; Severe: >10.0 cm.

d. Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity.

Table 8: Study 2 – Frequency and Percentages of Participants With Solicited Systemic Reactions, by Maximum Severity, Within 7 Days After the Booster Dose of Pfizer-BioNTech COVID-19 Vaccine – Participants 18 through 55 Years of Age*

Solicited Systemic Reaction	Pfizer-BioNTech COVID-19 Vaccine[†] Booster Dose N^a = 289 n^b (%)
Fever	
≥38.0°C	25 (8.7)
≥38.0°C to 38.4°C	12 (4.2)
>38.4°C to 38.9°C	12 (4.2)
>38.9°C to 40.0°C	1 (0.3)
>40.0°C	0
Fatigue^c	
Any	184 (63.7)
Mild	68 (23.5)
Moderate	103 (35.6)
Severe	13 (4.5)
Headache^c	
Any	140 (48.4)
Mild	83 (28.7)
Moderate	54 (18.7)
Severe	3 (1.0)
Chills^c	
Any	84 (29.1)
Mild	37 (12.8)
Moderate	44 (15.2)
Severe	3 (1.0)
Vomiting^d	
Any	5 (1.7)
Mild	5 (1.7)
Moderate	0
Severe	0
Diarrhea^c	
Any	25 (8.7)
Mild	21 (7.3)
Moderate	4 (1.4)
Severe	0

	Pfizer-BioNTech COVID-19 Vaccine[†] Booster Dose N^a = 289 n^b (%)
Solicited Systemic Reaction	
New or worsened muscle pain ^c	
Any	113 (39.1)
Mild	52 (18.0)
Moderate	57 (19.7)
Severe	4 (1.4)
New or worsened joint pain ^c	
Any	73 (25.3)
Mild	36 (12.5)
Moderate	36 (12.5)
Severe	1 (0.3)
Use of antipyretic or pain medication ^f	135 (46.7)

Note: Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary) from Day 1 to Day 7 after the booster dose.

Note: No Grade 4 solicited systemic reactions were reported.

* A subset of Phase 2/3 participants 18 through 55 years of age who received a booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) approximately 6 months after completing the primary series.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose.

b. n = Number of participants with the specified reaction.

c. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

d. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

e. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

f. Severity was not collected for use of antipyretic or pain medication.

In Phase 1 participants ≥ 65 years of age (n = 12), local reaction pain at the injection site (n = 8, 66.7%) and systemic reactions fatigue (n = 5, 41.7%), headache (n = 5, 41.7%), chills (n = 2, 16.7%), muscle pain (n = 4, 33.3%), and joint pain (n = 2, 16.7%) were reported after the booster dose. No participant in this age group reported a severe systemic event or fever after the booster dose.

Unsolicited Adverse Events

Overall, the 306 participants who received a booster dose, had a median follow-up time of 2.6 months after the booster dose to the cut-off date (June 17, 2021).

In an analysis of all unsolicited adverse events reported following the booster dose, through 1 month after the booster dose, in participants 18 through 55 years of age (N = 306), those assessed as adverse reactions not already captured by solicited local and systemic reactions were lymphadenopathy (n = 16, 5.2%), nausea (n = 2, 0.7%), decreased appetite (n = 1, 0.3%), rash (n = 1, 0.3%), and pain in extremity (n = 1, 0.3%).

Serious Adverse Events

Of the 306 participants who received a booster dose of Pfizer-BioNTech COVID-19 Vaccine, there were no serious adverse events reported from the booster dose through 30 days after the booster dose. One participant reported a serious adverse event 61 days after the booster dose that was assessed as unrelated to vaccination.

Safety of Five Month Booster Dose Interval

Real world evidence obtained from the Ministry of Health of Israel on the administration of over 4.1 million third doses of the Pfizer-BioNTech COVID-19 Vaccine given at least 5 months after the primary series revealed no new safety concerns in adults.

Booster Dose Following Primary Vaccination with Another Authorized COVID-19 Vaccine

The safety of a Pfizer-BioNTech COVID-19 Vaccine booster dose (30 mcg modRNA) in individuals who completed primary vaccination with another authorized COVID-19 Vaccine (heterologous booster dose) is inferred from the safety of a Pfizer-BioNTech COVID-19 Vaccine booster dose administered following completion of Pfizer-BioNTech COVID-19 Vaccine primary series (homologous booster dose) and from data from an independent National Institutes of Health (NIH) study Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA). Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported in the study following the Pfizer-BioNTech COVID-19 Vaccine heterologous booster dose did not identify any new safety concerns, as compared with adverse reactions reported following a Pfizer-BioNTech COVID-19 Vaccine primary series doses or homologous booster dose.

6.2 Post Authorization Experience

The following adverse reactions have been identified during post authorization use of Pfizer-BioNTech COVID-19 Vaccine. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis

Gastrointestinal Disorders: diarrhea, vomiting

Immune System Disorders: severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema)

Musculoskeletal and Connective Tissue Disorders: pain in extremity (arm)

Nervous System Disorders: syncope

8 REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS AND VACCINE ADMINISTRATION ERRORS⁵

See Overall Safety Summary (Section 6) for additional information.

The vaccination provider enrolled in the federal COVID-19 Vaccination Program is responsible for MANDATORY reporting of the listed events following Pfizer-BioNTech COVID-19 Vaccine to the Vaccine Adverse Event Reporting System (VAERS):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)

⁵ Vaccination providers administering COMIRNATY (COVID-19 Vaccine, mRNA) must adhere to the same reporting requirements.

- Cases of Multisystem Inflammatory Syndrome (MIS) in children and adults
- Cases of COVID-19 that result in hospitalization or death

*Serious adverse events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent 1 of the outcomes listed above

Instructions for Reporting to VAERS

The vaccination provider enrolled in the federal COVID-19 Vaccination Program should complete and submit a VAERS form to FDA using 1 of the following methods:

- Complete and submit the report online: <https://vaers.hhs.gov/reportevent.html>, or
- If you are unable to submit this form electronically, you may fax it to VAERS at 1-877-721-0366. If you need additional help submitting a report you may call the VAERS toll-free information line at 1-800-822-7967 or send an email to info@vaers.org.

IMPORTANT: When reporting adverse events or vaccine administration errors to VAERS, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient name, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of the Pfizer-BioNTech COVID-19 Vaccine
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the VAERS report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In Box 17, provide information on Pfizer-BioNTech COVID-19 Vaccine and any other vaccines administered on the same day; and in Box 22, provide information on any other vaccines received within 1 month prior.
2. In Box 18, description of the event:
 - a. Write “Pfizer-BioNTech COVID-19 Vaccine EUA” as the first line.
 - b. Provide a detailed report of vaccine administration error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved vaccine. Please see information to include listed above.

3. Contact information:

- a. In Box 13, provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
- b. In Box 14, provide the name and contact information of the best doctor/healthcare professional to contact about the adverse event.
- c. In Box 15, provide the address of the facility where vaccine was given (NOT the healthcare provider's office address).

Other Reporting Instructions

Vaccination providers may report to VAERS other adverse events that are not required to be reported using the contact information above.

To the extent feasible, report adverse events to Pfizer Inc. using the contact information below or by providing a copy of the VAERS form to Pfizer Inc.

Website	Fax number	Telephone number
www.pfizersafetyreporting.com	1-866-635-8337	1-800-438-1985

10 DRUG INTERACTIONS

There are no data to assess the concomitant administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a reproductive and developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (modRNA) (30 mcg) and other ingredients included in a single human dose of Pfizer-BioNTech COVID-19 Vaccine was administered to female rats by the intramuscular route on 4 occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

11.2 Lactation

Risk Summary

Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion.

11.3 Pediatric Use

Emergency Use Authorization of this formulation of Pfizer-BioNTech COVID-19 Vaccine, supplied in multiple dose vials with purple caps, in adolescents 12 through 17 years of age is based on safety and effectiveness data in this age group and in adults. A different formulation and presentation of the Pfizer-BioNTech COVID-19 Vaccine is also authorized for adolescents 12 through 17 years of age.

Real world evidence obtained from the Ministry of Health of Israel on the administration of third doses of the Pfizer-BioNTech COVID-19 Vaccine given at least 5 months after the primary series revealed no new safety concerns in adolescents 12 through 17 years of age.

For individuals 5 through 11 years of age, a different presentation and formulation of the Pfizer-BioNTech COVID-19 Vaccine is authorized.

Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine does not include use in individuals younger than 5 years of age.

11.4 Geriatric Use

Clinical studies of Pfizer-BioNTech COVID-19 Vaccine include participants 65 years of age and older who received the primary series and their data contributes to the overall assessment of safety and efficacy [see *Overall Safety Summary (6.1) and Clinical Trial Results and Supporting Data for EUA (18.1)*]. Of the total number of Pfizer-BioNTech COVID-19 Vaccine recipients in Study 2 (N=20,033), 21.4% (n=4,294) were 65 years of age and older and 4.3% (n=860) were 75 years of age and older.

The safety of a booster dose of Pfizer-BioNTech COVID-19 Vaccine in individuals 65 years of age and older is based on safety data in 12 booster dose recipients 65 through 85 years of age and 306 booster dose recipients 18 through 55 years of age in Study 2. The effectiveness of a booster dose of Pfizer-BioNTech COVID-19 Vaccine in individuals 65 years of age and older is based on effectiveness data in 306 booster dose recipients 18 through 55 years of age in Study 2.

11.5 Use in Immunocompromised

From an independent report (*Kamar N, Abravanel F, Marion O, et al. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med*), safety and effectiveness of a third dose of the Pfizer-BioNTech COVID-19 vaccine have been evaluated in persons that received solid organ transplants. The administration of a third dose of vaccine appears to be only moderately effective in increasing potentially protective antibody titers. Patients should still be counselled to maintain physical precautions to help prevent COVID-19. In addition, close contacts of immunocompromised persons should be vaccinated as appropriate for their health status.

13 DESCRIPTION

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials with purple caps; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine supplied in multiple dose vials with purple caps contains 30 mcg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine supplied in multiple dose vials with purple caps also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

The modRNA in the Pfizer-BioNTech COVID-19 Vaccine is formulated in lipid particles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

18.1 Efficacy of Primary Series in Participants 16 Years of Age and Older

Study 2 is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in participants 12 years of age and older. Randomization was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56 -year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

In the Phase 2/3 portion of Study 2, based on data accrued through November 14, 2020, approximately 44,000 participants 12 years of age and older were randomized equally and received 2 doses of Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) or placebo separated by 21 days. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the Pfizer-BioNTech COVID-19 Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. Table 9 presents the specific demographic characteristics in the studied population.

Table 9: Demographics (population for the primary efficacy endpoint)^a

	Pfizer-BioNTech COVID-19 Vaccine* (N=18,242) n (%)	Placebo (N=18,379) n (%)
Sex		
Male	9318 (51.1)	9225 (50.2)

	Pfizer-BioNTech COVID-19 Vaccine* (N=18,242) n (%)	Placebo (N=18,379) n (%)
Female	8924 (48.9)	9154 (49.8)
Age (years)		
Mean (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min, max	(12, 89)	(12, 91)
Age group		
≥12 through 15 years ^b	46 (0.3)	42 (0.2)
≥16 through 17 years	66 (0.4)	68 (0.4)
≥16 through 64 years	14,216 (77.9)	14,299 (77.8)
≥65 through 74 years	3176 (17.4)	3226 (17.6)
≥75 years	804 (4.4)	812 (4.4)
Race		
White	15,110 (82.8)	15,301 (83.3)
Black or African American	1617 (8.9)	1617 (8.8)
American Indian or Alaska Native	118 (0.6)	106 (0.6)
Asian	815 (4.5)	810 (4.4)
Native Hawaiian or other Pacific Islander	48 (0.3)	29 (0.2)
Other ^c	534 (2.9)	516 (2.8)
Ethnicity		
Hispanic or Latino	4886 (26.8)	4857 (26.4)
Not Hispanic or Latino	13,253 (72.7)	13,412 (73.0)
Not reported	103 (0.6)	110 (0.6)
Comorbidities^d		
Yes	8432 (46.2)	8450 (46.0)
No	9810 (53.8)	9929 (54.0)

* Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

- a. All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
- b. 100 participants 12 through 15 years of age with limited follow-up in the randomized population received at least 1 dose (49 in the vaccine group and 51 in the placebo group). Some of these participants were included in the efficacy evaluation depending on the population analyzed. They contributed to exposure information but with no confirmed COVID-19 cases, and did not affect efficacy conclusions.
- c. Includes multiracial and not reported.
- d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
 - Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
 - Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
 - Obesity (body mass index ≥ 30 kg/m²)
 - Diabetes (Type 1, Type 2 or gestational)
 - Liver disease
 - Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

The population in the primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 through November 14, 2020. Participants 18 through 55 years of age and 56 years of age and older began enrollment from July 27, 2020,

16 through 17 years of age began enrollment from September 16, 2020, and 12 through 15 years of age began enrollment from October 15, 2020.

The vaccine efficacy information is presented in Table 10.

Table 10: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2, by Age Subgroup – Participants Without Evidence of Infection and Participants With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	Pfizer-BioNTech COVID-19 Vaccine[†] N^a=18,198 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=18,325 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)
All subjects ^e	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.3, 97.6) ^f
16 through 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1) ^g
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9) ^g
First COVID-19 occurrence from 7 days after Dose 2 in participants with or without evidence of prior SARS-CoV-2 infection			
Subgroup	Pfizer-BioNTech COVID-19 Vaccine[†] N^a=19,965 Cases n^{1b} Surveillance Time^c (n^{2d})	Placebo N^a=20,172 Cases n^{1b} Surveillance Time^c (n^{2d})	Vaccine Efficacy % (95% CI)
All subjects ^e	9 2.332 (18,559)	169 2.345 (18,708)	94.6 (89.9, 97.3) ^f
16 through 64 years	8 1.802 (14,501)	150 1.814 (14,627)	94.6 (89.1, 97.7) ^g
65 years and older	1 0.530 (4044)	19 0.532 (4067)	94.7 (66.8, 99.9) ^g

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. No confirmed cases were identified in adolescents 12 through 15 years of age.

f. Credible interval for vaccine efficacy (VE) was calculated using a beta-binomial model with a beta (0.700102, 1) prior for $\theta=r(1-VE)/(1+r(1-VE))$, where r is the ratio of surveillance time in the active vaccine group over that in the placebo group.

g. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

18.2 Efficacy of Primary Series in Adolescents 12 Through 15 Years of Age

A descriptive efficacy analysis of Study 2 has been performed in approximately 2,200 adolescents 12 through 15 years of age evaluating confirmed COVID-19 cases accrued up to a data cutoff date of March 13, 2021.

The efficacy information in adolescents 12 through 15 years of age is presented in Table 11.

Table 11: Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2: Without Evidence of Infection and With or Without Evidence of Infection Prior to 7 Days After Dose 2 – Blinded Placebo-Controlled Follow-up Period, Adolescents 12 Through 15 Years of Age Evaluable Efficacy (7 Days) Population

First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age without evidence of prior SARS-CoV-2 infection*			
	Pfizer-BioNTech COVID-19 Vaccine[†] N^a=1005 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=978 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI^e)
Adolescents 12 through 15 years of age	0 0.154 (1001)	16 0.147 (972)	100.0 (75.3, 100.0)
First COVID-19 occurrence from 7 days after Dose 2 in adolescents 12 through 15 years of age with or without evidence of prior SARS-CoV-2 infection			
	Pfizer-BioNTech COVID-19 Vaccine[†] N^a=1119 Cases n1^b Surveillance Time^c (n2^d)	Placebo N^a=1110 Cases n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI^e)
Adolescents 12 through 15 years of age	0 0.170 (1109)	18 0.163 (1094)	100.0 (78.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

† Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

a. N = Number of participants in the specified group.

b. n1 = Number of participants meeting the endpoint definition.

c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

d. n2 = Number of participants at risk for the endpoint.

e. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted for surveillance time.

18.3 Immunogenicity of Primary Series in Adolescents 12 Through 15 Years of Age

In Study 2, an analysis of SARS-CoV-2 50% neutralizing titers (NT50) 1 month after Dose 2 in a randomly selected subset of participants demonstrated non-inferior immune responses (within 1.5-fold) comparing

adolescents 12 through 15 years of age to participants 16 through 25 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2 (Table 12).

Table 12: Summary of Geometric Mean Ratio for 50% Neutralizing Titer – Comparison of Adolescents 12 Through 15 Years of Age to Participants 16 Through 25 Years of Age (Immunogenicity Subset) – Participants Without Evidence of Infection up to 1 Month After Dose 2 – Dose 2 Evaluable Immunogenicity Population

		Pfizer-BioNTech COVID-19 Vaccine*		12 Through 15 Years/ 16 Through 25 Years	
		12 Through 15 Years n ^a =190	16 Through 25 Years n ^a =170		
Assay	Time Point ^b	GMT ^c (95% CI ^c)	GMT ^c (95% CI ^c)	GMR ^d (95% CI ^d)	Met Noninferiority Objective ^e (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer) ^f	1 month after Dose 2	1239.5 (1095.5, 1402.5)	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; NAAT = nucleic-acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: Participants who had no serological or virological evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit up to 1 month after Dose 2 were included in the analysis.

* Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

- n = Number of participants with valid and determinate assay results for the specified assay at the given dose/sampling time point.
- Protocol-specified timing for blood sample collection.
- GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times$ LLOQ.
- GMRs and 2-sided 95% CIs were calculated by exponentiating the mean difference of the logarithms of the titers (Group 1 [12 through 15 years of age] – Group 2 [16 through 25 years of age]) and the corresponding CI (based on the Student t distribution).
- Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
- SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

18.4 Immunogenicity of a Booster Dose Following a Pfizer-BioNTech COVID-19 Vaccine Primary Series in Participants 18 Through 55 Years of Age

Effectiveness of a booster dose of Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA) was based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). In Study 2, analyses of NT50 1 month after the booster dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4 -fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 13 and Table 14.

Table 13: Geometric Mean 50% Neutralizing Titer (SARS-CoV-2 USA_WA1/2020) – Comparison of 1 Month After Booster Dose to 1 Month After Primary Series – Participants 18 Through 55 Years of Age Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[±]

Assay	n ^a	1 Month After Booster Dose GMT ^b (95% CI ^b)	1 Month After Primary Series GMT ^b (95% CI ^b)	1 Month After Booster Dose/ 1 Month After Primary Series GMR ^c (97.5% CI ^c)	Met Noninferiority Objective ^d (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer) ^e	212	2466.0 (2202.6, 2760.8)	750.6 (656.2, 858.6)	3.29 (2.77, 3.90)	Y

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

Note: Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

- * Participants who had no serological or virological evidence (up to 1 month after receipt of a booster dose of Pfizer-BioNTech COVID-19 Vaccine) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the booster dose were included in the analysis.
- ± All eligible participants who had received 2 doses of Pfizer-BioNTech COVID-19 Vaccine as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Pfizer-BioNTech COVID-19 Vaccine, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.
 - a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
 - b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to $0.5 \times \text{LLOQ}$.
 - c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).
 - d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is >0.67 and the point estimate of the GMR is ≥ 0.80 .
 - e. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

Table 14: Seroreponse Rate for 50% Neutralizing Titer (SARS-CoV-2 USA_WA1/2020) – Comparison of 1 Month After Booster Dose to 1 Month After Primary Series – Participants 18 Through 55 Years of Age Without Evidence of Infection up to 1 Month After Booster Dose* – Booster Dose Evaluable Immunogenicity Population[±]

Assay	N ^a	1 Month After Booster Dose n ^b % (95% CI) ^c	1 Month After Primary Series n ^b % (95% CI) ^c	Difference (1 Month After Booster Dose - 1 Month After Primary Series) % ^d (97.5% CI) ^e	Met Noninferiority Objective ^f (Y/N)
SARS-CoV-2 neutralization assay - NT50 (titer) ^g	200	199 99.5 (97.2, 100.0)	196 98.0 (95.0, 99.5)	1.5 (-0.7, 3.7)	Y

Abbreviations: CI = confidence interval; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

Note: Seroreponse is defined as achieving a ≥ 4 -fold rise from baseline (before Dose 1). If the baseline measurement is below the LLOQ, a postvaccination assay result $\geq 4 \times$ LLOQ is considered a seroreponse.

Note: Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA).

- * Participants who had no serological or virological evidence (up to 1 month after receipt of booster vaccination) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after booster vaccination were included in the analysis.
- ± All eligible participants who had received 2 doses of Pfizer-BioNTech COVID-19 Vaccine as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a booster dose of Pfizer-BioNTech COVID-19 Vaccine, had at least 1 valid and determinate immunogenicity result after booster dose from a blood collection within an appropriate window (within 28 to 42 days after the booster dose), and had no other important protocol deviations as determined by the clinician.
 - a. N = number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the booster dose within specified window. These values are the denominators for the percentage calculations.
 - b. n = Number of participants with seroreponse for the given assay at the given dose/sampling time point.
 - c. Exact 2-sided CI based on the Clopper and Pearson method.
 - d. Difference in proportions, expressed as a percentage (1 month after booster dose – 1 month after Dose 2).
 - e. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.
 - f. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is $> -10\%$.
 - g. SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

18.5 Immunogenicity in Solid Organ Transplant Recipients

From an independent report (Kamar N, Abravanel F, Marion O, et al. *Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med*), a single arm study has been conducted in 101 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) 97 \pm 8 months previously. A third dose of the Pfizer-BioNTech COVID-19 vaccine was administered to 99 of these individuals approximately 2 months after they had received a second dose. Among the 59 patients who had been seronegative before the third dose, 26 (44%) were seropositive at 4 weeks after the third dose. All 40 patients who had been seropositive before the third dose were still seropositive 4 weeks later. The prevalence of anti-SARS-CoV-2 antibodies was 68% (67 of 99 patients) 4 weeks after the third dose.

18.6 Immunogenicity of a Booster Dose Following Primary Vaccination with Another Authorized COVID-19 Vaccine

Effectiveness of a Pfizer-BioNTech COVID-19 Vaccine booster dose (30 mcg modRNA) in individuals who completed primary vaccination with another authorized COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Pfizer-BioNTech COVID-19 Vaccine booster dose administered following completion of Pfizer-BioNTech COVID-19 Vaccine primary series and from immunogenicity data from an independent NIH study Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine (30 mcg modRNA). Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Pfizer-BioNTech COVID-19 Vaccine was demonstrated regardless of primary vaccination.

19 HOW SUPPLIED/STORAGE AND HANDLING

The information in this section applies to the Pfizer-BioNTech COVID-19 Vaccine that is supplied in multiple dose vials with a purple cap. These multiple dose vials are supplied in a carton containing 25 multiple dose vials (NDC 59267-1000-3) or 195 multiple dose vials (NDC 59267-1000-2). After dilution, 1 vial contains 6 doses of 0.3 mL. Vial labels and cartons may state that after dilution, a vial contains 5 doses of 0.3 mL. The information in this Full EUA Prescribing Information regarding the number of doses per vial after dilution supersedes the number of doses stated on vial labels and cartons.

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Do not refreeze thawed vials.

Frozen Vials Prior to Use

Cartons of Pfizer-BioNTech COVID-19 Vaccine multiple dose vials with purple caps arrive in thermal containers with dry ice. Once received, remove the vial cartons immediately from the thermal container and preferably store in an ultra-low temperature freezer between -90°C to -60°C (-130°F to -76°F) until the expiry date printed on the label. This information in the package insert supersedes the storage conditions printed on the vial cartons.

Cartons and vials of Pfizer-BioNTech COVID-19 Vaccine supplied in multiple dose vials with purple caps with an expiry date of September 2021 through February 2022 printed on the label may remain in use for 3 months beyond the printed date as long as approved storage conditions between -90°C to -60°C (-130°F to -76°F) have been maintained. Updated expiry dates are shown below.

<u>Printed Expiry Date</u>		<u>Updated Expiry Date</u>
September 2021	→	December 2021
October 2021	→	January 2022
November 2021	→	February 2022
December 2021	→	March 2022
January 2022	→	April 2022
February 2022	→	May 2022

If not stored between -90°C to -60°C (-130°F to -76°F), vials may be stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks. Vials must be kept frozen and protected from light, in the original cartons, until ready to use. Vials stored at -25°C to -15°C (-13°F to 5°F) for up to 2 weeks may be returned one time to the recommended storage condition of -90°C to -60°C (-130°F to -76°F). Total cumulative time the vials are stored at -25°C to -15°C (-13°F to 5°F) should be tracked and should not exceed 2 weeks.

If an ultra-low temperature freezer is not available, the thermal container in which the Pfizer-BioNTech COVID-19 Vaccine arrives may be used as temporary storage when consistently re-filled to the top of the container with dry ice. Refer to the re-icing guidelines packed in the original thermal container for instructions regarding the use of the thermal container for temporary storage. The thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F). Storage of the vials between -96°C to -60°C (-141°F to -76°F) is not considered an excursion from the recommended storage condition.

Transportation of Frozen Vials

If local redistribution is needed and full cartons containing vials cannot be transported at -90°C to -60°C (-130°F to -76°F), vials may be transported at -25°C to -15°C (-13°F to 5°F). Any hours used for transport at -25°C to -15°C (-13°F to 5°F) count against the 2-week limit for storage at -25°C to -15°C (-13°F to 5°F). Frozen vials transported at -25°C to -15°C (-13°F to 5°F) may be returned one time to the recommended storage condition of -90°C to -60°C (-130°F to -76°F).

Thawed Vials Before Dilution

Thawed Under Refrigeration

Thaw and then store undiluted vials in the refrigerator [2°C to 8°C (35°F to 46°F)] for up to 1 month. A carton of 25 vials or 195 vials may take up to 2 or 3 hours, respectively, to thaw in the refrigerator, whereas a fewer number of vials will thaw in less time.

Thawed at Room Temperature

For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes. Thawed vials can be handled in room light conditions.

Vials must reach room temperature before dilution.

Undiluted vials may be stored at room temperature for no more than 2 hours.

Transportation of Thawed Vials

Available data support transportation of one or more thawed vials at 2°C to 8°C (35°F to 46°F) for up to 12 hours.

Vials After Dilution

After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Any vaccine remaining in vials must be discarded after 6 hours. Do not refreeze.

20 PATIENT COUNSELING INFORMATION

Advise the recipient or caregiver to read the Vaccine Information Fact Sheet for Recipients and Caregivers.

The vaccination provider must include vaccination information in the state/local jurisdiction's Immunization Information System (IIS) or other designated system. Advise recipient or caregiver that more information about IISs can be found at: <https://www.cdc.gov/vaccines/programs/iis/about.html>.

21 CONTACT INFORMATION

For general questions, visit the website or call the telephone number provided below.

Website	Telephone number
<p data-bbox="304 909 584 943">www.cvdvaccine.com</p> 	<p data-bbox="1018 987 1278 1059">1-877-829-2619 (1-877-VAX-CO19)</p>

This Full EUA Prescribing Information may have been updated. For the most recent Full EUA Prescribing Information, please see www.cvdvaccine.com.



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