COURT FILE NUMBER	
COURT	COURT OF QUEEN'S BENCH OF ALBERTA
JUDICIAL CENTRE	WETASKIWIN
PLAINTIFFS	DR. BLAINE ACHEN, DR. GERT GROBLER DR. NADR JOMHA AND DR. TYLER MAY
DEFENDANT	ALBERTA HEALTH SERVICES
DOCUMENT	**AFFIDAVIT OF DR. GERT GROBLER**

ADDRESS FOR SERVICE AND CONTACT INFORMATION OF PARTY FILING THIS DOCUMENT	Ackroyd LLP Barristers and Solicitors 1500, 10665 Jasper Avenue Edmonton, Alberta T5J 3S9 Attention: Richard C. Secord	Justice Centre for Constitutional Freedoms #253, 7620 Elbow Drive SW Calgary, Alberta T2V 1K2 Attention: Eva Chipiuk

[redacted]

AFFIDAVIT OF DR. GERT GROBLER
Sworn on December 9, 2021

I, Dr. Gert Grobler, of the in the Hamlet of Dessert Blume, in the Province of Alberta, SWEAR AND SAY THAT:

1. I am one of the Plaintiffs herein, and as such have a personal knowledge of the matters herein deposed to, except where they are based on information and belief, in which case I verily believe same to be true.

Background Personal Information

2. I am a medical doctor with 27 years of practice experience, 15 years in Canada, 2 years in the United States, 1 year in the Netherlands, and 9 years in South Africa. I was the family doctor for President Nelson Mandela in South Africa for 8 months. I have a wife and 3 children, aged 8, 14, and 16 years old. Currently, I am a general practitioner in the City of Medicine Hat, Alberta. Since 2012, I have worked at a local clinic with 9

family physicians, 8 of which conduct weekly hospital on-call rotations at the Medicine Hat Regional Hospital (the "Hospital") throughout the year.

3. I have never been disciplined as a medical doctor, and my competence in treating my patients has never been questioned.

4. When I am working on-call at the Hospital, I work 24-hours for a full week, and this occurs approximately 7-9 times a year. I am treating 25 to 45 patients daily at the Hospital. At the Hospital, we admit and discharge patients, we consult with specialists, and we assist other family physicians in the surrounding area who do not have the "privileges" to work in the Hospital. I have worked in all levels of the Hospital with the exception of the Emergency and Intensive Care Units.

5. Prior to working in Medicine Hat, I was stationed in Viking, Alberta where I was responsible for all small surgeries and C-sections for that area. I have had hospital working privileges in Alberta for 15 years.

6. Since 2020, I worked on the Covid-19 Unit in the Hospital treating Covid-19 patients. I took the required precautions, including wearing proper protective equipment and handwashing, and did not get infected with, or transmit Covid-19, in the Hospital despite being in immediate proximity to infected patients.

7. On September 14, 2021, Alberta Health Services ("AHS") Policy 1189 – *Immunization of Workers for Covid-19* was put in place effective October 31, 2021 (the "Policy"). Attached hereto and marked as **Exhibit "A"** to this my Affidavit is a true copy of the Policy.

8. On or around September 27, 2021, I tested positive for Covid-19 after taking a PCR test. Attached hereto and marked as **Exhibit "B"** to this my Affidavit is a true copy of my PCR test results. I believe I contracted Covid-19 on September 26, 2021, when I was playing golf at the Medicine Hat Golf Club. I started to get sick that evening. I went for a PCR test which tested positive for Covid-19.

9. As per AHS Guidelines, I isolated for 10 days. AHS phoned me with their recommendations which I followed. I had flu symptoms, skin sensitivity, headaches, fever, metal taste, and chills. I also took 100mg/d of Zinc, 5,000IU/d of Vitamin D3, 0.6mg/d of Colchicine, and 81mg of ASA daily for four weeks. It took me another two

weeks to recover to my pre-Covid-19 fitness level. Nobody I have come in contact with since my recovery has been sick.

10. I have a higher risk of medical complications if I get the Covid-19 vaccine so soon after recovering from the Covid-19 infection. I have a high risk of Covid-19 vaccine complications, including myocarditis, pericarditis, heart attack, stroke, as well as and other severe side effects.

11. On November 24, 2021, I completed an ICHOR antibody test. As of November 27, 2021, it showed that my antibodies were over 250, which means I have high acquired antibodies and immunity against Covid-19, which are IgG anti-spike antibodies. Attached hereto and marked as **Exhibit "C"** to this my Affidavit is a true copy of my antibody test results.

The Policy and My Request for Accommodation

12. On October 18, 2021, Dr. Carl Nohr, Superintendent of Medicine Hospital, contacted me about my Covid-19 vaccination status and told me I would be put on an unpaid leave of absence ("LOA") if I was not fully vaccinated by November 1, 2021, and that I could no longer work at the Hospital after that date. I told him about my Covid-19 infection and that I had 100% fully recovered. I told him I have naturally acquired antibodies which will be at their maximum by 4-6 weeks post-infection with long-term T and B cell memory and immunity according to articles published by Brownstone Institute. Brownstown Institute is a body of scientists and doctors around the world that are putting together natural immunity studies regarding Covid-19. The number of studies is continually growing. As of November 25, 2021, Brownstone Institute listed 132 research studies affirming the effectiveness of naturally acquired immunity to Covid-19. Attached at Exhibit "M" to Dr. Nadr Jomha's Affidavit dated December 7, 2021, is a list of the Brownstone Institute research studies.

13. I further informed Dr. Nohr that according to a Vietnamese study, and several other studies, vaccinated health care workers have a higher viral load with minimal symptoms when re-infected with the Delta variant. In other words, vaccinated health care workers are asymptomatic super spreaders and have a higher risk infecting high-risk patients in hospitals, then those that have naturally acquired antibodies after a Covid-19 infection. Attached hereto and marked as **Exhibit "D"** to this my Affidavit is a copy of the Vietnamese study.

14. I also informed Dr. Nohr that I was not comfortable submitting any of my medical information to AHS due to privacy concerns and doctor-patient confidentiality. And that my understanding was that AHS denied even reasonable exemption request for several colleagues that had recovered from Covid-19. From my experience and understanding of the exemption request program, it is an illusion and no one is granted an exemption.

15. On October 27, 2021, Dr. Nohr called again and said the deadline was extended to November 30, 2021, with the unpaid LOA now being effective December 1, 2021. Dr. Nohr said he understood my point of view, but AHS wants all health care workers to be vaccinated to work at AHS facilities and I will be put on an unpaid LOA if I am not vaccinated. I again informed him that I have a high risk of complication and was not willing to take a chance of permanent disability or death.

16. On or about October 28, 2021, I received a letter from Dr. Nohr requesting I fill out a Clinical Leave of Absence form and agree to go on a voluntary unpaid LOA. The letter further states, if I sign their form, that commencing December 1, 2021, I would be put on unpaid LOA until May 31, 2022, when the Policy is to be renewed again or until I become fully vaccinated and disclose my status to AHS. Attached hereto and marked as **Exhibit "E"** to this my Affidavit is a true copy of the letter from Dr. Nohr.

17. On November 18, 2021, I received a phone call from Dr. Josh Foley, the family doctor head representative at the Hospital, who was asked to reach out to me by the administration and wanted to know if I was going to be vaccinated. I advised Dr. Foley that I would not be receiving the Covid-19 vaccine because I have recovered from Covid-19 and have acquired natural antibodies. He then advised I would be put on LOA at this time. This conversation was then followed up with an email from Marg Degen, South Zone Medical Affairs, again requesting me to sign the LOA form where they had pre-filled in my information. Attached hereto and marked as **Exhibit "F"** to this my Affidavit is a true copy of that email and the LOA form.

18. On November 18, 2021, I responded to the aforementioned email from Marg Degen advising her of all my reasons for not taking the vaccine and stating I would not be accepting a voluntary LOA or any LOA. Attached hereto and marked as **Exhibit "G"** to this my Affidavit is a true copy of my email response to Ms. Degen.

19. In addition, on November 2, 2021, my legal counsel, Ms. Eva Chipiuk, from the Justice Centre for Constitutional Freedoms, sent a letter to AHS via Dr. Verna Yiu requesting that she reverse the Covid-19 vaccination requirement or provide me with accommodation based on my natural immunity and my medical concerns. Attached hereto and marked as **Exhibit "H"** to this my Affidavit is a copy of the letter to AHS.

20. On November 5, 2021, John Siddons, Litigation Legal Counsel for AHS, acknowledged receipt of Ms. Chipiuk's letter and confirmed that AHS will not make changes to the Policy and is prepared to take action against me to enforce the Policy. Attached hereto and marked as **Exhibit "I"** to this my Affidavit is a copy of that letter.

21. On December 1, 2021, Mr. Siddons sent to my counsel a letter from Aaron Low, South Zone Medical Director, stating that I would be disciplined for non-conforming to the Policy. Attached hereto and marked as **Exhibit "J"** to this my Affidavit is a copy of Mr. Siddon's email and the letter and attachments.

Irreparable Harm

22. I am afraid of how the Covid-19 vaccine may affect me in the long term. I may get antibody-antigen autoimmune reactions due to my naturally acquired antibodies, if vaccinated soon after covid infection, the vaccine could be attacking cells that have the spike protein on their surfaces, as well as spike protein in the blood stream forming antibody antigen complexes triggering an immune response as noted in the bio distribution study. A Japanese biodistribution study showed that 75% of the mRNA went systemic to all the organs where they make spike proteins with possible autoimmune and antibody dependant enhancement if receiving any of the vaccines post-COVID infection. Attached hereto and marked as **Exhibit "K"** to this my Affidavit is the Japanese bio distribution study.

23. An increased number of articles are showing side effects post Covid vaccination. Due to this side effects, any organ may be affected causing micro thrombi, blood clots, VITT, pericarditis, myocarditis and vaccine induced ARDS. Attached hereto and marked as **Exhibit "L"** to this my Affidavit is a copy of an article reviewing adverse impacts.

24. I am the only income provider for my family. Becoming permanently sick or disabled will be disastrous for me and my family. None of the Covid-19 pharmaceutical companies

are liable under the emergency act, and with acquired antibodies, I am not willing to take a chance of death or disability.

25. The Policy has caused me undue hardship and distress both professionally and personally. AHS has used coercive tactic to force me to stop working at the Hospital. This will cause a severe loss of income for me and affect my family gravely. By stopping me from working at the Hospital and placing me on and involuntary, unpaid LOA will cause irreparable harm to me and my family personally and my professional reputation.

26. AHS has used extreme duress and coercive tactics which ultimately has forced me to stop working at the Hospital. This is an assault against my own free will and informed consent.

27. I am part of a 15,000-patient clinic and I will not be able to treat, admit or be part of the treatment for these patients. AHS has told me to stop working at the Hospital on December 1, 2021, and I believe my absence will harm the standard of care received by patients in Alberta. As a result of my termination, other doctors will have to cover my 24-hour Hospital shifts for 7-9 weeks per year. Rural Alberta communities are facing critical staff shortages causing bed closures, this is causing a health care crisis in rural communities and a burden on the public health system in Alberta. Attached hereto and marked as **Exhibit "M"** to this my Affidavit is a copy of an AHS Facilities Temporary Bed / Space Reductions News Releases. From January 8, 2021, to November 9, 2021, AHS put out 67 News Releases in respect of staff shortages and temporary bed closures across Alberta.

My Professional Judgement

28. Effective treatments for Covid-19 have been announced across the world by leading scientists and doctors which have led to a decrease in Covid-19 infections and severity. Treating and reducing Covid-19 severity ought to be the goal of medical doctors and it ought to be part of the strategy used by AHS. Dr. Pierre Kory and Dr. Peter McCullough are renowned cardiologists and epidemiologists who have used ivermectin and chloroquine successfully on their patients. According to this literature, I wanted to prescribe these options to my patients, but I was notified by a pharmacist that the College of Pharmacology was advised not to dispense these options.

29. As new medical interventions are introduced and patients are treated, medical doctors are constantly informed of developments and novel treatment options. The same is true for Covid-19. Since the start of the pandemic, medical doctors received literature on medication that demonstrated effectiveness to treat Covid-19. According to that literature, I started prescribing these options, including vitamin D3 and zinc, and was seeing very good results in my patients. However, I was soon notified by pharmacists that by a pharmacist that the College of Pharmacology told them not to dispense these medications and none would be available. I am still at a loss as to how a pharmacist or the College of Pharmacology has the authority to override my professional medical advice and treatment of patients. I never had the chance to prescribe any of my patients Ivermectin due to being blocked by the College of Pharmacology.

30. Throughout the pandemic, we received weekly recommendations from AHS regarding masks, hand hygiene, and isolation but never any information about other treatments and prevention like vitamin treatments. I was left to do my research without any direction from AHS on how to help my patients before their symptoms progressed. As a qualified medical professional, I undertook this responsibility in order to best treat my patients. I found a study dated which found that a combination of chloroquine and zinc helped treat SARS-CoV-1 and was supported by Dr. Fauci. Attached hereto and marked as **Exhibit "N"** to this my Affidavit is a copy of that study.

31. In addition to new and effective treatments for Covid-19, the vaccines are losing their effectiveness and we are seeing increased breakthrough infections in the vaccinated. This is evidenced in a study out of Israel, *Waning Immunity after the BNT162b2 Vaccine in Israel*, which retained data on over 4,791,398 people for the main analysis. Attached hereto and marked as **Exhibit "O"** to this my Affidavit is a copy of that study.

32. The Covid-19 vaccines are not vaccines in the true definition of a "vaccine", as it does not prevent infection or spreading of infection and does not give you immunity. As per the Israeli Study at Exhibit "O" there are breakthrough cases, and the Vietnamese Study at Exhibit "D" shows vaccinated health care workers are still contracting and spreading Covid-19.

33. The Covid-19 vaccines are still in clinical trials and will be until at least 2023. There is no long-term safety data available.

34. SARS-CoV-1 (the predecessor of SARS-CoV-2 virus) vaccines were pulled from the market due to the high number of human deaths. The current Covid-19 vaccines are approved under the emergency act and humans have been vaccinated with an experimental gene therapy which we have no long-term scientific or medical data on. No carcinogenic, gene toxicity or fertility studies have been done in humans. Vaccines usually take 8 to 10 years to be tested and marketed, whereas the experimental Covid-19 vaccines were developed in 9 months.

35. As of November 15, 2021, Vaccine Adverse Event Reporting System ("VAERS") recorded 18,000 deaths in the United States as of November 25, 2021, and more adverse side effects and deaths are reported daily. Attached hereto and marked as **Exhibit "P"** to this my Affidavit is a copy of the VAERS site as of November 25, 2021.

36. The original definition of immunity was changed by the World Health Organization and the Centre for Disease Control and Prevention. In June 2020, the WHO's definition of herd immunity, which was presented on one of their Covid-19 Q&A sites, was consistent with the generally recognized notion for decades saying, "Herd immunity is the indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection." By October 2020, the WHO revised their concept of "herd immunity" now stating "Herd immunity, 'also known as 'population immunity,' is a concept used for vaccination, in which a population can be protected from a certain virus if a threshold of vaccination is reached. Herd Immunity is achieved by protecting people from a virus, not by exposing them to it." Attached hereto and marked as **Exhibit "Q"** to this my Affidavit is a copy of their website evidencing this change. The way the human body's immune system works has not changed. It is the WHO's definition which has changed against decades of scientific data and medical knowledge.

37. My recent antibody test result (Exhibit "C") demonstrate that I have naturally acquired IgG anti-spike antibodies at levels higher than 250u/ml which is proof of a robust immune system. There is evidence that naturally acquired antibodies stay in the system 17 years post infection. Attached hereto and marked as **Exhibit "R"** to this my Affidavit is an article Naturally acquired immunity from Covid-19 gives you better protection than the Covid-19 vaccine, vaccinated people are experiencing breakthrough infections around the world, some of which are showing severe infection and symptoms. See Exhibits "D" and "K".

38. I cannot take the Covid-19 vaccine because:

a. I have natural antibodies with long term T and B cell memory and immunity which is much more effective and safer than the experimental Covid-19 vaccines;

b. I will be tested on November 24, 2021, by ICOR 8 weeks post-infection to test the levels of my antibodies and T cell immunity which will show the most accurate and current information about my immunity and infection levels;

c. I have a higher risk of medical complications if I get the Covid-19 vaccine, especially so soon after recovering from the Covid-19 infection;

d. I have a high risk of complication from the Covid-19 vaccine, including myocarditis, pericarditis, heart attack, stroke, as well as an autoimmune chronic disease;

e. Vaccinated health workers have to up 250 times the viral loads with minimal symptoms when re-infected with the Delta variant, in comparison with other variants in other words vaccinated health care workers are asymptomatic super spreaders and have a higher risk of infecting high-risk patients in hospitals;

f. No long-term clinical trials have been completed, including a review of long-term carcinogenic impacts;

g. I do not want to be a part of a medical experiment. The Covid-19 vaccines have not passed any of the ten standards laid down by the Nuremberg Code of which informed consent is most important;

h. The Covid-19 vaccines were approved in Canada on an emergency basis with an interim order;

i. More and more adverse side effects and deaths are reported daily;

j. Medical treatments in Alberta require at a minimum informed consent. Threats of job loss are coercive and are undermine the principle of informed consent; and

k. Under the Criminal Code of Canada, Sections 265(1) and 265(3) coercing a person against their will to be assaulted through the exercise of an authority constitutes a criminal assault.

39. After an extensive review of the scientific research and medical data, and as a medical doctor, I believe that my proven natural immunity is more effective than the Covid-19 vaccination and acts as a protective agent against contracting Covid-19. The risk of taking the Covid-19 vaccine to me is too high and does not provide a benefit to me or to AHS safety of staff and patients.

Informed Consent and Undue Influence

40. Informing patients about possible side effects so they can make a risk-benefit decision and to respect that decision as per the Standard of Care of the College of Physician and Surgeons of Alberta ("CPSA"). The CPSA also states that the minimum standard of care provided to a person in Alberta is that of "informed consent". AHS's coercive tactics of threatening job loss undermines the ability to obtain informed consent. It is consent under duress.

41. The Policy is contrary to Canada's Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans which states:

    a. The voluntariness of consent is important because it respects human dignity and means that individuals have chosen to participate in research according to their values, preferences, and wishes.

    b. Undue influence and manipulation may arise when prospective participants are recruited by individuals in a position of authority. The influence of power relationships (e.g., employers...) on the voluntariness of consent should be judged from the perspective of prospective participants, since the individuals being recruited may feel constrained to follow the wishes of those who have some form of control over them. This control may be physical, psychological, financial, or professional, for example, and may involve offering some form of inducement or threatening some form of deprivation. In such situations, the control exerted in a power relationship may place undue pressure on the prospective participants. **At the extreme, there can be no voluntariness if consent is secured by the order of authorities.** [emphasis added]

    Attached hereto and marked as **Exhibit "S"** to this my Affidavit is Canada's Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

42. The Policy is also contrary to, and violates, a number of the articles of the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research of Involving Human Subjects, specifically:

a. Articles 9 and 25 – Right to self-determination and the right to make informed decisions regarding participation, both initially and during the course of research;

b. Articles 3 and 4 - The subjects' welfare must always take precedence over the interests of science and society;

c. Articles 7 and 8 – Human rights and ethical considerations must always take precedence; and

d. Article 6 - Even the best-proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.

Attached hereto and marked as **Exhibit "T"** to this my Affidavit is a copy of that Policy.

Conclusion

43. The Policy is going against science, my medical knowledge and understanding, and my innate natural immunity. In addition, the Policy is coercive and is infringing on my Charter rights, human rights, the Nuremberg code as well as the Criminal Code of Canada to be coerced into taking an experimental medical intervention. This goes against everything I have learned as a medical professional.

44. AHS is going against clear and established science that natural immunity is more effective than the Covid-19 vaccine. A growing body of compelling evidence demonstrates that natural immunity is superior to vaccine immunity by every measure. It is unscientific and unethical for AHS to coerce or mandate a vaccine on an employee who already enjoys natural immunity as a result of having contracted and recovered from Covid-19 and I worked in AHS facilities throughout the pandemic with no incident of transmission to staff or patients.

45. AHS is also going against Alberta's Covid-19 Restriction Exemption Program which allows for rapid antigen testing. Rapid antigen testing is a clear alternative. Rapid antigen testing is an accurate and immediate method to minimize the risk that a person infected

with Covid-19 may spread the SARS-CoV-2 virus to staff and patients. I am aware of other health care facilities engaged in the care of vulnerable people are enacting testing policies whereby both vaccinated and unvaccinated individuals are regularly tested for Covid-19. Such a policy is based on the fact that both vaccinated and unvaccinated individuals may contract and transmit Covid-19.

46. It is unreasonable and unethical for AHS to place me on an involuntary LOA or terminate me when alternative options, such as rapid testing are available, and I have naturally acquired antibodies. By not providing reasonable, safe, and efficient alternatives to preserve workforce capacity and support the healthcare system, AHS is causing irreparable harm to me personally and the public health care system in Alberta generally.

47. It is unreasonable and unethical for AHS to threaten me with my livelihood and not allow me the professional courtesy and respect to treat myself with professional discretion as a qualified and competent doctor.

48. Apart from disciplinary threats, AHS has not informed me how this will affect my ability to practice medicine in the Province of Alberta moving forward. I do not know if I have lost my ability to practice for a few months of forever. AHS' actions given all of the above is unconscionable.

49. I went into medicine to help patients. I feel I am being attacked and vilified personally and publicly for refusing to comply with AHS' Policy which is arbitrary and unscientific. In my opinion, the Policy is causing more harm than good, and I should not be disciplined or threatened for doing my job competently and holding onto my ethical and professional responsibilities.

50. I undertake to indemnify the Defendant in the event of a loss of this application.

51. I swear this affidavit *bona fide*, in support of the within action and injunction application and for no improper purpose.

SWORN BEFORE ME at Edmonton, Alberta, this 9, day of December, 2021

[redacted]

A Commissioner for Oaths
in and for the Province of Alberta

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

[redacted]

DR. GERT GROBLER

Exhibit "A"

Alberta Health Services

TITLE
IMMUNIZATION OF WORKERS FOR COVID-19

SCOPE
Provincial

DOCUMENT #
1189

APPROVAL AUTHORITY
Alberta Health Services President and Chief Executive Officer

INITIAL EFFECTIVE DATE
September 14, 2021

SPONSOR
Workplace Health and Safety

REVISION EFFECTIVE DATE
October 22, 2021

PARENT DOCUMENT TITLE, TYPE, AND NUMBER
Not applicable

SCHEDULED REVIEW DATE
April 22, 2022

NOTE: The first appearance of terms in bold in the body of this document (except titles) are defined terms – please refer to the Definitions section.

If you have any questions or comments regarding the information in this document, please contact Policy Services at policy@ahs.ca. The Policy Services website is the official source of current approved policies, procedures, directives, standards, protocols, and guidelines. Only the electronic version of this document, as hosted on the Policy Services website or www.ahs.ca, is valid.

OBJECTIVES

- To set out **worker** immunization requirements for COVID-19 to protect the health and safety of workers, patients, and the communities that Alberta Health Services (AHS) serves.

PRINCIPLES

AHS is committed to protecting the health and safety of its workers, patients, visitors, and others accessing AHS sites. Immunization against COVID-19 is the most effective means to prevent the spread of COVID-19, to prevent outbreaks in AHS facilities, to preserve workforce capacity to support the health care system, and to protect our workers, patients, visitors, and others accessing AHS sites. Immunization against COVID-19 also supports the AHS Values of Compassion, Accountability, Respect, Excellence, and Safety.

This Policy is in addition to other AHS policy documents supporting worker and patient safety during the COVID-19 pandemic including, but not limited to, the AHS *Use of Masks During COVID-19* Directive, *Attending Work with COVID-19 Symptoms, Positive Test, or Close Contact* Directive, and the *Fit for Work Screening (COVID-19)* Protocol.

This Policy shall be reviewed regularly, and at least every six (6) months, to ensure alignment with public health measures and regulations, and to confirm it adequately covers the health and safety risks that it addresses.

APPLICABILITY

Compliance with this document is required by Alberta Health Services, Alberta Precision Laboratories, Carewest, CapitalCare, and Covenant Health employees, members of the medical and midwifery staffs, students, volunteers, and other persons acting on their behalf. Compliance requirements for other contracted service providers, such as continuing care, will be

communicated directly to the contracted service providers. This document does not apply to physicians with Community Appointments.

ELEMENTS

1. Immunization Requirements

1.1 Effective November 30, 2021, all workers must be **fully immunized** against COVID-19.

1.2 A worker on an approved Leave of Absence must be fully immunized prior to returning to work.

1.3 A worker hired after November 30, 2021 must be fully immunized prior to commencing work.

2. Proof of Immunization Records

2.1 No later than November 15, 2021, workers shall disclose accurate proof of their immunization status to:

a) AHS or an AHS subsidiary, if the worker is an AHS employee, medical staff, midwifery staff, or volunteer;

b) Covenant Health, if the worker is a Covenant Health employee, medical staff, or volunteer;

c) their educational institution, if the worker is a student or instructor; or

d) their employer, if the worker is a contracted service provider.

2.2 Proof of immunization is being collected to protect the health and safety of workers, patients, and other persons accessing AHS sites and to preserve AHS' workforce capacity to support the health care system.

2.3 Proof of immunization records collected under this Policy shall be securely and confidentially retained, accessed, and used as necessary to determine fit for work status of workers, to manage and administer employment and other working relationships with workers, to address accommodation requests, and to comply with all applicable laws, such as the *Occupational Health and Safety Act* (Alberta) and *Regional Health Authorities Act* (Alberta).

2.4 Proof of immunization records are collected under the authority of Section 33(c) of the *Freedom of Information and Protection of Privacy Act* (Alberta) and shall be used, accessed, and disclosed in accordance with the legislation and the AHS *Collection, Access, Use, and Disclosure of Information* Policy.

3. Workplace Accommodation

3.1 Any AHS employee who is unable to be immunized due to a medical reason, or for another protected ground under the *Alberta Human Rights Act*, will be reasonably accommodated, up to the point of undue hardship, in accordance with the AHS *Workplace Accommodation* Policy.

3.2 Employees of AHS subsidiaries, Covenant Health, and applicable contracted service providers, who are unable to be immunized due to a medical reason, or for another protected ground under the *Alberta Human Rights Act,* will be reasonably accommodated, up to the point of undue hardship, in accordance with their applicable workplace accommodation policies.

3.3 Any current AHS employee requesting workplace accommodation shall make a request for the accommodation as soon as reasonably possible, and no later than October 16, 2021, and provide required information in accordance with the AHS *Workplace Accommodation* Policy (or the appropriate accommodation policy of an AHS subsidiary or Covenant Health, if applicable).

3.4 Any current AHS member of the medical or midwifery staff who is not an employee of AHS, an AHS subsidiary, or Covenant Health, and who is unable to be immunized due to a medical reason, may request an exception as soon as reasonably possible and no later than October 16, 2021. A request for an exception shall be made on the *Medical or Midwifery Staff Request for Exception COVID-19 Mandatory Immunization for Workers* form and shall be submitted as directed on the form. The lack of immunization may affect the safe exercise of their Clinical Privileges as described in the *Medical Staff Bylaws* and *Rules* (Rule 3.4.4.2), or may directly impact their ability to practice and patient safety as described in the *Midwifery Staff Bylaws* and *Rules* (Rule 3.3.4), as applicable.

4. Non-Compliance

4.1 With respect to students, instructors, and applicable contracted service providers, failure to comply with this Policy shall result in AHS reviewing the applicable contract or other relevant circumstances and initiating further discussions with the applicable educational institution or contracted service provider and, in this respect, AHS reserves all rights it has at law, equity, or pursuant to any applicable agreement to address such non-compliance.

4.2 In all other cases not outlined in Section 4.1 above, except where a workplace accommodation or exception (for medical or midwifery staff) applies, failure to comply with this Policy shall result in:

a) a meeting being held with the worker to discuss their concerns with vaccination against COVID-19 and provide educational materials on the COVID-19 vaccines; and

b) if the worker remains non-compliant with this Policy, the worker being placed on an unpaid leave of absence for the period of time required to

become fully immunized or, in the case of medical or midwifery staff, Immediate Action being taken as set out in Part 6 of the *Medical Staff* Bylaws or *Midwifery Staff* Bylaws.

DEFINITIONS

Fully immunized means a worker:

a) who has received two doses of a vaccine considered valid by Alberta Health in a two-dose COVID-19 vaccine series or one dose of a vaccine considered valid by Alberta Health in a one-dose COVID-19 vaccine series; and
b) for whom fourteen days have elapsed since the date on which the person received the second dose of the COVID-19 vaccine considered valid by Alberta Health of a two-dose series or one dose of the COVID-19 vaccine considered valid by Alberta Health in a one-dose vaccine series.

Worker means AHS, its subsidiaries and Covenant Health employees, members of the medical and midwifery staffs, students and instructors, volunteers, and applicable contracted service providers (including anyone providing services for AHS on behalf of an applicable contracted service provider).

REFERENCES

- Alberta Health Services Governance Documents:
  - *Attending Work with COVID-19 Symptoms, Positive Test, or Close Contact* Directive (#1188)
  - *Collection, Access, Use, and Disclosure of Information* Policy (#1112)
  - *Fit for Work Screening (COVID-19)* Protocol (#1184-01)
  - *Medical Staff Bylaws* and *Rules*
  - *Midwifery Staff* Bylaws and *Rules*
  - *Use of Masks During COVID-19* Directive (#HCS-267)
  - *Workplace Accommodation* Policy (#1156)
- Alberta Health Services Forms:
  - *Employee Request for Accommodation* Form (#19566)
  - *Got My COVID-19 Immunization* Form
  - *Medical or Midwifery Staff Request for Exception COVID-19 Mandatory Immunization for Workers* Form
- Alberta Health Services Resources:
  - AHS Immunization Information Insite Page
  - AHS Values
- Non-Alberta Health Services Documents:
  - *Alberta Human Rights Act*
  - *Freedom of Information and Protection of Privacy Act* (Alberta)
  - *Occupational Health and Safety Act* (Alberta)
  - *Regional Health Authorities Act* (Alberta)

[redacted]

This is Exhibit A referred to
in the affidavit of Dr. Gerit Grover
Sworn before me herein this 9
day of December, 2021

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

Exhibit "B"

Patients Reports Sign Out Help

[redacted]

Display Note History | Move to Different Patient Chart | Order New Lab Tests

Electronic Investigation
Documents
Incoming Consults
Incoming Referrals
Hide Notes
Note:
Declined eReferrals

Practitioner:
<< ALL >>
Signed Out
New
Corrected
Abnormal
Date
Include Excellens Text Reports
Grobler, Gert

27-Sep-21	Grobler, Gert
19-Dec-20	Grobler, Gert
19-Dec-20	Grobler, Gert
19-Dec-20	Grobler, Gert
19-Dec-20	Grobler, Gert
25-Aug-20	Grobler, Gert
25-Aug-20	Grobler, Gert
26-Jun-20	Grobler, Gert
26-Jun-20	Grobler, Gert
26-Jun-20	Grobler, Gert
26-Jun-20	Grobler, Gert
26-Jun-20	Grobler, Gert
26-Jun-20	Grobler, Gert
26-Jun-20	Grobler, Gert
12-Mar-20	Grobler, Gert
25-Feb-20	Grobler, Gert
25-Feb-20	Grobler, Gert
15-Jan-20	Grobler, Gert

Ordered By: Suttorp, Vivien Valerie
Copies To: Van der Westhuizen, Solomon(Monty) MOH, Palliser Public Health MOH, Alberta Health CDC
TxnID: 20210928212629968113931 21-270-030946
Filler Order: 3243760731:101LA
Sending Facility: PROV
Sending Application: OPEN ENGINE
(Preliminary Reports Hidden)
Order Number:

Patient: GROBLER, GERT [redacted] Born [redacted]
Reported: [redacted] Collected: 27-Sep-2021 14:30 Specimen Received: 28-Sep-2021 21:26

Patient Class: V
Patient Location: [redacted]

TEST NAME	FLAGS	RESULT	(REFERENCE RANGE / UNITS / STATUS)

COVID-19 Variant Nucleic Acid Test (Status: Final, Reviewed By Sv on 30-Sep-2021)
Reported to Health Agency Patient Address: [redacted]
Performed at ProvLab Calgary
COVID-19 (RNA) Variant NAT — A Positive (ABNORMAL)

Information and Comments:
Specimen: Swab - Throat Specimen: Swab - Throat

INTERPRETATION: This specimen is confirmed positive for a variant of concern. This is the final result. See https://www.albertahealthservices.ca/topics/Page17381.aspx for more information on COVID-19 variants of concern.
METHOD: This nucleic acid test (NAT) detects the presence of mutations associated with SARS-CoV-2 variants of concern using real-time reverse-transcriptase PCR assays developed and validated at ProvLab. Nucleic acid sequencing may be used to determine the lineage.
DISCLAIMER: These methods are for surveillance purposes, not clinical diagnostic purposes. They have not been cleared or approved by the US FDA or Health Canada and results should be interpreted in the clinical and epidemiological context.

COVID-19 (RNA) Lineage B.1.617.2

[redacted]

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This is Exhibit B referred to in the affidavit of Dr. Gert Grobler
Sworn before me herein this 29 day of December, 2021

Exhibit "C"

5:06

MAYO CLINIC LABORATORIES

1-800-533-1710

COVSQ

SARS-CoV-2 Spike Ab, Semi-Quant, S

Patient ID	Patient Name		Birth Date	Gender	Age
[redacted]	Grobler, Gert		[redacted]	M	[redacted]
Order Number	Client Order Number	Ordering Physician	Report Notes		
[redacted]	[redacted]	NA			
Account Information		Collected			
[redacted] Ichor Blood Services - Medicine Hat		24 Nov 2021 08:00			

SARS-CoV-2 Spike Ab, Semi-Quant, S

SARS-CoV-2 Spike Ab, Interp, S SDL

Reference Value: Negative

⚠ Positive

Abn

Antibodies to the SARS-CoV-2 spike glycoprotein detected. These results suggest recent or prior SARS-CoV-2 infection and/or vaccination. No minimum antibody level or threshold has been established to indicate long-term protective immunity against re-infection. Correlation with epidemiologic risk factors and other clinical and laboratory findings is recommended. Serologic results should not be used to diagnose recent SARS-CoV-2 infection. False-positive results for IgG antibodies may occur due to cross-reactivity from pre-existing antibodies or other possible causes.

SARS-CoV-2 Spike Ab, Quant, S SDL

Reference Value: <0.80

⚠ >250 U/mL

High

ADDITIONAL INFORMATION

Testing was performed using the Roche Elecsys Anti-SARS-CoV-2 S Reagent assay from Roche Diagnostics, which has received Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration.

Fact sheets for this Emergency Use Authorization (EUA) assay can be found at the following links:
For Healthcare Providers:
https://www.fda.gov/media/144635/download
For Patients:
https://www.fda.gov/media/144636/download

Patient's Race SDL

Unknown

Patient's Ethnicity SDL

Unknown

Received: 27 Nov 2021 14:07 **Reported:** 27 Nov 2021 14:39

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
SDL	Mayo Clinic Laboratories - Rochester Superior Drive	3050 Superior Drive NW, Rochester MN 55901	William G. Morice M.D. Ph.D	2401040592

Printed 27 Nov 2021

Report Status: Final

Received and reported dates and times are reported in US Central Time.

Page 1 of 1

[redacted]

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This is Exhibit C referred to in the affidavit of Dr. Gert Grobler Sworn before me herein this 9 day of December, 2021

central-1.amazonaws.com

Exhibit "D"

Transmission of SARS-CoV-2 Delta variant among vaccinated healthcare workers, Vietnam

Nguyen Van Vinh Chau[1], Nghiem My Ngoc[1], Lam Anh Nguyet[2], Vo Minh Quang[1], Nguyen Thi Han Ny[2], Dao Bach Khoa[1], Nguyen Thanh Phong[1], Le Mau Toan[1], Nguyen Thi Thu Hong[2], Nguyen Thi Kim Tuyen[2], Voong Vinh Phat[2], Le Nguyen Truc Nhu[2], Nguyen Huynh Thanh Truc[1], Bui Thi Ton That[1], Huynh Phuong Thao[1], Tran Nguyen Phuong Thao[1], Vo Trong Vuong[1], Tran Thi Thanh Tam[1], Ngo Tan Tai[1], Ho The Bao[1], Huynh Thi Kim Nhung[1], Nguyen Thi Ngoc Minh[1], Nguyen Thi My Tien[1], Nguy Cam Huy[1], Marc Choisy[2,3], Dinh Nguyen Huy Man[1], Dinh Thi Bich Ty[1], Nguyen To Anh[2], Le Thi Tam Uyen[1], Tran Nguyen Hoang Tu[1], Lam Minh Yen[2], Nguyen Thanh Dung[1], Le Manh Hung[1], Nguyen Thanh Truong[1], Tran Tan Thanh[2], Guy Thwaites[2,3], and Le Van Tan[2], for the OUCRU COVID-19 research group*

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Word count: abstract: 250 words, full text 2354 words

Key words: Delta variant, Oxford-AstraZeneca, COVID-19, vaccine breakthrough, Vietnam

[redacted]

This is Exhibit "D" referred to
in the affidavit of Dr. Gert Grubler
Sworn before me herein this 9
day of December, 2021

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ABSTRACT

Background: Data on breakthrough SARS-CoV-2 Delta variant infections are limited.

Methods: We studied breakthrough infections among healthcare workers of a major infectious diseases hospital in Vietnam. We collected demographics, vaccination history and results of PCR diagnosis alongside clinical data. We measured SARS-CoV-2 (neutralizing) antibodies at diagnosis, and at week 1, 2 and 3 after diagnosis. We sequenced the viruses using ARTIC protocol.

Findings: Between 11th–25th June 2021 (week 7–8 after dose 2), 69 healthcare workers were tested positive for SARS-CoV-2. 62 participated in the clinical study. 49 were (pre)symptomatic with one requiring oxygen supplementation. All recovered uneventfully. 23 complete-genome sequences were obtained. They all belonged to the Delta variant, and were phylogenetically distinct from the contemporary Delta variant sequences obtained from community transmission cases, suggestive of ongoing transmission between the workers. Viral loads of breakthrough Delta variant infection cases were 251 times higher than those of cases infected with old strains detected between March-April 2020. Time from diagnosis to PCR negative was 8–33 days (median: 21). Neutralizing antibody levels after vaccination and at diagnosis of the cases were lower than those in the matched uninfected controls. There was no correlation between vaccine-induced neutralizing antibody levels and viral loads or the development of symptoms.

Interpretation: 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. Physical distancing measures remain critical to reduce SARS-CoV-2 Delta variant transmission.

47 **Funding**: Wellcome (106680/B/14/Z and 204904/Z/16/Z).

RESEARCH IN CONTEXT

Evidence before this study

We conducted a literature search of PubMed Central for studies or reports of SARS-CoV-2 breakthrough infections up to 1st August 2021. We used the terms "breakthrough Delta variant infection", "Delta variant breakthrough infection" and "SARS-CoV-2 breakthrough infections" without language restriction. We identified 14 relevant scientific papers including one published in medRxiv. Of these, only the medRxiv paper described 6 cases of breakthrough Delta variant infections. Of the remaining 12, 10 described breakthrough infections associated with non-Delta variants of concerns (Alpha, Beta and Gama variants).

None of the above mentioned studies described the transmission between vaccinated people, while one study reported the transmission between vaccinated people and household members. Likewise, there was only one paper comparing the viral loads between fully vaccinated and partially vaccinated individuals with breakthrough Alpha variant infection and found no difference between the two group. And there was one paper comparing the viral load between vaccinated and unvaccinated people infected with the Alpha variant but found no difference in viral load between the two groups. Only one paper had follow-up data on PCR testing after infection and found low viral loads and short duration of viral shedding (2-7 days) in cases of breakthrough infections without information about the causal variant. Most recently, a study in Israel identified a correlation between neutralizing antibody titers after the second dose and at diagnosis and break through infection. The causal variant was the Alpha variant.

Added value of this study

We studied 62 breakthrough cases among healthcare workers of a major hospital for infectious diseases in Ho Chi Minh City (HCMC), Vietnam between 11th-25 June 2021. We captured the infected cases at a very early phase of the infection and carefully followed them up during hospitalization to assess the kinetic of viral loads and neutralizing antibodies, and the development of clinical symptoms. To dissect the epidemiological link and the transmission potential between the vaccinated healthcare workers, we conducted whole genome sequencing of SARS-CoV-2.

49/62 case patients were (pre)symtomatic) and all recovered uneventfully. A total of 23 complete genome sequences were obtained from the breakthrough cases. The obtained sequences were all belonged to the Delta variant, but distinct from contemporary sequences obtained from cases of community transmission in HCMC, suggesting that the ongoing transmission had occurred between vaccinated healthcare workers. Viral loads peaked at around 2-3 days before and after the development of clinical symptoms with prolonged PCR positivity of up to 33 days. Viral loads were 251 times higher than those in cases infected with old SARS-CoV-2 strains detected in Vietnam between March and April 2020. Vaccine-induced neutralizing antibodies after the second dose and at diagnosis were lower than those in the matched uninfected controls. There was no correlation between vaccine-induced neutralizing antibody levels and viral loads (i.e. infectivity) or the development of symptoms during the course of infection.

Implications of all the available evidence

Our study provided strong evidence demonstrating for the first time the transmission between vaccine breakthrough cases infected with the Delta variant. High viral loads coupled with prolonged PCR positivity and poorly ventilated indoor setting without in-

94 office mask wearing might have facilitated the transmission between vaccinated healthcare
95 workers. The absence of correlation between neutralizing antibody levels and peak viral
96 loads suggested that vaccine might not lower the infectivity of breakthrough cases. Given
97 the rapid spread of the Delta variant worldwide, physical distancing measures remain
98 critical to reduce the transmission of SARS-CoV-2 Delta variant, event in countries where
99 vaccination coverage is high.

INTRODUCTION

SARS-CoV-2 Delta variant is approximately 60% more transmissible than the Alpha (B.1.1.7) variant, and has rapidly spread worldwide[1], posing a significant threat to global COVID-19 control. The Delta variant possesses mutations in the spike protein (including L452R and T478K) that makes the virus less susceptible to neutralizing antibodies generated by current vaccines or natural infection.[2,3] This has raised concern about vaccine escape potential.

Data on vaccine breakthrough infections, especially those caused by the Delta variant, are limited.[4] Likewise, it remains unknown regarding the transmission potential of vaccine breakthrough infection cases, especially those infected with the Delta variant. These data however are critical to informing the development and deployment of COVID-19 vaccine, and the implementation of infection control measures. Here, we investigate breakthrough SARS-CoV-2 Delta variant infections among double-vaccinated healthcare workers of a major infectious diseases hospital in Ho Chi Minh City (HCMC), Vietnam.

MATERIALS AND METHODS

Setting

The study was conducted at the Hospital for Tropical Diseases (HTD) in HCMC. HTD is a 550-bed tertiary referral hospital for patients with infectious diseases in southern Vietnam.[5] The hospital has around 900 members of staff and 34 departments. All offices, except one, one are equipped with air conditioners that recirculate the air without mechanical ventilation (Supplementary Figure 1).

HTD staff members were amongst the first people in Vietnam to be offered the Oxford-AstraZeneca COVID-19 vaccine. The first doses were given on 8th March 2021; the second doses were given in the last two weeks of April 2021.[6]

Data collection

We collected demographics, vaccination history and clinical data alongside the results of SARS-CoV-2 PCR diagnosis from the study participants. For SARS-CoV-2 antibody measurement, we obtained 2ml of EDTA plasma from each study participants at diagnosis and at week 1, 2 and 3 after admission.

Nasopharyngeal-throat swab collection, PCR testing and viral load conversion

Nasopharyngeal swabs were collected and placed in 1mL of viral transport medium, and 200uL was used for viral RNA extraction using the MagNApure 96 platform (Roche Diagnostics, Germany), according to the manufacturer's instructions. For SARS-CoV-2 RNA detection, we used real-time RT-PCR assay with primers and probe targeted at the envelope protein-coding gene (TIB MOLBIOL)[7]. PCR Ct values were converted to RNA loads using an in-house established formula ($y = -0.3092x + 12.553$, $R^2 = 0.9963$, where y is viral load and x is Ct value) based on 10-fold dilution series of in-vitro transcribed RNA[7,8].

Whole genome sequencing and sequence analysis

Whole-genome sequences of SARS-CoV-2 were directly obtained from leftover RNA after PCR testing using ARTIC protocol and Illunina reagents on a MiSeq platform with the inclusion of a negative control in every sequencing run. The obtained reads from individual samples were mapped to a SARS-CoV-2 reference genome (GISIAD sequence ID: EPI_ISL_1942165) to generate the consensuses using Geneious software (Biomatter, New

Zealand). SARS-CoV-2 variant assignment was carried out using Pangolin.[9] Detection of amino acid changes as compared to the original Wuhan strain was done using COV-GLUE.[10] Maximum likelihood phylogenetic tree was reconstructed using IQ-TREE.[11]

SARS-CoV-2 antibody measurement

We measured antibodies against SARS-CoV-2 nucleocapsid (N) protein using Elecsys Anti-SARS-CoV-2 assay (Diagnostics, Germany), and SARS-CoV-2 neutralizing antibodies using SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) (GenScript, USA).[12] The experiments were carried according to the manufacturers' instructions.

Additional data for analysis

Because the breakthrough infections coincided with the sampling schedule at month 3 after dose 1 (week 7 after the second dose) of the vaccine study,[6] we used available data on neutralizing antibodies of the vaccine study for case-control analyses. We matched cases with the controls for age and gender with a matching ratio of 1:3 (when data of the controls are available) or 1:1 (when data of the controls are limited).

For viral load comparison, we used previously reported data of SARS-CoV-2 infected cases detected in Vietnam during the early phase of the pandemic in Vietnam between March and April 2020.[5]

Data analysis

Data analysis was carried in Graphpad Prims 9.0.2. For comparisons between groups, we used the Fisher exact test or the Mann-Whitney U test. We performed linear regression analysis to assess the correlation between neutralizing antibody levels at diagnosis and peak viral loads.

Ethics

The study was approved by the Institutional Review Board of HTD and the Oxford Tropical Research Ethics Committee, University of Oxford, UK. Written informed consents were obtained from all the participants.

RESULTS

The outbreak and initial investigations

On 11th June 2021 (week 7 after the second dose), a 41-year old member of HTD staff (patient 1) complained of body pain and tiredness. Because community transmission of SARS-CoV-2 has been increasing in HCMC since May 2021, he was tested that day and found to be positive for SARS-CoV-2 (PCR Ct value: 18.5 (equivalent to $\log_{10}$ viral load of 8.5 copies per mL)). PCR screening for SARS-CoV-2 was then expanded to all hospital staff and was completed by the end of 12th June 2021. A total of 52 additional members were found positive, including all 6 members sharing an office with patient 1 (Figure 1 and Supplementary Figure 1).

Following Vietnamese Government recommendations, HTD was locked down for two weeks (12th-26th June 2021), with no one allowed to enter or leave the hospital. Further PCR testing of all staff during this period identified 16 additional positive cases, totaling 69 infected members from 19/34 departments (Figure 1 and Supplementary Table 1). Serological testing for SARS-CoV-2 N protein antibodies was carried out on 683 members (including those stayed in the HTD during the lockdown and the infected cases) between 14th and 16th June 2021, but none was positive.

Demographics and clinical features

All the 69 members of HTD staff infected with SARS-CoV-2 were isolated for clinical follow up and management at HTD. Apart from patient 1, one additional member

190 presented with symptoms at diagnosis (15th June 2021). Thus only 1 out of the first 53
191 members tested positive between 11th and 12th June 2021 was symptomatic at diagnosis.
192 Sixty-two consented to have their demographics and clinical features reported. Of these,
193 two received one dose, and 60 (including patient 1) were fully vaccinated. The infected
194 cases (29 females and 33 males) were aged between 24-60 years (median 41.5 years).
195 Forty-seven developed respiratory symptoms between 1-15 days (median: 4) after
196 diagnosis. Three had pneumonia on chest x-ray examination. Of these, one required
197 oxygen supplementation for three days. Otherwise, they all were either asymptomatic or
198 mildly symptomatic (Table 1). All those with symptoms recovered uneventfully.
199 **Viral loads**
200 At diagnosis, median PCR Ct value was 31.7 (range: 37.6–14.0), equivalent to $\log_{10}$ copies
201 per mL of 4.5 (range: 2.6–9.9); eleven (20.8%) of the first 53 cases from 5 different
202 departments had high viral loads, median Ct value (range): 17.9 (14.0–22.6), equivalent to
203 $\log_{10}$ copies per mL of 8.7 (range: 7.3–9.9), including patient 1 and 4/6 members sharing
204 the office with him.
205 The viral loads of the 49 (pre)symptomatic cases peaked within 2-3 days before and after
206 symptom onset, with a median Ct value (range) of 16.8 (13.1–36.9), corresponding to $\log_{10}$
207 copies per mL of 9.1 (range: 2.8–10.2) (Figure 2A). During the course of infection, peaks
208 of viral loads measured at any time point of the symptomatic cases were higher than that of
209 asymptomatic cases; 16.5 (13.6–32) vs. 30.8 (13.1–36.9), equivalent to median $\log_{10}$ viral
210 load of 9.2 copies per mL (range: 4.3–10.1) vs. 4.7 copies per mL (range: 2.8–10.2),
211 p=0.005, respectively (Supplementary Figure 2). The median time from diagnosis to PCR
212 negative prior discharge was 21 days (range: 8–33).

213 Compared with peak viral loads of cases infected with old SARS-CoV-2 strains detected in
214 Vietnam between March and April 2020, peak viral loads of breakthrough cases were
215 significantly higher, median log10 viral load in copies per mL (range): 9.1 (range: 2.8–
216 10.2) vs. 6.7 (1.9–9.5), equivalent to 251 times higher for median viral loads. The
217 differences were more profound among symptomatic cases while there was no difference
218 in viral loads among asymptomatic cases between the two groups (Figure 2B).

219 **Whole genome sequencing**

220 A total of 23 whole genome sequences of SARS-CoV-2 were obtained from 35 samples
221 with sufficient viral loads. The obtained sequences were derived from 23 members
222 (including patient 1) of 10 different departments of HTD (Supplementary Table 1). All
223 were assigned to SARS-CoV-2 Delta variant. They were either identical or different from
224 each other by only 1 to 7 nucleotides, but no novel amino acid changes were identified
225 among them. Phylogenetically, the 23 sequences clustered tightly together but were
226 separated from the contemporary Delta variant sequences obtained from cases of
227 community transmission in HCMC (Figure 3), suggestive of ongoing transmission between
228 the vaccinated people.

229 **Antibody development and case-control analyses**

230 A total of 209 plasma samples were collected from the 62 study participants; 61 at
231 diagnosis and week 1, and 57 at week 2 and 31 at week 3 after admission. At diagnosis, all
232 but three had detectable neutralizing antibodies, with comparable levels between
233 (pre)symptomatic and asymptomatic cases (Supplementary Figure 3). Likewise, there was
234 no correlation between neutralizing antibodies at diagnosis and peak viral loads during the
235 course of infection (Figure 4).

At week 2 and 3 after diagnosis, neutralizing antibody levels of the case patients significantly increased, and were higher than neutralizing antibody levels measured at week 2 after the second dose of the 62 matched uninfected controls (Supplementary Figure 3).

Ten patients had data on neutralizing antibodies measured at both two weeks after the second dose and at diagnosis. Neutralizing antibody levels measured at these two time points of the 10 case patients were significantly lower than those in the 30 matched uninfected controls, median % of inhibition (range): 69.4 (13.7-96.3) vs. 91.3 (57.5-97.6), p=0.012 and 59.4 (12.5-95.0) vs. 91.1 (20.9-97.0), p=0.001, respectively (Figure 5). Similarly, the 62 case patients had lower levels of neutralizing antibodies measured at diagnosis than those in the 62 matched uninfected controls, median % of inhibition (range): 68.6 (12.5-97.0) vs. 82.3 (19.3-96.7), p=0.002.

The seroconversion rates for antibodies against N protein steadily increased from 0% at baseline to 65% (20/31) at week 3. Asymptomatic patients had slightly lower seroconversion rates than symptomatic patients (Supplementary Figure 4). There was no difference in neutralizing antibodies between the N protein antibody negative and positive groups (data not shown).

DISCUSSION

We studied Oxford-AstraZeneca vaccine breakthrough infections associated with SARS-CoV-2 Delta variant among healthcare workers of a major hospital for infectious diseases in HCMC, Vietnam between 11th and 25th June 2021 (week 7 and 8 after the second dose). 62/69 infected cases participated in the clinical study. One required cannula oxygen supplementation for three days but all made full recovery in line with recent reports

regarding the vaccine effectiveness in protecting against severe disease.[13-15] However, we found strong evidence demonstrating for the first time that fully vaccinated healthcare workers could still pass the virus between each other.

Indeed, the 23 whole-genome sequences of SARS-CoV-2 obtained from the infected cases clustered tightly on the phylogenetic tree, but separately from the contemporary Delta variant genomes obtained from cases of community transmission in HCMC. This strongly suggested that these individuals likely caught the virus from a single introduction into the hospital. Additionally, because only 1 out of the first 53 infected cases of the outbreak were symptomatic at diagnosis, presymptomatic and/or asymptomatic transmission had occurred between the vaccinated members of staff of HTD. This was likely attributed to several factors. Firstly, high viral loads, >7 $\log_{10}$ copies per mL, which was strongly correlated with positive culture (i.e. infectiousness),[8,16] was recorded in 11 of the first 53 positive cases of the outbreak at diagnosis. Second, HTD offices are typically equipped with air conditioners without mechanical ventilation systems, a well-known indoor setting that could facilitate the transmission of SARS-CoV-2.[17] Third, mask wearing in the office was not mandatory at the time.

Lower levels of neutralizing antibodies after vaccination and at diagnosis were associated with breakthrough infections in a recent report from Israel,[18] supporting findings of the present study. However, we found no correlation between vaccine-induced neutralizing antibody levels at diagnosis and the development of respiratory symptoms or viral loads (i.e. infectivity). Thus, while neutralizing antibodies might be a surrogate of protection, especially against severe diseases as a whole,[19] they might not be good indicators of disease progression and infectiousness for breakthrough Delta variant infection. The rapid

increase in neutralizing antibodies after infection among cases of the present study in turn suggested that a third dose may improve the immunity and potentially the protection.

At the beginning of the outbreak, none of the HTD members of staff (including the PCR confirmed cases) were tested positive for N-protein antibodies, which only develop in response to whole-virus based vaccine and natural infection. Additionally, between 12th and 14th May 2021, all members of HTD staff were subjected to a periodic testing for SARS-CoV-2 by PCR, but none was positive. The data thus suggested that the infected cases were captured at an early phase of the infection. Therefore, by carefully following up the patients during hospitalization, we have also provided new insights into the natural history of breakthrough Delta variant infections. We found viral loads of breakthrough Delta variant infection cases peaked around 2-3 days before and after the development of symptoms, and were 251 times higher than those of the infected cases detected during the early phase of the pandemic in 2020.[5] Additionally, there has been only one report showing that 9/11 cases of vaccine breakthrough infection had no detectable RNA when retested within 2–7 days after diagnosis.[20] Yet, we found prolonged PCR positivity was up to 33 days in our study participants. These factors might explain the current rapid expansion of the Delta variant, even in the countries with high vaccination coverage.

In summary, we report the transmission SARS-CoV-2 Delta variant among vaccinated health care workers. Breakthrough Delta variant infections are associated with high viral loads, prolonged PCR positivity, and low levels of neutralizing antibodies after vaccination and at diagnosis. These factors coupled with poorly ventilated indoor settings and without mask wearing might have facilitated presymptomatic and/or asymptomatic transmission among the vaccinated workers. Physical distancing measures remain critical to reduce

305 SARS-CoV-2 Delta variant transmission, thereby mitigating the impact of the ongoing
306 COVID-19 pandemic.

ACKNOWLEDGEMENTS

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We thank our colleagues at the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam for their participations in this study and for their logistic support with the data collection. We thank Ms Le Kim Thanh for her logistics support.

OUCRU COVID-19 Research Group

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LEGENDS TO TABLES AND FIGURES

Table 1: Demographics and clinical characteristics of the study participants

Figure 1: Flowchart showing timelines and results of SARS-CoV-2 RT-PCR screening before and during the lockdown (11-25 June 2021)

Notes to Figure 1: *The remaining members of staff were working from home.

Figure 2: Viral load analyses, A) plot outlining kinetics of viral loads in relation to illness onset of the 49 study participants who were either symptomatic or presymtomatic at admission, B) comparison between peak viral loads of breakthrough infections (cases) and those (controls) infected with old SARS-CoV-2 strains detected between March and April 2020 in Vietnam

Notes to Figure 2: Vertical dashed line indicates the time point of illness onset. Horizontal dashed line indicates detection limit of PCR assay. A) Black lines indicates median viral loads, B) black dots represent for whole groups, red dots represent for symptomatic cases and blue dots represent for asymptomatic cases. Peak viral loads comparison between symptomatic and asymptomatic groups of the cases and controls: median $\log_{10}$ viral load in copies per mL (range): 9.2 (4.3–10.1) vs. 6.9 (3.7–9.5), $p<0.001$ and 4.7 (2.8–10.2) vs. 4.9 (1.9–8.6), $p=0.511$.

Figure 3: Maximum likelihood tree illustrating the relatedness between SARS-CoV-2 Delta variant strains obtained from cases of vaccine breakthrough infection (red) and contemporary Delta variant sequences obtained from cases of community transmission in Ho Chi Minh City (blue) and other provinces in Vietnam or countries (black).

Note to Figure 3: Cases of vaccine breakthrough infections were derived from 12/19 affected department of the Hospital for Tropical Diseases

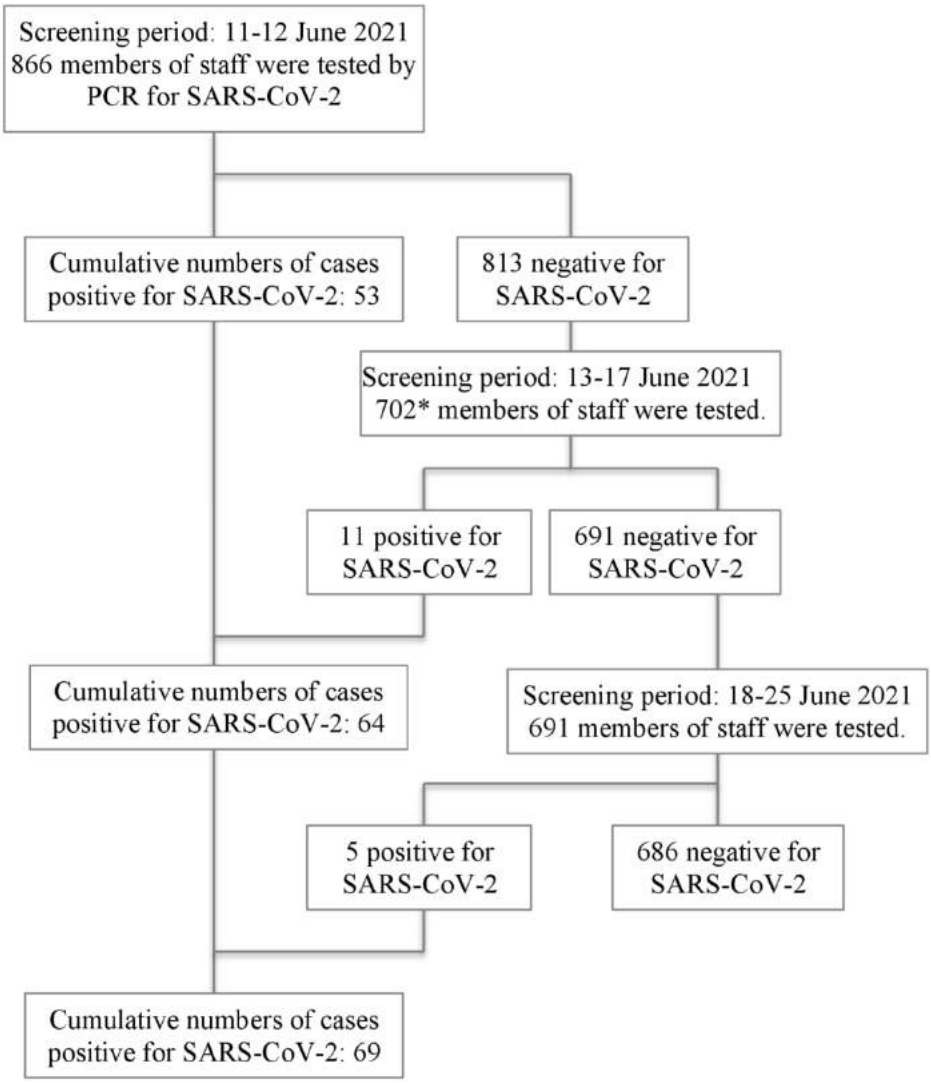
Figure 4: Correlation between neutralizing antibodies at diagnosis and peak viral loads during the course of infection

Figure 5: Comparison between neutralizing antibody levels of case patients (red) and uninfected controls (grey green). A) between the 10 case patients whose data on neutralizing antibodes at both week 2 after the second doses (8 weeks after the first dose) abd at diagnosis were available and the uninfected controls, B) between the 62 case patients and the uninfected controls for data at diagnosis

Table 1: Demographics and clinical characteristics of the study participants

Signs/Symptoms	**All cases (n=62)**	**Male (n=33)**	**Female (n=29)**
Age, y, median (range)	41.5 (24-60)	41 (27-60)	43 (24-59)
Occupation, n (%)			
Nurse	13	5	8
Pharmacist	10	3	7
IT	7	7	0
Clinician	7	5	2
Accountant	4	0	4
Technical staff	3	3	0
Cleaner	2	2	0
Others	16	8	8
Symptomatic, n (%)	49 (79.0)	24 (72.7)	25 (86.2)
PCR diagnosis to illness onset, d, (median; range)*	4 (0-15)	3 (0-8)	5 (0-15)
Comorbidity[#], n (%)	17 (27.4)	9 (27.3)	8 (27.6)
COVID-19 vaccination[¥], n (%)	62 (100)	33 (100)	29 (100)
Two doses	60 (96.7)	33 (100)	27 (93.1)
One dose	2 (3.3)	0	2 (6.9)
Fever, n (%)	17 (27.4)	9 (27.3)	8 (27.6)
Cough, n (%)	23 (37.1)	19 (57.6)	14 (48.3)
Sore throat, n (%)	21 (33.9)	9 (27.3)	12 (41.4)
Runny nose, n (%)	22 (35.5)	9 (27.3)	13 (44.8)
Loss of smell, n %)	24 (38.7)	14 (42.4)	10 (34.5)
Loss of taste, n (%)	5 (8.1)	3 (9.1)	2 (6.9)
Muscle pain, n (%)	17 (27.4)	13 (39.4)	4 (13.8)
Headache, n (%)	12 (19.4)	6 (18.2)	6 (20.7)
Chest pain, n (%)	2 (3.2)	0	2 (6.9)
Nausea, n (%)	5 (8.1)	3 (9.1)	2 (6.9)
Others, n (%)[$]	5 (8.1)	1 (3.0)	4 (13.8)
Pneumonia, n (%)**	3 (4.8)	0	3 (10.3)

Notes to Table 1:
*Symptomatic cases only
[¥]All receiving AstraZeneca vaccine; The second doses were given in last 2 weeks of April 2021.
[#]Overweight (n=6), obese (n=3), hypertension (n=3), hepatitis B (n=2), diabetes (n=1), pregnancy (n=1), diabetes and hepatitis B (n=1).
[$]Chills (n=2), sweating (n=1), giddiness (n=1), red eyes (n=1), and diarrhea (n=1)
**One requiring oxygen supplementation via cannula route for 3 days.



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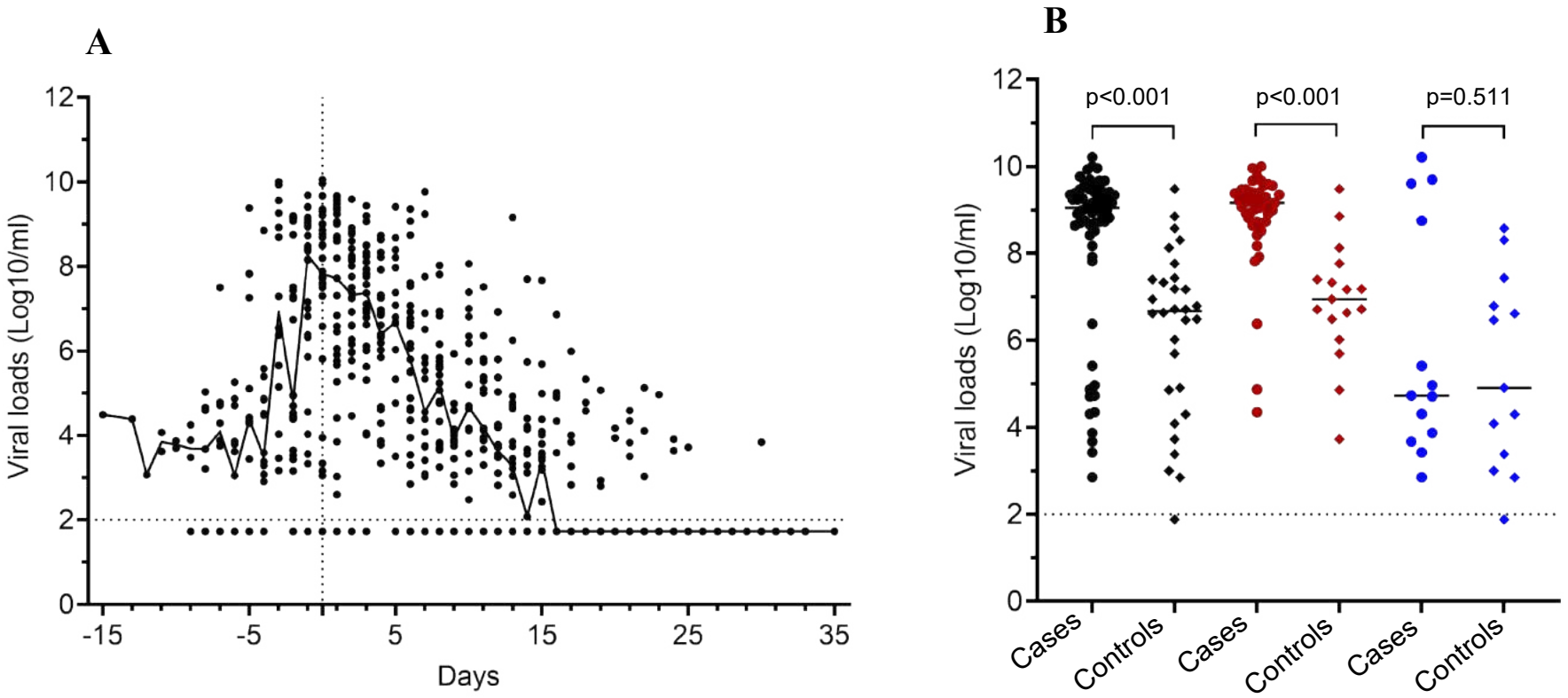
A
Viral loads (Log10/ml)
Days
B
p<0.001
p<0.001
p=0.511
Viral loads (Log10/ml)
Cases
Controls
Cases
Controls
Cases
Controls

Figure 2: Viral load analyses, A) plot outlining kinetics of viral loads in relation to illness onset of the 49 study participants who were either symptomatic or presymtomatic at admission, B) comparison between peak viral loads of breakthrough infections (cases) and those (controls) infected with old SARS-CoV-2 strains detected between March and April 2020 in Vietnam

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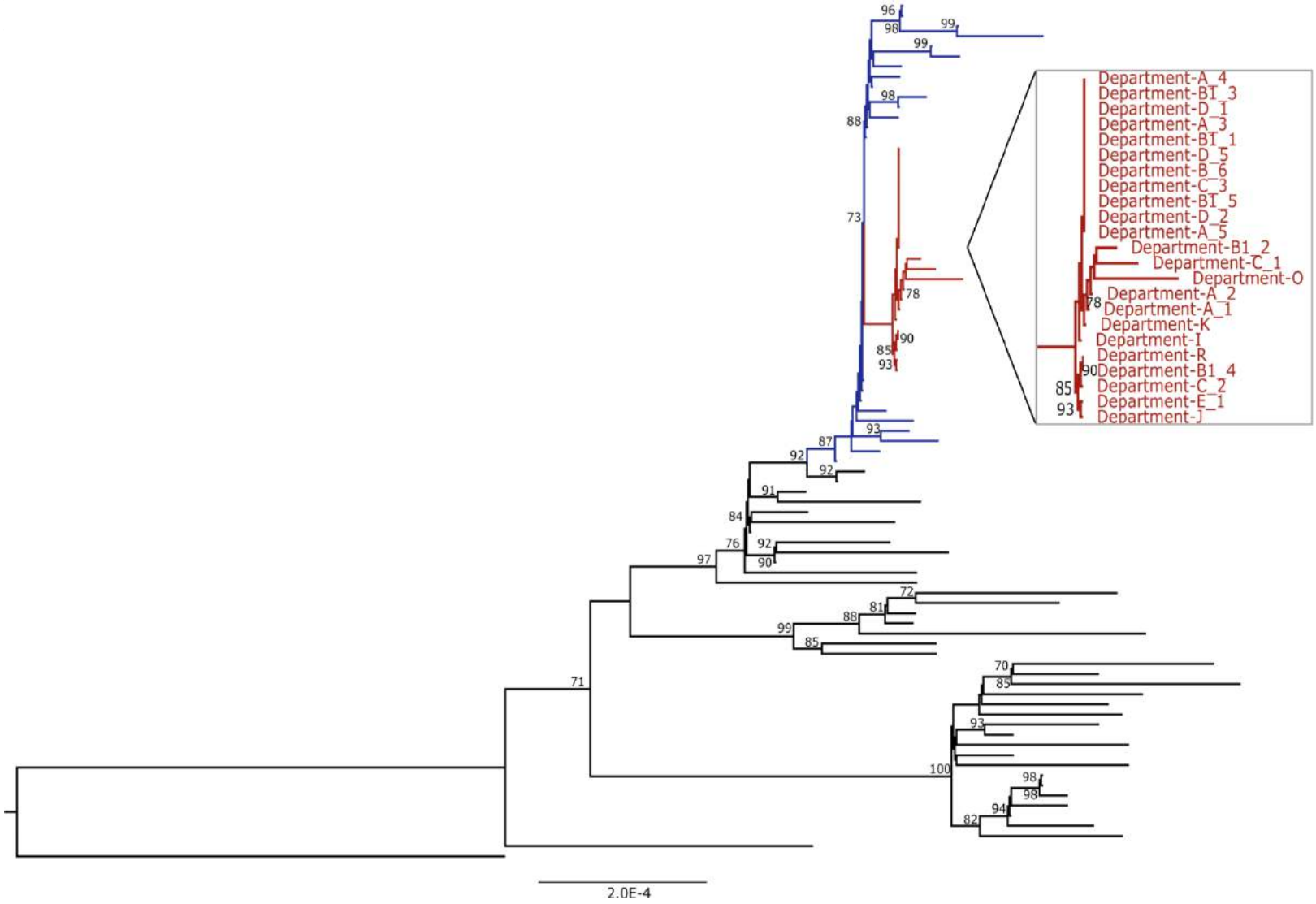

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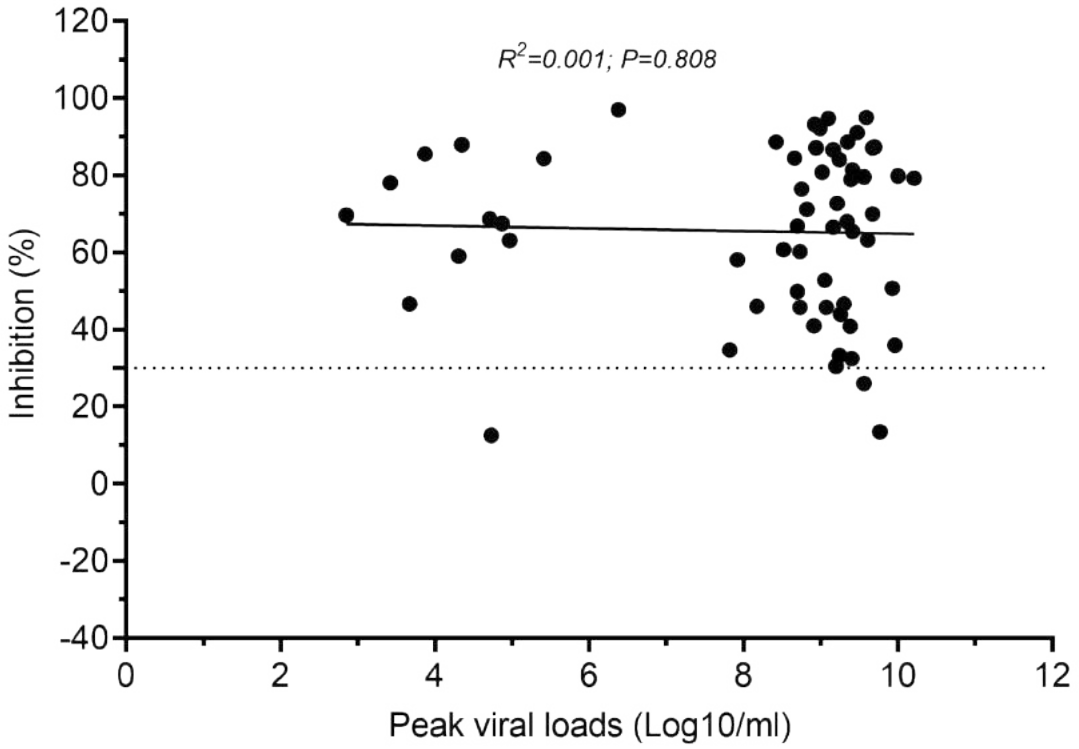
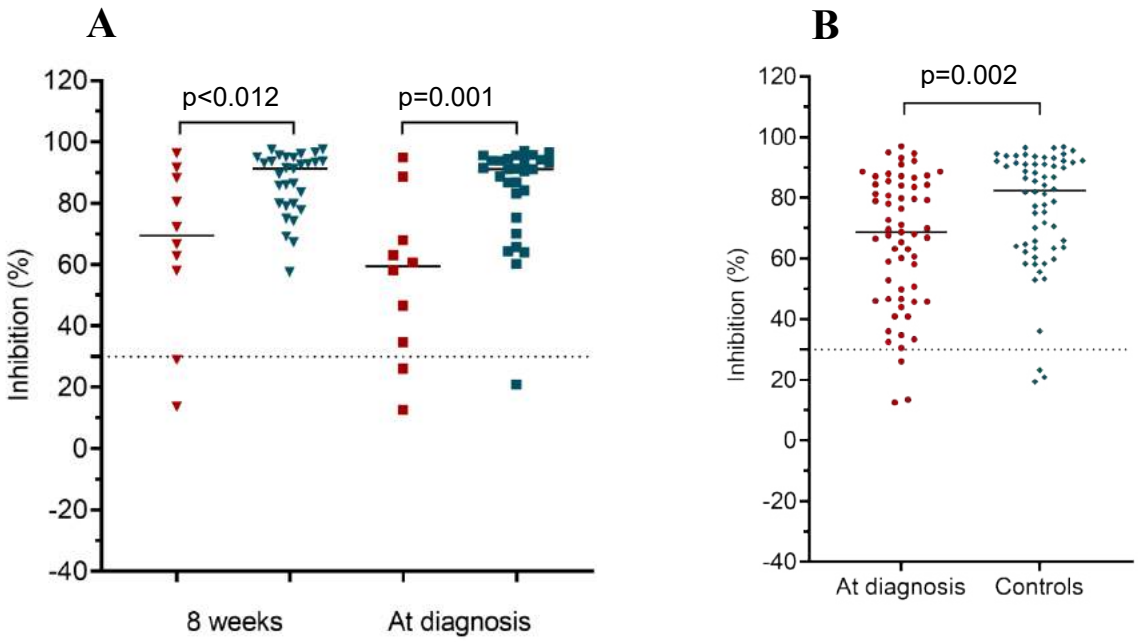


Figure 4: Correlation between neutralizing antibodies at diagnosis and peak viral loads during the course of infection



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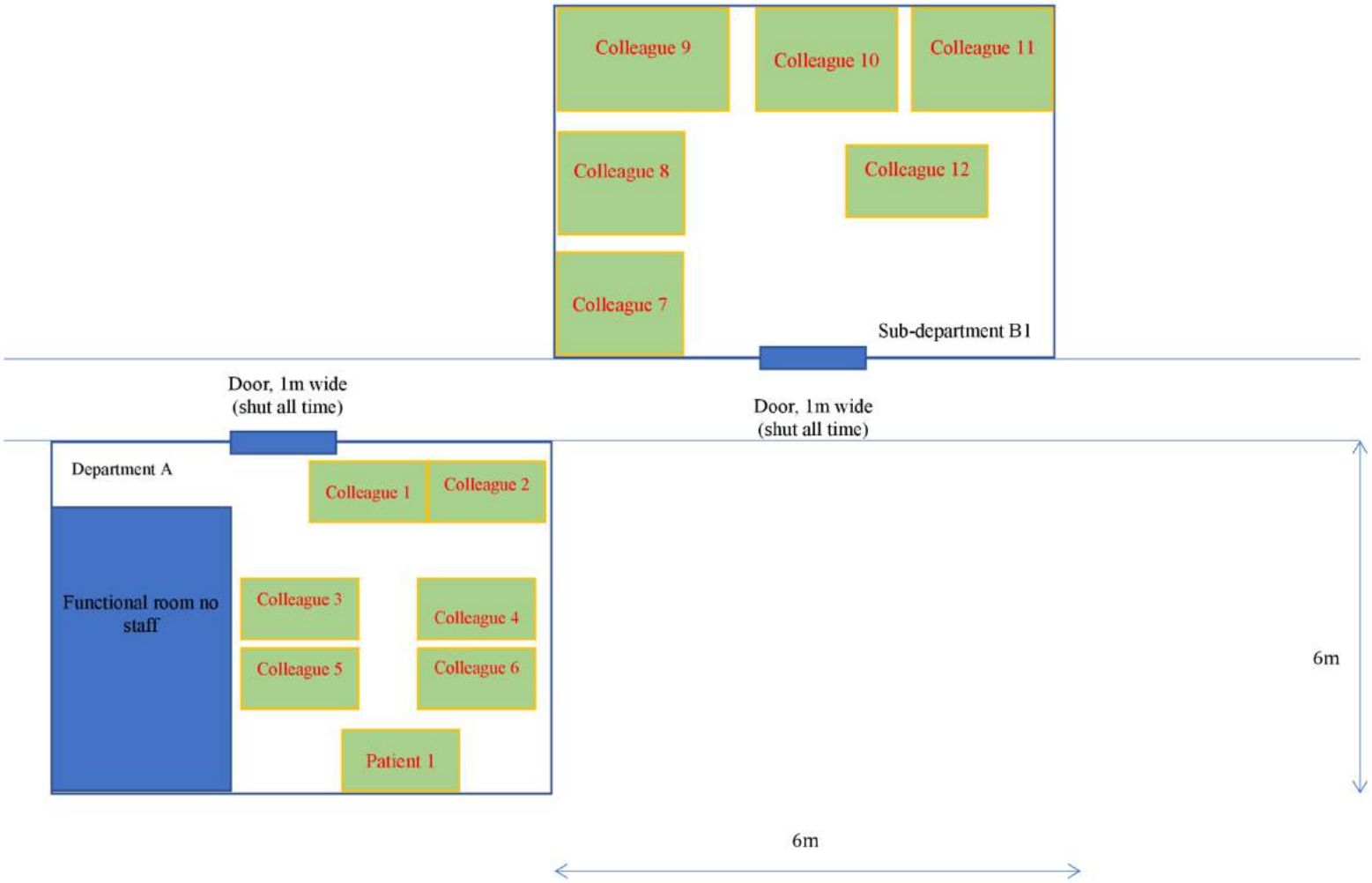
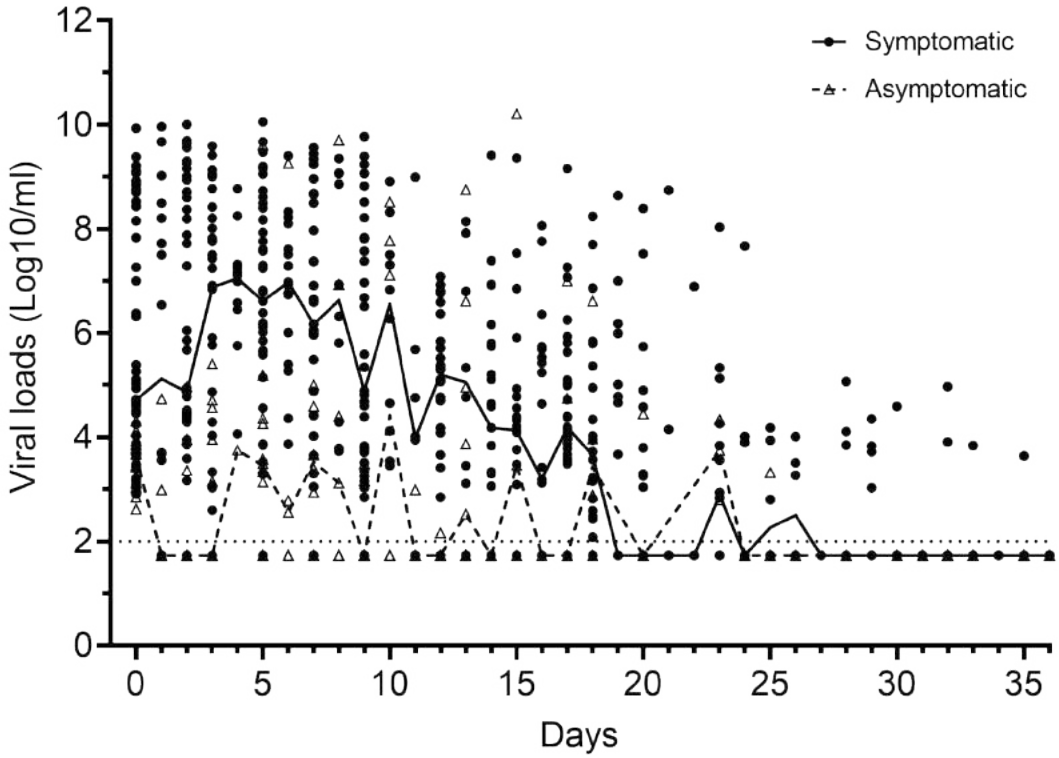
SUPPLEMENTARY MATERIALS

Supplementary Table 1: Numbers of PCR confirmed cases detected per department

Name of department*	Functions	Number of staff	Number of staff tested positive (%)	Numbers genomes obtained
Department A	Supportive service	7	7 (100)	5
Department B	Supportive service	56	16 (29)	6
Sub-department B1	Supportive service	8	7 (88)	6
Sub-department B2	Supportive service	7	4 (57)	0
Sub-department B3	Supportive service	8	3 (38)	0
Sub-department B4	Supportive service	9	2 (22)	0
Department C	Supportive service	3	3 (100)	3
Department D	Supportive service	60	12 (20)	3
Department E	Patient care	75	6 (8)	1
Department F	Supportive service	36	4 (11)	0
Department G	Patient care	50	3 (6)	0
Department H	Supportive service	20	3 (15)	0
Department I	Supportive service	6	2 (33)	1
Department J	Patient care	28	1 (4)	1
Department K	Patient care	31	1 (3)	1
Department L	Patient care	32	1 (3)	0
Department N	Patient care	28	1 (4)	0
Department O	Patient care	19	1 (5)	1
Department P	Patient care	29	1 (3)	0
Department Q	Supportive service	11	1 (9)	0
Department R	Supportive service	15	1 (7)	1
Department S	Patient care	17	1 (5.9)	0
Department T	Patient care	18	1 (5.6)	0

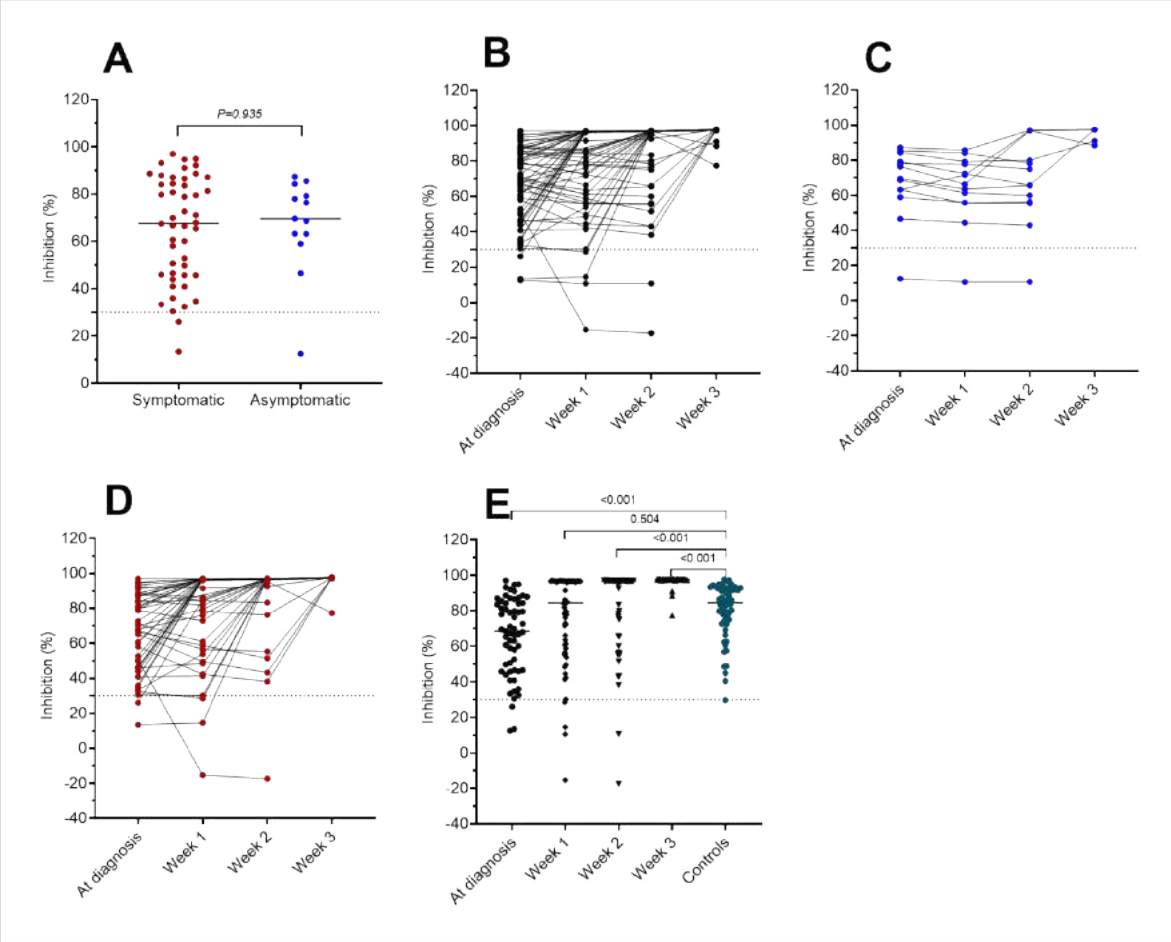


Supplementary Figure 1: Layout of office of patient 1 and a close office where 7/8 members were tested positive on 11th-12th June 2021. Office names are linked with Supplementary Table 1. Offices are equipped with air conditioners without mechanical ventilation. During working hours, doors are kept closed to maintain cooling air.



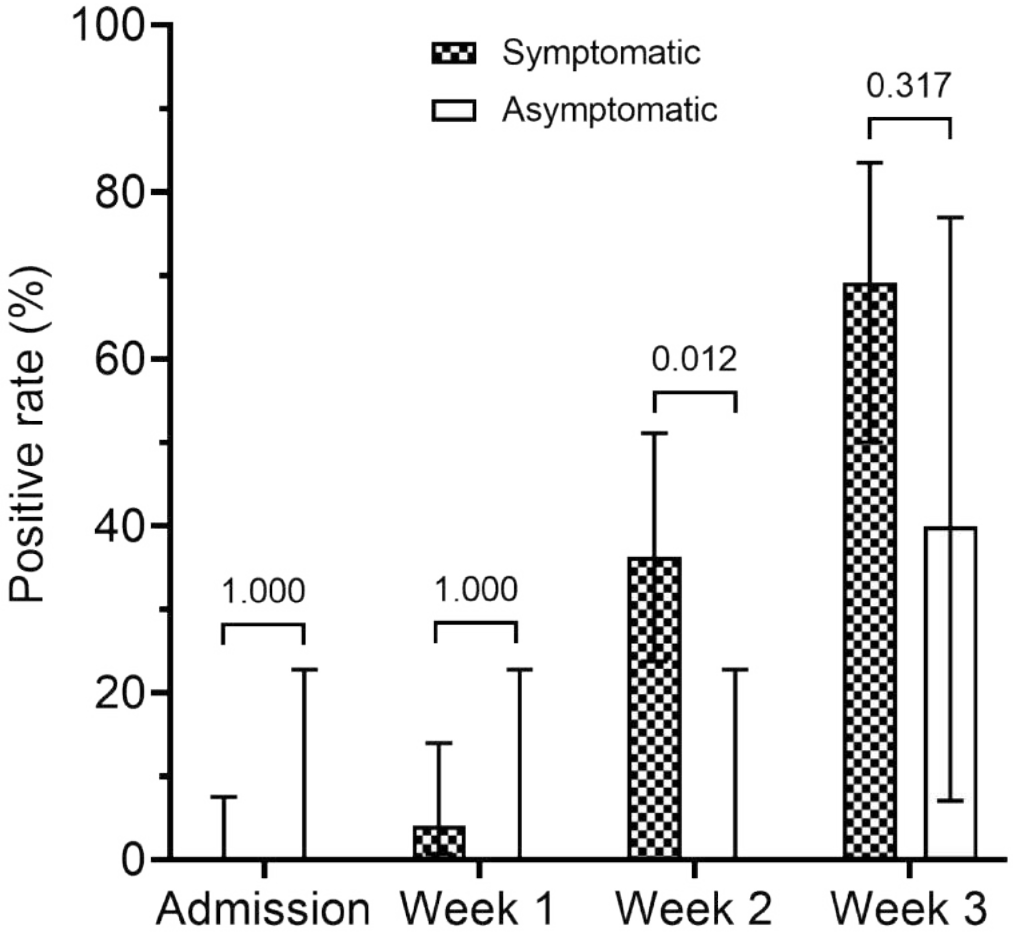
Supplementary Figure 2: Plot outlining kinetics of viral loads since PCR diagnosis during the course of hospitalization of the asymptomatic and symptomatic cases

Notes to Supplementary Figure 2: (Dashed) lines indicate median viral loads.



Supplementary Figure 3: Results of neutralizing antibody measurement, A) at diagnosis of symptomatic (including those developed symptoms after diagnosis) and asymptomatic cases, and kinetics of neutralizing antibodies at admission and at week 1, 2 and 3 after admission of B) the whole group, C) the asymptomatic group, D) the symptomatic group, and E) in comparison with the control group

Supplementary Notes to Figure 3: Dashed line indicates assay cut-off (30%). The asymptomatic case (panel C) who remained seronegative during infection did not respond to the vaccine (data not shown). Neutralizing antibody measurement were repeated twice for the symtomatic case who became seronegative at week 1 and week 2. Age and gender comparison between cases and controls: median in years (ragne): 41.5 (24-60) vs. 37.5 (24-58), p=0.47, and male/female 33/29 vs. 23/29, p=0.07.



Supplementary Figure 4: Seroconverion rates against N protein at admission, and week 1, 2 and 3 after admission.

Note to Supplementary Figure 4: For the whole group, the seroconverstion rates for antibodies against N protein increased from 0% at baseline to 3.3% (2/61) at week 1, 28.1% (16/57) at week 2 and 65% (20/31) at week 3.

Exhibit "E"

Alberta Health Services

Carl Nohr, MDCM, PhD, FRCSC, FACS, PRP, ICD.D
Associate Zone Medical Director, Medicine Hat and South Zone
[redacted]

October 28, 2021

Confidential

Dr. Gert Grobler
Department of Family Medicine
Medicine Hat, AB

[delivered via email [redacted]

Dear Dr. Grobler:

Re: Follow up - Immunization of Workers for COVID-19 Policy

Thank you for speaking with me on October 18, 2021 to discuss the compliance requirement of medical staff to the AHS Immunization of Workers for COVID-19 Policy (the "Policy"). I appreciated the opportunity to have an open discussion of this matter with you.

During our meeting, we discussed whether you would become fully immunized and the path forward. You indicated you are not willing to become fully immunized at this time and it was agreed that you will go on a voluntary leave of absence. There has been an extension to the compliance deadline for all medical staff to be fully vaccinated against COVID-19. The deadline is now November 30, 2021.

If you are not intending to be fully vaccinated and in compliance with the Policy by November 30, 2021, please find enclosed a Clinical Leave of Absence (LOA) form for your completion. The completed LOA form can be returned to Krystle Heikkinen [redacted] who can support you in submitting the LOA and ensuring any further requirements for the LOA are completed. In relation to your leave of absence, please ensure that appropriate clinical care coverage is arranged and advise Dr. Sandra Duke of your absence.

The LOA will be in effect commencing December 1, 2021 until the earlier of the following:

(a) May 31, 2022, at which time it will be reviewed to determine whether it should be continued; or

(b) until you are fully vaccinated and accurate proof of your immunization status has been disclosed to AHS.

If during the LOA you do become fully vaccinated please contact myself directly to discuss your return to work and ensure you have submitted your Proof of Immunization Record to COVID19immunization@ahs.ca.

Thank you for your engagement in this process.

[redacted]

This is Exhibit "E" referred to
In the affidavit of Dr. Gert Grobler
Sworn before me herein this 9
day of December, 2021

Regards,

[redacted]

Carl Nohr, MDCM, PhD, FRCSC, FACS, PRP, ICD.D
Associate Zone Medical Director, Medicine Hat and South Zone

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

Encl: Clinical Leave of Absence Form

Exhibit "F"

[redacted]

On Thursday, November 18, 2021, 12:08 PM, Marg [redacted] wrote:

Greetings, Dr. Grobler:

In follow up the telephone conversation between yourself and Dr. Foley this AM, and SZ Medical Affairs has now been directed to start the credential documents for your placement on "leave of absence" effective Nov 19, 2021:

Would you have a few minutes today to review the attached form and complete the "absence details" on page one, and sign and date page two ?

Your reply is appreciated prior to Friday, Nov 19, 0900 .

Thankyou in advance.

[redacted]

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

This is Exhibit F referred to
in the affidavit of Dr. Gert G Grobler
Sworn before me herein this 9
day of December, 2021

[redacted]

EA- South Zone Medical Affairs

[redacted]

Alberta Health Services

Medicine Hat Regional Hospital

[redacted]

[redacted]

[redacted]

Absence From Clinical Practice REQUEST FORM

Alberta Health Services

PERSONAL INFORMATION

Last Name	First Name	Middle Name
Grobler	Gert	
Primary Zone: South	[redacted]	[redacted] ☑ CPSA ☐ ADA+C ☐ APA

Instructions

- Complete all sections of this form.
- Submit this form to each applicable Zone Medical Affairs Office (or Zone Clinical Department). Requests will be approved by each Zone separately.
- Absences greater than 30 consecutive days must be approved by all applicable Zone Clinical Department Heads and the Zone Medical Director.
- Please refer to section 4.16 Absence from Clinical Practice in Sites of Clinical Activity of the AHS Medical Staff Rules for more information. Also note that some Zones or Clinical Departments may have additional rules or guidelines regarding absences (i.e. may require approval of the relevant Section Chief(s), etc).

CURRENT APPOINTMENT PROFILE

Current Appointment Category

- ☑ Active
- ☐ Community
- ☐ Locum Tenens
- ☐ Probationary (Active)
- ☐ Probationary (Locum)
- ☐ Temporary

Appointment End Date *(if applicable)*

#	Current Zone(s)	Current Department(s)
1	South	**PRIMARY**: Family Medicine w admitting privileges
2		**Supp.**:
3		**Supp.**:
4		**Supp.**:
5		**Supp.**:
6		**Supp.**:

ABSENCE DETAILS

Start Date *(of this request)*	Original Start Date *(if extending a leave)*	End Date
November 19, 2021		

Reason(s) for leave

Patient Coverage

- ☐ On Call Schedule/Roster *(for leaves less than or up to 96 hours, unless otherwise permitted)*
- ☐ Personal On Call Group
- ☐ Transfer of Responsibility to:

Is there a requirement to maintain access to Patient Information Systems during this Leave? ☐ Yes ☐ No

Reason(s):

Is there a requirement to provide direct or indirect patient care during this Leave? ☐ Yes ☐ No

If YES, appropriate licensure and malpractice coverage must be kept current.

REQUESTOR *(if not the affected Practitioner)*

Requestor Name	Requestor Title/Role	Requestor Phone Number

Requestor Zone	Requestor Department

APPROVALS			
Practitioner Signature	Printed Name Dr. Gert Grobler	Date	
	☐ Written consent attached		
Primary ZCDH Signature	Printed Name Dr. Josh Foley	Date	☐ Accept ☐ Deny
	Zone, Department, Section South / Family Practice - MHRH		
Supplementary ZCDH or Primary Section Chief Signature	Printed Name	Date	☐ Accept ☐ Deny
	Zone, Department, Section		
Supplementary ZCDH or Section Chief Signature	Printed Name	Date	☐ Accept ☐ Deny
	Zone, Department, Section		
Supplementary ZCDH or Section Chief Signature	Printed Name	Date	☐ Accept ☐ Deny
	Zone, Department, Section		
Zone Medical Director Signature	Printed Name Dr. Aaron Low	Date	☐ Accept ☐ Deny
	Zone South		

Exhibit "G"

[redacted]

This is Exhibit G referred to in the affidavit of Dr. Gert Grobler Sworn before me herein this 9 day of December, 2021

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

From: [redacted]
Sent: November 18, 2021 6:54 PM
To: Marg [redacted]
Cc: Josh [redacted]
Subject: Re: LOA Dr. G. Grobler - time sensitive to Nov 18
Importance: High

Good Day

As discussed with Dr Foley and DR Nohr, I have had covid on 27 September 2021 with acquired natural antibodies.I do not accept a voluntary LOA or any LOA.It is AHS decision to terminate my employment at Medicine Hat Hospital after 15 years of service, and preventing me to serve my patients as per my Hippocratic oath,The Health Act,and Standards of The College of Alberta with informed conscent prerequisite as a minimum.I am coerced by AHS against my Charter rights ,Bill of Rights and Human rights to be forced to take an experimental mRNA injection,against The Neurenburg Code,The Helsinki Declaration as well as The Geneva Convention, losing my right to practise medicine, looking after my patients, with no liability taken by AHS if i have detrimental side effects, disability or death. Taking an experimental, non FDA approved covid vaccine with increasing side effects, soon after having covid with decrease effectiveness as seen worldwide with breakthrough infections, goes against my human rights, and is unacceptable.I will also lay a complaint with The Human Rights Commission.

Regards
Dr Gert Grobler

On Nov 18, 2021, at 11:08 AM, Marg [redacted] wrote:

Greetings, Dr. Grobler:

In follow up the telephone conversation between yourself and Dr. Foley this AM, and SZ Medical Affairs has now been directed to start the credential documents for your placement on "leave of absence" effective Nov 19, 2021:
Would you have a few minutes today to review the attached form and complete the "absence details" on page one, and sign and date page two ?

Your reply is appreciated prior to Friday, Nov 19, 0900 .

Thankyou in advance.

Marg [redacted]
EA- South Zone Medical Affairs
[redacted]
Alberta Health Services
Medicine Hat Regional Hospital
[redacted]

<2021 11 18 - Grobler, Gert - LOA.pdf>

Exhibit "H"

Justice Centre
for Constitutional Freedoms

[redacted]

This is Exhibit 17 referred to in the affidavit of Dr. Gert Grobler
Sworn before me herein this 9 day of December, 2021

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

November 2, 2021

Via Email [redacted]

Alberta Health Services
Seventh Street Plaza
14th Floor, North Tower
10030 – 107 Street N.W.
Edmonton, Alberta T5J 3E4

ATTENTION: Alberta Health Services President and Chief Executive Officer

Dear Dr. Yiu,

Re: AHS Vaccination Policy
Dr. Gert Grobler

We write on behalf of Dr. Gert Grobler concerning the actions taken by Alberta Health Services ("AHS") regarding the AHS Policy of September 14, 2021, entitled *Immunization of Workers for COVID 19* (the "Policy"), requiring all physicians, staff, and contracted providers to be fully immunized by October 31, 2021,[1] and without notice extended the deadline to November 30, 2021.[2]

Dr. Grobler has practiced in rural Alberta for 15 years, 6 years in Viking where he performed all C-Section and small surgeries. In 2012 he relocated to Medicine Hat. He is part of a 9-person team of family General Practitioners of which 8 do weekly hospital calls. During the weekly hospital calls, he looked after the patients admitted on a 24-hour basis and the clinic has 24-45 patients daily.

Throughout the Covid-19 pandemic, Dr. Grobler worked in all levels of the hospital ward except for the Intensive Care Unit and Emergency Unit. Moreover, he was actively involved with patient cases in the Covid-19 Unit without getting infected with Covid-19. However, on September 26, 2021, he contracted the virus outside of the hospital setting from a vaccinated friend. Dr. Grobler advised his supervisor, Dr. Carl Nohr, of his natural immunity and that he does not consent to provide further private, medical information to AHS. He was further advised that as of November 1, 2021, his hospital privileges were unilaterally revoked and that he is not allowed to attend at the four facilities he does rounds in, specifically Wellington, Meadowlands, Meadowridge and Chinook village.

This letter addresses several concerns arising from AHS' actions and the Policy, and Dr. Grobler demands an exemption to the Policy for the following reasons:

---

[1] https://extranet.ahsnet.ca/teams/policydocuments/1/clp-ahs-immunization-workers-1189.pdf - Document # 1189 – Immunization of Workers for Covid 19.

[2] AHS extends mandatory COVID-19 immunization deadline | Alberta Health Services.

Privacy Concerns

The Policy requires workers to divulge personal medical information to prove their vaccination status to their employers, which is an unreasonable invasion of the worker's privacy, in violation of the *Personal Information Protection and Electronic Documents Act*, SC 2000, c.5 and the Personal Information Protection Act, SA 2003, c.P-6.5.

Medical records contain very sensitive personal and private information, which is confidential and not normally disclosed without the consent of the patient, see *Carleton University and Carleton University Academic Staff Association*, unreported award dated March 29, 2019 (Pamela Cooper Picher).
Gathering personal, medical information must be developed and implemented in compliance with applicable privacy laws. They should also incorporate privacy best practices in order to achieve the highest level of privacy protection commensurate with the sensitivity of the personal health information that will be collected, used or disclosed.

Above all, and considering the significant privacy risks involved, the necessity, effectiveness and proportionality of such record keeping must be established for each specific context in which they will be used. The necessity, effectiveness and proportionality of private, medical gathering must be continually monitored to ensure that they continue to be justified, and such measures must be decommissioned if, at any time, it is determined that they are not a necessary, effective, or proportionate response to address their public health purposes. AHS has not provided any information to demonstrate that these measures are evidence-based and that no other less privacy-intrusive measures are available and equally effective in achieving the specific purpose.

Furthermore, AHS has not provided the authority under which it is proceeding gather private, medical information. Absent such order or law, consent must be voluntary and meaningful, based on clear and plain language describing the specific purpose to be achieved. The purpose must be one that a reasonable person would consider appropriate in the circumstances. And most importantly, individuals must have a true choice: consent must not be required as a condition of service.

The issue of safekeeping of private, medical information has already been raised in Ottawa Hospital after a major privacy breach wherein the medical status of employees was inadvertently sent on a mass email to a subset of the staff.[3]

We submit that AHS do not have the authority to enact these measures, and moreover has failed to meet the conditions required to gather such information. Accordingly, Dr. Grobler does not have to consent to providing his personal, medical information.

The Policy is Unscientific and Unethical

The definition of "Fully Immunized" in the Policy does not recognize enhanced immunity, established by settled science, possessed by individuals who have recovered from Covid-19. Dr. Grobler has fully recovered from Covid-19.

The science on the effectiveness of natural immunity after infection with Covid-19 has been researched and proven. A National Institutes of Health (the "NIH") publication, dated January 26, 2021, stated:

[3] Ottawa Hospital apologizes for privacy breach among unvaccinated employees | CTV News.

> The researchers found durable immune responses in the majority of people studied. Antibodies against the spike protein of SARS-CoV-2, which the virus uses to get inside cells, were found in 98% of participants one month after symptom onset. As seen in previous studies, the number of antibodies ranged widely between individuals. But, promisingly, their levels remained fairly stable over time, declining only modestly at 6 to 8 months after infection.[4]

Another recent article in *Clinical Infectious Diseases* (published Oct. 5, 2021) by Jie Zhang, et al. demonstrated further evidence of a robust and long-lasting immunity in Covid-19 convalescents stating: "SARS-CoV-2 specific cellular and humoral immunities are durable at least until one year after disease onset."[5] The World Health Organization also confirms this understanding, stating: "Current evidence points to most individuals developing strong protective immune responses following natural infection with SARSCoV-2."[6]

In a letter addressed to the Center for Disease Control ("CDC") dated May 28, 2021, a number of medical experts urged it to lift of restrictions on the naturally immune to the same extent such restrictions have been lifted on the vaccinated:

> First, in contrast to having had COVID-19, there is no proof that the COVID-19 vaccines prevent infection or transmission. The applications for emergency use authorization ("EUA") for all currently authorized COVID-19 vaccines were based on data which supports that these products may reduce certain symptoms of COVID-19 for some individuals, but the FDA's EUAs made clear that there is no evidence the COVID-19 vaccines can prevent recipients from becoming infected with and transmitting the virus. As the FDA explains, at the time of the EUA approval, the data was "not available to make a determination about how long the vaccine will provide protection, nor is there evidence that the vaccine prevents transmission of SARS-CoV-2 [i.e., the virus that causes COVID-19] from person to person." Similarly, the FDA Briefing Documents for the COVID-19 vaccines supporting the grant of an EUA list the following as still unknown: "effectiveness against asymptomatic infection," and "effectiveness against transmission of SARS-CoV-2." Nonetheless, your recommendations lift restrictions on individuals that have been vaccinated, despite the lack of proof that these products prevent infection and transmission, but do not lift restrictions on those that have had COVID-19 despite clear proof that having had the virus prevents them from becoming reinfected and transmitting the virus.[7]

A growing body of compelling evidence demonstrates that natural immunity is superior to vaccine immunity by every measure. It is unscientific and unethical for AHS to coerce or mandate a vaccine on an employee who already enjoys natural immunity as a result of having contracted and recovered from the virus, particularly since recent evidence suggests that the vaccines tend to diminish the protection natural immunity provides.[8] Furthermore, as far back as October 2020, it was known that "COVID-19 vaccines

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[4] https://www.nih.gov/news-events/nih-research-matters/lasting-immunity-found-after-recovery-covid-19.
[5] https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab884/6381561.
[6] See "Conclusions" https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Natural_immunity-2021.1.
[7] See Appendix A, Exhibit A: Reply-to-CDC-Re-Natural-Immunity-v-Vaccine-Immunity.pdf (icandecide.org) at p. 4.
[8] Sivan Gazit, et al., Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections medRxiv (August 25, 2021) https://www.medrxiv.org/content/10.1101/2021.08.24.21262415v1; https://www.israelnationalnews.com/News/News.aspx/309762; Yair Goldberg, et al., Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel, medRxiv (April 24, 2021) https://www.medrxiv.org/content/10.1101/2021.04.20.21255670v1.

designed to elicit neutralising antibodies may sensitise vaccine recipients to more severe disease than if they were not vaccinated."[9]

We demand that you provide the scientific evidence upon which the Policy is based and the rationale for not recognizing natural immunity, given the above.

The Policy contradicts other AHS polices

According to the Government of Alberta website:

> Health-care workers are strongly encouraged to get immunized. AHS reported the number of AHS health-care workers vaccinated against influenza in 2020-21 was 66%, compared to 67% in 2019-20.
>
> Alberta has a voluntary immunization policy for health-care workers. The focus is on education, promotion, and making it easy for health-care workers to get immunized.[10]

In 2018-2019 Alberta recorded 179 cases per 100,000 for influenza, and in 2017-2018, 215 per 100,000,[11] yet AHS did not implement a mandatory vaccination program for employee and patient safety and wellbeing. The discrepancy between vaccination polices for influenza and COVID-19 are unfounded and are particularly troubling when influenza has been ranked among the top 10 leading causes of death in Canada for the last 20 years.[12]

Furthermore, what is startling and very concerning is the actual rate of hospitalization and death rates when comparing influenza and Covid-19. In 2014-2015 Alberta recorded its highest rate of hospitalization case rates at 39.9/100 cases and death rates at 2.3/100 cases.[13] If we compare the total hospitalization and death rates from Covid-19 from start to present - which is well over 1 year of data – Alberta has recorded in total hospitalization case rates at 4.4/100 cases and death rates at 1.0/100 cases for Covid-19.[14] According to government data, in one year influenza was more than twice as deadly as total Covid-19 deaths, yet AHS did not impose a mandatory influenza vaccine policy at that time.

The Policy is Baseless

The electronic version of the Policy, as hosted on AHS Policy Services website[15] (which claims to be the only "valid" document) is shrouded with the following disclaimer (the "Disclaimer"):

> This work is licensed under a Creative Commons Attribution-Non-Commercial-Share Alike 4.0 International license. The licence does not apply to AHS trademarks, logos or content for which Alberta Health Services is not the copyright owner. This material is intended for general information only and is provided on an "as is", "where is" basis. **Although reasonable efforts were made to confirm the accuracy of the information, Alberta Health Services does not make any representation or warranty, express, implied or statutory, as to the accuracy, reliability, completeness, applicability or fitness for a**

[9] See "Results of the study": Cardozo, T. and Veazey, R. (2021), Informed consent disclosure to vaccine trial subjects of risk of COVID-19. vaccines worsening clinical disease. Int J Clin Pract, 75: e13795. https://doi.org/10.1111/ijcp.13795.
[10] See "About Influenza": https://www.alberta.ca/influenza-the-flu.aspx. Influenza – the flu | Alberta.ca.
[11] See Table 1: health-influenza-summary-report-2018-2019.pdf. (alberta.ca) at p. 3.
[12] Leading causes of death, total population, by age group (statcan.gc.ca).
[13] See Table 3 at page 14 Seasonal Influenza in Alberta: 2019-2020 Season.
[14] See Table 16 COVID-19 Alberta statistics | alberta.ca.
[15] https://extranet.ahsnet.ca/teams/policydocuments/1/clp-ahs-immunization-workers-1189.pdf.

> **particular purpose of such information. This material is not a substitute for the advice of a qualified health professional. Alberta Health Services expressly disclaims all liability for the use of these materials, and for any claims, actions, demands or suits arising from such use.** [Emphasis added]

The Disclaimer is an affront to AHS' Values of Compassion, Accountability, Respect, Excellence and Safety. It renders the Policy an unscientific proclamation of medical authority avoiding all responsibility.

AHS has declared it will not, "represent or warrant, express, implied or statutory, as to the accuracy, reliability, completeness, applicability or fitness for a particular purpose of such information," while making mandatory an experimental inoculation, with threat of unemployment. As a result, the Policy itself is an incongruity and does not support what it stands for.

Given that all material in the Policy is "not a substitute for the advice of a qualified health professional," Dr. Grobler has since:

1. Sought the advice of a qualified health professional;
2. Assessed his professional knowledge of vaccine breakthrough cases (it is important to note here that anesthesiologists give more intravenous drugs than all other types of physicians combined and are the only physicians with expert knowledge of potent drugs and how they affect the body);
3. Weighed the potential outcomes of taking the injection against the risk of contracting Covid-19 again; and
4. Come to the personal decision not to receive the Covid-19 vaccines.

To further threaten and coerce Dr. Grobler violates the fundamental tenet of medicine known as informed consent, and the Hippocratic medical maxim – "do no harm."

Unproven and Unfounded Claims

Many effective medicines carry risks and have side effects which may occur in some patients. Therefore a doctor should inform his or her patient of the benefits and risks of a medication, including possible side effects. With this information, the patient can decide whether or not to accept the treatment. This is called informed consent, which is a basic tenet of medicine.

The Covid-19 vaccines remain subject to ongoing clinical trials;[16] the vaccines bear Health Canada warning labels;[17] and the vaccinated and unvaccinated are both able to spread Covid-19 to others.[18] In short, there are significant reasons for individuals to have concerns about the safety and efficacy of these vaccines, and to make their own informed decisions not to receive them.

Statements in the Policy like, "Immunization against Covid-19 is the most effective means to prevent the spread of Covid-19, to prevent outbreaks in AHS facilities, to preserve workforce capacity to support the health care system, and to protect our workers, patients, visitors, and others accessing AHS sites," cannot be relied upon as accurate science, as expressly stated in AHS's disclaimer. If AHS wishes to maintain this position, we ask that AHS provide the scientific evidence to support the claim that immunization is the **most** effective means to prevent the spread of Covid-19 **and** to preserve workforce capacity **and** to protect

[16] See estimated completion study date, July 30, 2023: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California - Full Text View - ClinicalTrials.gov.
[17] See "Key Messages": https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/75479a-eng.php.
[18] Novel Coronavirus (COVID-19) Frequently Asked Questions (albertahealthservices.ca) at paras. 54 and 181.

those accessing AHS sites. The failure of AHS to provide support for its purportedly scientific positions is causing substantial reputational harm to AHS and will lead to a loss of confidence in its future endeavours, even those unrelated to Coavid-19.

The Policy claims to be for the safety and wellbeing of staff and patients; however, to date, no data has been provided by AHS to confirm that the contents of the vaccines themselves meet AHS employee safety standards or that they do not contain concerning levels of toxicity.

According to the Vaccine Adverse Event Reporting System ("VAERS"), the adverse events reporting database operated by the Food and Drug Administration ("FDA") and the CDC, Covid-19 vaccines have resulted in 9,010 reported deaths in the United States during a period of only eight months.[19] In addition, VAERS reports that the vaccines are associated with 10,333 life-threatening events, 10,124 permanent disability events, 42,353 hospitalizations, 324 hospitalization prolongations, and 82,081 emergency room visits. Reported adverse events associated with the Covid-19 vaccines total 635,842.[20] These figures represent Covid vaccine-related adverse events (including death) over the past <11 months and exceed all adverse events (including death) figures, for all other vaccines combined, over the past 14 years.

A 2011 study in which Pilgrim Health Care and Harvard University collaborated,[21] and a 2021 study published in the *Journal of the American Medical Association,*[22] find that actual adverse events occur at approximately 100 times the rate VAERS reports indicate, placing estimated total adverse events within the US at over 63.5 million. Applying the 2011 and 2021 studies, the Covid-19 vaccines may have resulted in over 1 million life threatening events, over 1 million cases of some variety of permanent disability, 4.2 million hospitalizations, over 30,000 prolonged hospital stays, 8.2 million emergency room visits, and 1 million deaths.

Does AHS accept liability for any harm to employees negatively affected by the injections?

Wrongful Dismissal

Via the Policy and actions taken by AHS, AHS has unilaterally changed the terms of employment, threatening to revoke employment and privileges, thus pressuring its employees to take a leave of absence of quit. Constructive dismissal is prohibited under Canadian and provincial employment laws. Constructive dismissal qualifies an employee for the same damages he or she would have received in an outright termination.

Upon acceptance of their offers of employment with the AHS, employees did not agree to any condition of employment involving injections, let alone subjection to an inoculation which bears a Health Canada warning and is linked to the death and injury of untold recipients, and which is still undergoing clinical trials. The effect of the Policy is causing severe hardship and irreparable harm which cannot be undone. It is alleged that some or all of them may be compelled to take the vaccine against their will because they cannot in their personal and family circumstances take the risk of being left destitute by the Policy they are seeking to challenge.

[19] https://wonder.cdc.gov/vaers.html.
[20] https://openvaers.com/covid-data.
[21] Harvard Pilgrim Health Care, Inc. Electronic Support for Public Health-Vaccine Adverse Event Reporting System (ESP:VAERS), online: https://digital.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system.
[22] Blumenthal KG, Robinson LB, Camargo CA, et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. JAMA. 2021;325(15):1562–1565. doi:10.1001/jama.2021.3976.

Finally, employers are legally obligated to respect the autonomy and dignity of their employees, and the confidentially of their medical information;[23] they are obliged not to use medical knowledge to violate the human rights and civil liberties of their employees, even under threat from government authority. Via the Policy, AHS has in fact violated its duties and obligations as a responsible and competent employer.

Nuremberg Code

Following the horrors of the Holocaust and the Nuremberg Military Tribunals, where horrendous practices of "doctors" were brought to light, the Nuremberg Code, established in 1947, placed limitations upon human experimentation. Paragraph 1 of the Nuremberg Code states:

> The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.
>
> The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

The AHS vaccine mandate introduces elements of duress, overreach and coercion since employees will be obliged to take experimental shots or face losing their jobs. Even the FDA's Pfizer factsheet for healthcare providers indicates deference to the principle of informed consent, for it states: "The recipient or their caregiver has the option to accept or refuse (Pfizer-BioNTech) vaccine."[24]

Criminal Assault

Forcing a medical intervention on AHS employees under threat of loss of livelihood is a clear violation of the *Criminal Code of Canada* (the "*CCC*")[25] which states in part:

> 265(1) A person commits an assault when
> (a) Without consent of another person he applies force intentionally to the person directly or indirectly...
>
> 265(3) For the purposes of this Section, **no consent** is obtained where the complainant submits or does not resist by reason of...
> (d) The exercise of authority. [emphasis added]

Forcing employees under threat of loss of livelihood is a violation of the *CCC*. Every member of the AHS who supports the Policy supports the criminal assault of his or her fellow medical professionals.

[23] Personal employee information | Alberta.ca.
[24] Healthcare Providers for 12 years of age and older, gray cap (no dilution) (fda.gov) at page 12.
[25] *Criminal Code* R.S.C., 1985, c. C-46 at sections 265(1) and 265(3).

Violation of the *Charter*

The Policy is unconstitutional as it unjustifiably violates sections 2, 7 and 8 of the *Canadian Charter of Rights and Freedoms*[26] (the "*Charter*"), which protects the right to a religious exemption based on the guarantee of "freedom of conscience" and "freedom of religion," and the right to informed consent based on the guarantee of "right to life, liberty and security of the person" and the "right to be secure against unreasonable search and seizure." The Policy also discriminates against an identifiable and increasingly marginalized group, the Covid "unvaccinated", contrary to section 15 of the *Charter*.

Harm Outweighs the Benefit

The medical system in Alberta is struggling. The recent treatment of health care workers in this province, in addition to the current AHS policies, are driving physicians out of Alberta and will further exacerbate an already dire situation. The forced departure of Dr. Grobler will cause harm to patients in Alberta and will cause a further strain on an already struggling medical system in Alberta as a whole.

In order for the Policy to be justified in the public interest, the Policy must be necessary to achieve the intended health purposes and the effectiveness in meeting the goals should be evidence-based. Moreover, the Policy must be proportionate to the purpose and ought to have an expiry date.

Terminating or suspending medical professionals during a health crisis ought to be exercised with extreme caution and in cases of negligent behaviour or willful wrongdoing which is not the case here. Employees are being faulted and threatened for simply maintaining and expressing their personal and professional beliefs. AHS itself has put a greater burden on the public health system in Alberta and AHS workers themselves.[27]

With respect to the Covid-19 vaccine itself, it is impossible to ignore the serious injection-related health risks have come to light[28] and that Covid-19 cases continue to flourish among areas with high vaccination rates such as Alberta itself.[29] It is time to publicly acknowledge that the Covid-19 vaccine is not, and cannot, be relied upon as the only answer in response to a constantly evolving SARS-CoV-2 virus.

No Alternatives Provided

AHS has not offered any alternative options, and it is our position that AHS has not taken requests for exemptions seriously.

Rapid antigen testing is a clear alternative. Rapid antigen testing is an accurate and immediate method to minimize the risk that a person infected with Covid-19 may spread the SARS-CoV-2 virus to staff and patient. The first paragraph of the Policy states the purpose "is to protect the health and safety of our workers, patients and the public, and to preserve workforce capacity to support the healthcare system."[30] By not providing reasonable, safe, and efficient alternatives to its employees in order to preserve workforce capacity and support the healthcare system, AHS is in fact going against its stated purpose.

Furthermore, we are aware that many health care facilities engaged in the care of vulnerable people are enacting testing policies whereby both vaccinated and unvaccinated individuals are regularly tested for

[26] *The Constitution Act*, 1982, Schedule B to the *Canada Act* 1982 (UK), 1982, c 11.
[27] So far, over 26,000 healthcare workers face discipline or firing for being unvaccinated | True North (tnc.news).
[28] *Supra* note 19.
[29] Covid-19 Breakthrough Infections in Vaccinated Health Care Workers | NEJM.
[30] COVID19 Vaccine Immunization Policy FAQs For Staff (albertahealthservices.ca) at p. 2.

Covid-19. Such a policy is based on the fact that both vaccinated and unvaccinated individuals may contract Covid-19, in which case both vaccinated and unvaccinated individuals can potentially transmit the virus.

As you know, or ought to know, the vaccines do not prevent Covid-19 infection, nor do they prevent the spread of Covid-19; vaccinated and unvaccinated alike contract Covid-19 and spread it to others. Consistent with these facts, the vaccines are marketed as useful only for reducing the severity of Covid-19 symptoms.

The draconian actions taken by AHS to enforce its Policy as well as the Policy itself are not in line with its claims of promoting safety and wellbeing. Which state in part:

> **A Safe, Healthy and Inclusive Workplace**
> Provide work environments that protect and support physical health, mental wellbeing and a sense of belonging for all.
>
> A safe workplace is essential for diversity and inclusion. We will become diverse and inclusive by ensuring all of us—employees, volunteers, physicians, midwives, patients and family members—feel safe, welcome and valued regardless of race, religious beliefs, colour, gender, gender identity, gender expression, physical disability, mental disability, age, ancestry, place of origin, marital status, source of income, family status, sexual orientation, education or diversity of perspective.[31]

Conclusion

On September 27, 2021, the Australian Fair Work Commission delivered a landmark decision concerning the legality and moral propriety of vaccine mandates and stated as follows:

> [181] Blanket rules, such as mandating vaccinations for everyone across a whole profession or industry regardless of the actual risk, fail the tests of proportionality, necessity and reasonableness. It is more than the absolute minimum necessary to combat the crisis and cannot be justified on health grounds. It is a lazy and fundamentally flawed approach to risk management and should be soundly rejected by courts when challenged.
>
> [182] All Australians should vigorously oppose the introduction of a system of medical apartheid and segregation in Australia. It is an abhorrent concept and is morally and ethically wrong, and the antithesis of our democratic way of life and everything we value.[32]

Dr. Grobler has been working in all levels of the hospital wards, with the exception of ICU and Emergency, for 15 years and is well regarded by his colleagues and patients, and he has never been disciplined or reprimanded by AHS or the College of Physician and Surgeons of Alberta. He remains committed to his role, and is willing and able to continue working, serving the medical needs of the people of Alberta. The Policy is causing undue hardship and irreparable harm to Dr. Grobler. His personal beliefs have been attacked and their professional credibility has been undermined.

[31] https://www.albertahealthservices.ca/assets/about/msd/ahs-msd-ahs-people-strategy.pdf at pp 15 and 19.
[32] Jennifer Kimber v. Sapphire Coast Community Aged Care Ltd., [2021] FWCFB 6015.

Relieving Dr. Grobler of his services will unnecessarily cancel needed medical care and surgeries, exacerbating patient's pain and suffering and further adding unnecessary strain on an overburdened medical staff. As a result, the Policy is causing undue hardship and irreparable harm to an already struggling public health system, which will be further exacerbated with the loss of much needed medical staff.

For the reasons stated, there is no rational or legal basis for mandating Covid-19 vaccinations as a condition of employment with AHS. The Policy violates provincial, federal and international human rights statutes, agreements and conventions. The Policy is morally and ethically wrong and not founded on well-established science.

This is notice to AHS that if Dr. Grobler does not receive accommodation by November 5, 2021, or if AHS should proceed to act upon its threat of revoking his hospital privileges, the following actions may be taken without further notice:

1. Commencement of legal action against AHS, including a request for injunctive relief against AHS to prevent irreparable harm to individuals serving in Alberta's medical field and to the Alberta public in need of medical care;

2. Human rights claims alleging violation of *Alberta Human Rights Act*; and/or

3. Labour rights claims filed, alleging violation of applicable provincial and federal legislation.

We expect AHS shall govern itself accordingly. In the interim, we look forward to hearing from you or your legal counsel.

Yours truly,

[redacted]

Justice Centre for Constitutional Freedoms
Counsel for Dr. Gert Grobler

Cc. Dr. Carl Nohr, Superintendent, Alberta Health Services
Cc. Jason Copping, Minister of Health responsible for AHS
Cc. Councillors, College of Physicians and Surgeons of Alberta

Exhibit "I"

Healthy Albertans.
Healthy Communities.
Together.

Eva Chipiuk
Justice Centre for Constitutional Freedoms
253-7620 Elbow Drive SW
Calgary, AB T2V 1K2

November 5, 2021

Via Email

Dear Ms. Chipiuk:

RE: Dr. Gert Grobler

I write as legal counsel on behalf of Alberta Health Services ("AHS") in response to your correspondence dated November 2, 2021, with respect to Dr. Gert Grobler.

Your letter contains many inaccuracies, questionable legal argument, and a plethora of misinformation, and as such, AHS disagrees with the claims and assertions contained therein. You are advised that AHS will not be changing the Immunization of Workers for COVID-19 Policy ("Policy") at this time, and is prepared to take further action against Dr. Grobler to enforce the Policy in the event he remains non-compliant, including restricting his clinical activities.

Please note, members of the Medical Staff are not employees of AHS.

Yours truly,
Alberta Health Services

[redacted]

John Siddons, Litigation Legal Counsel

[redacted]

This is Exhibit 1 referred to
in the affidavit of Dr. Gert Grobler
Sworn before me herein this 9
day of December, 2021

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

Alberta Health Services

Legal & Privacy
10301 Southport Lane SW, Calgary AB T2W 1S7
[redacted]

Exhibit "J"

[redacted]

This is Exhibit J referred to
in the affidavit of Dr. Gert Grobler
Sworn before me herein this 9
day of December, 2021

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

From: John [redacted]
Sent: Wednesday, December 1, 2021 12:16:50 PM
To: Eva Chipiuk [redacted] Leighton Grey [redacted]
Subject: Dr. Grobler - Immediate Action Notice

Good day Mr. Grey, Ms. Chipiuk. Please refer to the attached correspondence for transmission to Dr. Grobler.

Regards,

John Siddons
Legal Counsel, Litigation
Alberta Health Services
[redacted]

Alberta Health Services
www.albertahealthservices.ca

R Aaron Low MD FRCPC
Zone Medical Director, South Zone
Alberta Health Services
960 19th Street S
Lethbridge, AB T1J 1W5
[redacted]

December 1, 2021 **Confidential**

Dr. Gert Grobler
c/o Ms. Eva Chipiuk
Justice Centre for Constitutional Freedoms
253-7620 Elbow Drive SW
Calgary, AB T2V 1K2

Dear Dr. Grobler:

Re: Part 6 Process – Alberta Health Services Medical Staff Bylaws

AHS has implemented a mandatory COVID-19 vaccination policy:
IMMUNIZATION OF WORKERS FOR COVID-19 Policy 1189 (ahsnet.ca)

The AHS Immunization of Workers for COVID-19 Policy (the "Policy") requires all AHS workers, which includes members of the AHS Medical Staff, to be fully immunized by December 13, 2021 with accurate proof of immunization status to be provided no later than November 28, 2021.

We have not received proof of your immunization status. As such, at present, you do not appear to be in compliance with this Policy. You have received multiple general reminders about the requirement. I am also aware you had a telephone meeting with Dr. Carl Nohr, Associate Zone Medical Director, on October 18, 2021 regarding your immunization status and required compliance to the Policy. You also received a specific follow up letter from Dr. Nohr on this matter dated October 28, 2021.

As AHS has not received proof of your immunization status and you have not applied for an exception to the Policy, I anticipate that I will be required to take Immediate Action on December 13, 2021 to suspend your AHS Medical Staff Appointment and Clinical Privileges, effective 12:01 a.m. on December 13, 2021. This means that, as of December 13, 2021, your Clinical Privileges will be suspended, you will not be permitted to enter AHS sites (except as a patient), and notification of the Immediate Action will be given to the College of Physicians & Surgeons of Alberta.

The basis for the Immediate Action will be your failure to comply with the portions of the Policy regarding disclosure of your immunization status and regarding the requirement to be fully immunized by November 30, 2021. As such, steps are required to be taken to protect the health and safety of others. For your reference, I have enclosed a copy of the AHS Medical Staff Bylaws, and refer you to section 6.7 which contains the provisions regarding Immediate Action.

Dr. Foley will be informed this week of the anticipated suspension of your AHS Medical Staff Appointment and Clinical Privileges at 12:01 a.m. on December 13, 2021 to ensure clinical coverage for you is arranged.

Immediate Action may not be required if you advise me by way of an email, [redacted] with a copy to [redacted], **by noon on December 8, 2021**, that one of the following applies:

- You have been fully immunized **and** you have disclosed proof of your immunization status by submitting confirmation of immunization through the online tool. This online tool can be accessed at: COVID-19 Got My COVID-19 Immunization Form | Insite (albertahealthservices.ca).

- You have initiated the process with the South Zone Medical Affairs Office at [redacted] submit a Change Request to change your AHS Medical Staff Appointment to a Community Appointment without Clinical Privileges **or** to resign your AHS Appointment with such change to be effective before or on November 30, 2021.

- You would like to go on a voluntary leave of absence, commencing December 13, 2021. If this is your preferred option, please email me with a copy to [redacted] by 5 p.m. on December 8, 2021 to request a meeting to discuss.

As previously indicated, there are educational materials available regarding COVID-19 vaccination. I recommend that you review the follow websites in this regard.

- COVID-19 Vaccine Frequently Asked Questions | Alberta Health Services
- COVID-19 Immunization FAQ for Community Physicians (albertahealthservices.ca)
- COVID-19 vaccines and records | Alberta.ca

To provide further clarification to AHS' announcement of November 29, 2021, AHS will temporarily introduce frequent, targeted COVID-19 testing as part of the Policy. Only work locations at significant risk of service disruptions due to staffing shortages resulting from employees who are not fully immunized will be part of the testing program, which will be reviewed by the end of March 2022. Rapid testing is not otherwise available for AHS physicians.

Medicine Hat Regional Hospital in South Zone has not been determined to be a facility at significant risk of service disruption. As such, under the Policy, you would not eligible for rapid testing in relation to your activities in South Zone.

Sincerely,

[redacted]

R Aaron Low MD FRCPC
Zone Medical Director, South Zone

Encl: AHS Immunization of Workers for COVID-19 Policy
AHS Medical Staff Bylaws

Approved and Effective as of
8 February 2021

THE ALBERTA HEALTH SERVICES MEDICAL STAFF BYLAWS

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DEFINITIONS

In this document the following words have the meanings set opposite to them:

Academic Physician	A physician Practitioner who also possesses an appointment as a Full-Time Faculty or Clinical Faculty member with either the Faculty of Medicine & Dentistry of the University of Alberta or the Faculty of Medicine of the University of Calgary.
Active Staff	The Practitioners who are appointed to the Active Staff category pursuant to these Bylaws.
Advisor	A person, lay or professional, who provides guidance, support, or counsel to a Practitioner pursuant to these Bylaws.
Affected Practitioner	A Practitioner who is the subject of a Triggered Initial Assessment, Triggered Review or Immediate Action.
AHS Agent	A person, other than an AHS employee, Senior Officer or board member, who is authorized to bind AHS, purports to bind AHS or who directly or indirectly controls AHS funds.
AHS Code of Conduct	The code of conduct established by AHS.
AHS Conflict of Interest Bylaw	The conflict of interest bylaw established by AHS.
AHS Programs and Professional Services	Diagnostic and treatment services and programs operated by or for AHS to which Practitioners with relevant Clinical Privileges can refer Patients.
AHS Representative	An AHS employee, Senior Officer, Agent or board member.
AHS Senior Officer	The Chief Executive Officer, president or vice-presidents of AHS, any other executive directly accountable to the Chief Executive Officer or president of AHS, and any other person so designated by the Chief Executive Officer or board of AHS.
Alberta Health Services	The health authority established pursuant to applicable legislation for the Province of Alberta.
Application	The forms and process used to apply for a Medical Staff Appointment and Clinical Privileges in the manner specified in these Medical Staff Bylaws and the Medical Staff Rules.
Bylaws and Rules Review Committee	A committee established as such pursuant to these Bylaws.
Chief Executive Officer or CEO	The chief executive officer appointed by the Chief Executive Officer to be responsible for the function of Medical Affairs within AHS.
Chief Medical Officer or CMO	The CMO is the most senior medical administrative leader appointed by the CEO to be responsible for the function of Medical Affairs within AHS.
College	The relevant regulatory body which governs the Practitioner.
Community Physician, Dentist, Oral & Maxillofacial Surgeon or Podiatrist	A Physician, Dentist, Oral & Maxillofacial Surgeon or Podiatrist with a scope of practice limited to community office or clinic practice.
Community Staff	The Practitioners who are appointed to the Community Staff category pursuant to these Bylaws.

Complainant	A Patient or his/her legal representative(s), a member of the public, or another Practitioner(s) who initiate(s) a Concern.
Concern	A written complaint or concern from any individual or group of individuals about a Practitioner's professional performance and/or conduct, either in general or in relation to a specific event or episode of care provided to a specific Patient.
Consensual Resolution	A consensual and confidential process to resolve a Concern. Consensual Resolution includes the Affected Practitioner, the relevant AHS medical administrative leader(s), and any other relevant person(s).
Dentist or Oral & Maxillofacial Surgeon	A person licensed in independent practice and in good standing with the Alberta Dental Association and College pursuant to the *Health Professions Act* (Alberta).
Facilities	Approved hospitals, continuing care facilities, community health, urgent care, and public health centres, and any other facilities operated by AHS.
Hearing	The process of addressing Concerns where a Triggered Initial Assessment and Consensual Resolution have not resolved the matter or are not considered appropriate means to resolve the matter.
Hearing Committee	A committee established as such pursuant to these Bylaws.
Immediate Action	An immediate suspension or restriction of a Practitioner's Medical Staff Appointment and/or Clinical Privileges without first conducting a Triggered Review pursuant to these Bylaws.
Immediate Action Review Committee	A committee established as such pursuant to these Bylaws.
In Writing	The requirement for documents to be submitted in writing can be met by returning the document through e-mail from a secure AHS or other enterprise organization e-mail system requiring sign-in and verification. The requirement may also be met in situations where an individual has chosen or requested AHS communicate with them using another electronic format or address. In certain specific situations, original paper copies of documents will be required because of legislative or other legal requirements.
Medical Affairs Office	An operational and organizational office of the Executive Vice President & Chief Medical Officer portfolio.
Medical Director	The Practitioner who is the medical administrative leader of a Zone (Zone Medical Director); one or more Facilities (Facility Medical Director), one or more communities (Community Medical Director), an AHS provincial portfolio or program (Senior Medical Director or Medical Director); or a Zone program (Zone Program Medical Director).
Medical Organizational Structure	The medical organizational structure of AHS aligned with these Bylaws and the Rules.
Medical Staff	Collectively, all Practitioners who possess a Medical Staff Appointment pursuant to these Bylaws.
Medical Staff Appointment or Appointment	The admission of a Practitioner to the AHS Medical Staff.

Medical Staff Letter of Offer	An offer to join the Medical Staff which specifies the category of Appointment, assignment to a Zone(s) Clinical Department(s), delineation of specific Clinical Privileges (if applicable), and the details of major responsibilities and roles.
Minister	The member of the Executive Council of Alberta who is charged with carrying out the statutory responsibilities conferred on him as Minister of Health and Wellness.
Patient	An individual receiving health services from a Practitioner.
Periodic Review	A periodic review of the professional performance and all matters relevant to the Appointment and Clinical Privileges of a Practitioner with an Appointment in the Active and Locum Tenens Staff categories.
Physician	A person with a practice permit not requiring supervision from the College of Physicians and Surgeons of Alberta pursuant to the *Health Professions Act* (Alberta).
Podiatrist	A person with a practice permit not requiring supervision from the Alberta Podiatry Association pursuant to the *Podiatry Act*/*Health Professions Act* (Alberta).
Policies	Administrative and operational objectives, plans, values, principles, practices and standards established by AHS with respect to its operations and Facilities, programs and services.
Practitioner	A Physician, Dentist, Oral & Maxillofacial Surgeon; Podiatrist, or a Scientist Leader, who has an AHS Medical Staff Appointment.
Practitioner Workforce Plan	An AHS plan which provides projections and direction with respect to the recruitment, retention and organization of an appropriate number, mix and location of Practitioners with the required skill sets.
Primary Zone Clinical Department	The Zone Clinical Department in which a Practitioner undertakes the majority of his/her Medical Staff responsibilities and roles, and through which changes in Appointment, Periodic Reviews, and other administrative actions pursuant to these Bylaws will be managed.
Probationary Staff	The Practitioners who are appointed to the Probationary Staff category pursuant to these Bylaws.
Procedure	A diagnostic or therapeutic intervention for which a grant of Clinical Privileges is required.
Professional Codes of Conduct	The Code of Conduct established by the College of Physicians and Surgeons of Alberta, the Code of Conduct established by the Alberta Podiatry Association, and the Code of Ethics established by the Alberta Dental Association and College.
Provincial Practitioner Executive Committee or PPEC	A committee established as such pursuant to these Bylaws.
Request to Change	A request to change the category of Appointment and/or the Clinical Privileges of a Practitioner pursuant to these Bylaws.
Rules	The specific provisions established as Medical Staff Rules pursuant to these Bylaws.
Scientist Leader	A person other than a Physician, Dentist, Oral & Maxillofacial Surgeon or Podiatrist who holds a doctorate degree in a recognized health-related scientific or biomedical discipline, and who is an AHS medical administrative leader responsible for, and accountable to, Physician, Dentist, Oral & Maxillofacial Surgeon and/or Podiatrist Practitioners.

Sites of Clinical Activity	The locations and programs, listed in the grant of Clinical Privileges, where a Practitioner may perform Procedures, or provide care or services to Patients. The Sites of Clinical Activity may include Zones, Facilities, specific AHS Programs and Professional Services within Facilities, and/or Telemedicine.
Telemedicine	The provision of services for Patients, including the performance of Procedures, via telecommunication technologies, when the Patient and the Practitioner are geographically separated. This may include Practitioners in Alberta, as well as those outside Alberta who are on the Telemedicine Register of the College of Physicians and Surgeons of Alberta.
Temporary Staff	The Practitioners who are appointed to the Temporary Staff category pursuant to these Bylaws.
Triggered Initial Assessment	An investigation and initial assessment of a Concern or other information/complaints about a Practitioner.
Triggered Review	A review undertaken in response to a Concern about a Practitioner's professional performance and/or conduct.
Universal Programs and Professional Services	Those diagnostic and therapeutic services and programs available, within their respective scope of practice, to all Alberta Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists without the need for an AHS Medical Staff Appointment or grant of Clinical Privileges.
Zone	A geographically defined organizational and operational sub-unit of AHS, the boundaries of which may be revised from time-to-time by AHS.
Zone Application Review Committee or ZARC	A committee established as such pursuant to these Bylaws.
Zone Clinical Department or ZCD	An organizational unit of Practitioners established by the Zone Medical Director and Zone Medical Administrative Committee to which members of the Zone Medical Staff are assigned.
Zone Clinical Department Head or ZCDH	The Practitioner who is the leader of a Zone Clinical Department.
Zone Clinical Department Site Chief	The Practitioner who is the leader of Zone Clinical members at a particular Facility or Site.
Zone Clinical Section	An organizational sub-unit of a Zone Clinical Department established by the Zone Medical Director and the Zone Medical Administrative Committee.
Zone Clinical Section Chief	The Practitioner who is the leader of a Zone Clinical Section.
Zone Medical Administrative Committee or ZMAC	A committee established as such pursuant to these Bylaws.
Zone Medical Staff	Collectively, all Practitioners who are assigned to Zone Clinical Departments within a particular Zone.
Zone Medical Staff Association	An association of the Zone Medical Staff.

The definitions, captions, and headings are for convenience only and are not intended to limit or define the scope or effect of any provisions of these Bylaws.

The Alberta Health Services Medical Staff Bylaws

PART 1 – GENERAL PROVISIONS

1.0 GENERAL

These Medical Staff Bylaws, and the Medical Staff Rules, govern the Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists who provide medical care to Patients, and the Scientist Leaders who provide medical administrative leadership, in relation to an Alberta Health Services (AHS) Medical Staff Appointment. They establish and describe:

a) the terms and conditions on which AHS may grant Practitioners Clinical Privileges;
b) the responsibility of the Medical Staff to AHS for the quality and safety of all professional services provided by Practitioners to Patients and to AHS;
c) the responsibilities of the Medical Staff and AHS to each other for the organization and conduct of the Medical Staff, and in particular the processes relating to Medical Staff Appointments and delineation of Clinical Privileges; and
d) the administrative structures for the governance of Practitioners working in AHS Facilities or other AHS Sites of Clinical Activity.

1.1 OBJECTIVES

1.1.1 AHS, subject to legislation and direction of the Minister, has the responsibility and mandate to take appropriate actions to:

a) promote and protect the health of Albertans;
b) assess the health needs of Albertans;
c) ensure reasonable access to appropriate, high quality and safe health services;
d) determine priorities and allocate resources accordingly; and
e) promote the efficient and sustainable provision of health services in a manner that is responsive to the needs of individuals and communities, as well as the employees and Practitioners of AHS, and that supports the integration of services and facilities in Alberta.

1.1.2 In order to carry out these responsibilities, AHS shall, in consultation with Practitioners who have been appointed to the Medical Staff, prepare and adopt Medical Staff Bylaws and Medical Staff Rules governing the creation, organization and operation of the Medical Staff, including:

a) administrative structures, committees and positions for the governance of the Medical Staff;
b) granting Appointments to Practitioners as members of the Medical Staff;
c) granting Clinical Privileges to Practitioners;
d) defining the responsibilities of all Practitioners who are granted Appointments and Clinical Privileges;
e) determining the accountability of Practitioners for discharging the responsibilities related to Medical Staff Appointments and Clinical Privileges;
f) establishing principles and process for the Periodic Review of Practitioners; and
g) establishing principles and process for the Triggered Initial Assessment, Triggered Review, and resolution of a Concern, as well as the remediation of associated factors (if any) contributing to a Concern.

1.2 BINDING EFFECT

In the application for and acceptance of an Appointment to the Medical Staff of AHS, all Practitioners and AHS agree to be bound by these Bylaws and the Rules.

1.3 RECORDS AND DISCLOSURE

1.3.1 AHS shall, as a minimum, keep a record of:

a) all Medical Staff Appointments,
b) all Clinical Privileges granted; and
c) all changes to Medical Staff Appointments and amendments to Clinical Privileges granted.
d)

1.3.2 AHS shall, on request of a Practitioner, provide that Practitioner with a copy of the subsisting Medical Staff Appointment and Clinical Privileges, or other information on the Practitioner's file(s). All responses to access requests will be made according to the provisions of applicable legislation.

1.3.3 AHS may disclose information requested by the College of Physicians and Surgeons of Alberta, the Alberta Dental Association and College, the Alberta Podiatry Association and other authorized bodies or persons, provided such disclosure is required by law or is necessary to ensure public or Patient safety, or the disclosure is agreed to, in writing, by the Practitioner.

1.4 ADVISOR

Notwithstanding the mutual desire and expectation of AHS and the Medical Staff to encourage prompt and consensual resolution of disputes by the involved parties, whenever an applicant for a Medical Staff Appointment or a Practitioner is requested to appear before a person or persons in authority, the applicant/Practitioner may be accompanied by an advisor of his/her choice, and shall provide advance notice of the Advisor's identity.

1.5 MEDICAL STAFF RULES

1.5.1 The Medical Staff Bylaws and Rules Review Committee (for provincial Rules) or the Zone Medical Administrative Committee (for Zone Rules) shall recommend such Medical Staff Rules, or amendments to existing Rules, as it deems necessary for Patient care and the conduct of the Medical Staff. All new or amended Medical Staff Rules shall be forwarded to the Provincial Practitioner Executive Committee for review and recommendation for approval, amendment (if applicable) or rejection. The recommendation of the Provincial Practitioner Executive Committee shall be subject to final approval by the Executive Vice President & Chief Medical Officer (Chief Medical Officer).

1.5.2 The Medical Staff Rules shall be reviewed by the Medical Staff Bylaws and Rules Committee (for provincial Rules) and the Zone Medical Administrative Committees (for Zone Rules) at least once in each three year period from the date of most recent adoption or more frequently as required.

1.5.3 New provincial Rules or amendments to existing provincial Rules may be proposed by any member of the Medical Staff Bylaws and Rules Review Committee or any member of the Provincial Practitioner Executive Committee. All proposed new Rule(s) or amendment to existing Rule(s) will be considered by the Medical Staff Bylaws and Rules Review Committee which shall forward a recommendation to approve, amend (if applicable) or reject the proposed new or amended Rule(s) to the Provincial Practitioner Executive Committee.

1.5.4 New Zone Rules or amendments to existing Zone Rules may be proposed by any member of the Zone Medical Administrative Committee. All proposed new Rules or amendments to existing Rules shall be considered by the Zone Medical Administrative Committee which shall forward a recommendation to approve, amend (if applicable) or reject the proposed new or amended Rule(s) to the Provincial Practitioner Executive Committee.

1.5.5 All proposed recommendations to approve, amend (if applicable) or reject a proposed new Rule(s) or an amendment to existing Rule(s) shall require a two-thirds majority of those present and entitled to vote at any duly constituted meeting of the Medical Staff Bylaws and Rules Review Committee (for provincial Rules), a Zone Medical Administrative Committee (for Zone Rules) or the Provincial Practitioner Executive Committee (for all Rules). A notice of motion is necessary and must be given at a previous meeting or at least thirty days prior to the meeting.

1.5.6 The input of the Medical Staff shall occur through representation on the Medical Staff Bylaws and Rules Review Committee, the Zone Medical Administrative Committees and the Provincial Practitioner Executive Committee, pursuant to Part 2 of these Bylaws.

1.6 BYLAWS REVIEW AND AMENDMENTS

1.6.1 These Bylaws shall be reviewed by the Medical Staff Bylaws and Rules Review Committee at least once in each three year period from the date of the most recent adoption or more frequently as required. The Medical Staff Bylaws and Rules Review Committee shall define the process and timelines for the reviews and the required approval through a vote by ballot of all members of the Medical Staff.

1.6.2 Amendments to these Medical Staff Bylaws may be proposed by the Medical Staff, AHS or the Medical Staff Bylaws and Rules Review Committee.

1.6.2.1 Amendments to the Bylaws proposed by the Medical Staff shall be forwarded to the Medical Staff Bylaws and Rules Review Committee by:

a) one or more Zone Medical Staff Associations; or
b) one or more of the Medical Staff representative members of the Zone Medical Administrative Committee(s) or the Provincial Practitioner Executive Committee.

1.6.2.2 Amendments to the Bylaws proposed by AHS shall be forwarded to the Medical Staff Bylaws and Rules Review Committee.

1.6.3 The Medical Staff Bylaws and Rules Review Committee shall consider all proposed amendments.

1.6.4 If the Medical Staff Bylaws and Rules Review Committee members unanimously agree to recommend a proposed amendment(s), it will forward the proposed amendment(s) to the Medical Staff for consideration:

a) a vote by ballot of the members of the Medical Staff shall be conducted by the Medical Affairs Office and the Zone Medical Staff Associations pursuant to the process described in the Medical Staff Rules.
b) the recommendation of the Medical Staff Bylaws and Rules Review Committee shall be included with the proposed amendment(s) when forwarded for consideration by the Medical Staff.
c) the required majority for Medical Staff support of the proposed amendment shall be two-thirds of the properly cast ballots returned.

1.6.4.1 A proposed amendment(s) to the Bylaws supported by the Medical Staff will be forwarded by the Chief Medical Officer to the Minister for approval.

1.6.4.2 If the Medical Staff fail to support a proposed amendment(s) recommended by the Medical Staff Bylaws and Rules Review Committee, the Medical Staff Bylaws and Rules Review Committee may:

a) withdraw its recommendation to support the proposed amendment(s) and notify, in writing, the party proposing the amendment(s) of its decision and the reason(s) for its decision;
b) meet with the party proposing the amendment(s) to revise the proposed amendment(s) in consideration of the reason(s) for the failure of the Medical Staff to support it; or
c) request that the proposed amendment be forwarded to the Minister for resolution. The Medical Staff Bylaws and Rules Review Committee and the Zone Medical Staff Associations shall provide a written opinion regarding the proposed amendment(s) and the reason(s) for the failure of the Medical Staff to support it.

1.6.5 If the Medical Staff Bylaws and Rules Review Committee agrees to recommend a proposed amendment(s) by a minimum two-thirds majority of those members present and entitled to vote at any duly constituted meeting, but is not unanimous in its recommendation, the party proposing the amendment(s) will be notified, in writing, of the reason(s) why the Medical Staff Bylaws and Rules Review Committee did not reach unanimity. The party proposing the amendment(s) may:

a) withdraw the proposed amendment(s);
b) revise the proposed amendment(s) in consideration of the reason(s) that the Medical Staff Bylaws and Rules Review Committee did not reach unanimity, and forward the revised proposed amendment to the Medical Staff Bylaws and Rules Review Committee; or
c) request that the proposed amendment(s), and the written dissenting opinions of the members of the Bylaws and Rules Review Committee, be forwarded to the Medical Staff for consideration pursuant to the processes described in section 1.6.4 of these Bylaws.

i. If the Medical Staff support the proposed amendment(s), the proposed amendment(s) will be forwarded by the Chief Medical Officer to the Minister for approval.
ii. If the Medical Staff fail to support the proposed amendment(s), and the amendment(s) has (have) been proposed by a representative of the Medical Staff pursuant to section 1.6.2.1 of these Bylaws, the proposed amendment(s) will be considered as being rejected.
iii. If the Medical Staff fail to support the proposed amendment(s), and the amendment(s) has (have) been proposed by AHS, AHS may withdraw the proposed amendment(s); revise the

proposed amendment(s); or request that the proposed amendment(s), the written dissenting opinions of the members of the Medical Staff Bylaws and Rules Review Committee and the written opinion of the Zone Medical Staff Associations as to the reasons for the failure of the Medical Staff to support it be forwarded by the Chief Medical Officer to the Minister for resolution.

1.6.6. If a proposed amendment(s) is supported by less than the minimum two-thirds majority of those members present and entitled to vote at any duly constituted meeting of the Medical Staff Bylaws and Rules Review Committee, it shall not be forwarded to the Medical Staff for consideration. The Medical Staff Bylaws and Rules Committee will notify, in writing, the party proposing the amendment of its decision and the reason(s) for the decision.

PART 2 – MEDICAL ORGANIZATIONAL STRUCTURE OF AHS

2.0 GENERAL

2.0.1 This part of the Bylaws describes provincial and Zone-based committees and medical administrative leadership positions that are central to these Bylaws. The Medical Organizational Structure of AHS is further described in the Medical Staff Rules.

2.0.2 In some instances, the Medical Organizational Structure, as well as the assignment of responsibilities and the reporting relationships of medical administrative leaders, will vary between Zones. This reflects the distinct nature of each Zone. Such variation is required to ensure that the Zone Medical Staff are able to function optimally in consideration of such Zone characteristics as geography; population demographics; mix of urban and rural / large and small communities; size and location of Facilities; and availability of specific specialized services and specialist Practitioners.

2.0.2.1 Policy development, organizational planning and strategic decision-making related but not limited to recruitment and retention, resource allocation, service delivery models and the quality and safety of Patient care, shall be undertaken and/or coordinated by medical administrative leaders and committees with either provincial or Zone-wide responsibilities and duties.

2.0.2.2 Operational decision-making and reporting, particularly pertaining to implementation of Zone and Zone Clinical Department policies, the local provision of services to Patients, and the management of Concerns, may be undertaken and/or coordinated by medical administrative leaders with either Zone-wide or Facility and/or community-based responsibilities and duties.

2.0.3 All committees and other groups within the Medical Organizational Structure of AHS shall be subject to the collective responsibilities identified in these Bylaws and the Rules.

2.0.4 All medical administrative leaders within the Medical Organizational Structure of AHS, including all those described in this part of these Bylaws, shall be members of the Medical Staff.

2.1 CHIEF MEDICAL OFFICER

2.1.1 **Appointment and Accountability**

2.1.1.1 The Chief Medical Officer is the most senior medical administrative leader in AHS and shall be appointed by the CEO.

2.1.1.2 The Chief Medical Officer shall be a member of the executive of AHS and shall be directly accountable to the CEO.

2.1.2 **Responsibilities and Duties**

The Chief Medical Officer will be responsible for implementation of policies established by AHS related to the Medical Staff. Without limiting the authority of AHS relative to its administrative structures, the responsibilities of the Chief Medical Officer include, but are not limited to:

a) establishing and implementing the processes for Medical Staff Appointments, granting Clinical Privileges and conducting reviews of the Medical Staff;
b) establishing and maintaining Medical Affairs Office(s);
c) advancing the perspectives, advice and resource requirements of the Medical Staff within AHS;
d) advocating for the provision of high quality and safe Patient care within AHS;
e) implementing and maintaining appropriate measures to ensure that the quality and safety of services offered by all Medical Staff are evaluated on a regular basis, that corrective actions are taken when problems are identified, and that ongoing enhancement of the skills and training of the Medical Staff is encouraged;
f) implementing procedures to monitor and ensure Medical Staff compliance with the Bylaws, the Rules and AHS policies;
g) approving new Medical Staff Rules or amendments to existing Rules;
h) approving the establishment and organization of Zone Clinical Departments;
i) rendering final decisions related to recommendations emanating from Triggered Review processes;

j) implementing and maintaining the processes related to Practitioner workforce planning, recruitment and retention;
k) implementing and maintaining appropriate measures to review and manage the use of AHS resources by the Medical Staff;
l) within available resources and to the extent agreed to by AHS, ensuring appropriate learning experiences and clinical supervision of postgraduate medical trainees, undergraduate medical students and other Practitioner-taught learners within AHS facilities;
m) reporting on the activities of the Medical Staff to the CEO;
n) performing all other duties assigned to him/her by these Bylaws and the Rules,
o) performing duties delegated by the AHS Board to the CEO and then to him/her; and
p) performing other duties as may be assigned by the CEO.

2.2 ASSOCIATE CHIEF MEDICAL OFFICER(S)

2.2.1 Appointment and Accountability

2.2.1.1 One or more Associate Chief Medical Officers shall be appointed by the Chief Medical Officer after consideration of the recommendation of a search committee pursuant to the process specified in the Rules.

2.2.1.2 The Associate Chief Medical Officer shall be directly accountable to the Chief Medical Officer.

2.2.2 **Responsibilities and Duties**

The Associate Chief Medical Officer shall assist the Chief Medical Officer in fulfilling his/her duties. Without limiting the authority of AHS relative to its administrative structures, the responsibilities of the Associate Chief Medical Officer include, but are not limited to:

a) performing all duties assigned to him/her by these Bylaws and the Rules,
b) performing duties delegated to him/her by the Chief Medical Officer;
c) acting for the Chief Medical Officer in his/her absence and as his/her designate for those duties assigned to the Chief Medical Officer by these Bylaws and the Rules;
d) advancing the perspective, advice and resource requirements of the Medical Staff within AHS; and
e) advocating for the provision of high quality and safe Patient care within AHS.

2.3 ZONE MEDICAL DIRECTORS

2.3.1 **Appointment and Accountability**

2.3.1.1 Each Zone shall have a Zone Medical Director. The Zone Medical Director is the most senior medical administrative leader in the Zone and shall be appointed by the Chief Medical Officer after consideration of the recommendation of a search committee pursuant to the process specified in the Rules.

2.3.1.2 The Zone Medical Director shall be directly accountable to the Chief Medical Officer for activities related to the Medical Staff Bylaws and Medical Affairs.

2.3.2 **Responsibilities and Duties**

Without limiting the authority of AHS relative to its administrative structures, the responsibilities of the Zone Medical Director include, but are not limited to:

a) accountability for all Practitioner-related matters, as well as all operational and strategic issues and decisions requiring Practitioner input or leadership that arise within the Zone;
b) ensuring clinical operational coordination across the Zone, collaboration between Zones, and the development and implementation of AHS strategies;
c) advancing the perspective, advice and resource requirements of the Zone Medical Staff within AHS;
d) advocating for the provision of high quality and safe Patient care within AHS;
e) performing all other duties assigned to him/her by these Bylaws and the Rules; and
f) performing other duties as may be assigned by the Chief Medical Officer.

2.4 ASSOCIATE ZONE MEDICAL DIRECTORS

2.4.1 **Appointment and Accountability**

2.4.1.1 One or more Associate Zone Medical Directors may be appointed by the Zone Medical Director after consideration of the recommendation of a search committee pursuant to the process specified in the Rules.

2.4.1.2 The Associate Zone Medical Director shall be directly accountable to the Zone Medical Director.

2.4.2 **Responsibilities and Duties**

The Associate Zone Medical Director shall assist the Zone Medical Director in fulfilling his/her duties. Without limiting the authority of AHS relative to its administrative structures, the responsibilities of the Associate Zone Medical Director include, but are not limited to:

a) performing all duties assigned to him/her by these Bylaws and the Rules;
b) performing other duties delegated to him/her by the Chief Medical Officer or the Zone Medical Director; and
c) acting for the Zone Medical Director in his/her absence.

2.5 FACILITY AND COMMUNITY MEDICAL DIRECTORS

2.5.1 **Appointment and Accountability**

a) Each Facility will have a Facility Medical Director. The Facility Medical Director is the most senior administrative leader for a Facility and shall be appointed by the Zone Medical Director. An individual may be the Medical Director of more than one Facility.
b) Smaller/rural communities, or groupings of such communities in close proximity to each other, shall have a Community Medical Director. The Community Medical Director is the most senior medical administrative leader of the community(ies), and any Facilities within the community(ies), and shall be appointed by the Zone Medical Director.
c) Facility and Community Medical Directors shall be appointed by the Zone Medical Director after consideration of a search committee pursuant to process specified in the Rules.
d) Facility and Community Medical Directors shall be directly accountable to the Zone Medical Director or designate. Community Medical Directors shall also collaborate closely with the relevant Zone Clinical Department Head.
e) If appropriate, a Facility or a Community Medical Director may concurrently hold another medical administrative leadership position within the Zone medical organizational structure, such as Associate Zone Medical Director or Zone Program Medical Director.

2.5.2 **Responsibilities and Duties**

Without limiting the authority of AHS relative to its administrative structures, the responsibilities of the Facility or a Community Medical Director include, but are not limited to:

a) accountability for Practitioner-related matters, as well as operational decisions requiring Practitioner input or leadership, that arise within the Facility(ies) and/or community(ies);
b) advancing the perspective, advice and resource requirements of the Medical Staff providing services in the Facility(ies) and/or community(ies);
c) advocating for the provision of high quality and safe Patient care in the Facility(ies) and/or community(ies);
d) performing all duties assigned to him/her in these Bylaws and the Rules; and
e) performing all duties as may be delegated by the Zone Medical Director or designate.

2.6 ZONE CLINICAL DEPARTMENTS

2.6.1 The Zone Medical Staff shall be assigned to organizational units of Practitioners called Zone Clinical Departments. A Zone Clinical Department shall consist of Practitioners who provide Patient care and clinical service:

a) related to a specialty or subspecialty recognized by the Royal College of Physicians and Surgeons of Canada or the College of Family Physicians of Canada or the Royal College of Dentists of Canada; and

b) that the Zone Medical Director and Zone Medical Administrative Committee determine are best organized and operated as a Zone Clinical Department, subject to approval by the Chief Medical Officer.

2.6.2 The organization and establishment of Zone Clinical Departments shall represent the optimal approach to:

a) supporting the delivery of high quality and safe Patient care and clinical services within the Zone;
b) credentialing and oversight of the Medical Staff within the Zone; and
c) advancing the perspective, advice and resource requirements of the Zone Medical Staff to AHS.

2.6.3 Each Zone Clinical Department shall be led by a Zone Clinical Department Head whose duties and responsibilities are specified by these Bylaws and the Rules.

2.6.4 A Zone Clinical Department may be further divided, as appropriate, into Zone Clinical Sections, organizational sub-units which shall be directly accountable to the Zone Clinical Department within which they function.

2.6.4.1 A Zone Clinical Section shall be established if the Zone Medical Director and the Zone Medical Administrative Committee determine that it will assist the Zone Clinical Department in optimally fulfilling its functions and responsibilities pursuant to these Bylaws and the Medical Staff Rules.

2.6.4.2 Each Zone Clinical Section shall have a Zone Clinical Section Chief whose duties and responsibilities are specified in the Medical Staff Rules.

2.6.5 A Zone Clinical Department that is responsible for providing services to Patients in more than one Facility in the Zone may, as appropriate, appoint Zone Clinical Department Facility Chiefs who shall assist the Zone Clinical Department Head. The Zone Clinical Department Facility Chief shall be accountable to the Zone Clinical Department Head for those matters pursuant to section 2.0.2.1 of these Bylaws. For matters pertaining to section 2.0.2.2 of these Bylaws, the Zone Clinical Department Facility Chief may be accountable to either the Facility Medical Director or the Zone Clinical Department Head, as determined by the Zone Medical Director.

2.6.6 **Establishment of Zone Clinical Departments and Zone Clinical Sections**

2.6.6.1 The Zone Medical Director may create, modify or dissolve Zone Clinical Departments and Zone Clinical Sections upon the recommendation of the Zone Medical Administrative Committee, and subject to the approval of the Chief Medical Officer. The process to create, modify or dissolve Zone Clinical Departments and Zone Clinical Sections is specified in the Rules.

2.6.6.2 The Clinical Departments and Clinical Sections of each Zone shall be listed in Part 5 of the Rules.

2.6.7 **Zone Clinical Department Executive Committee**

2.6.7.1 Each Zone Clinical Department shall establish a Zone Clinical Department Executive Committee composed of the Zone Clinical Department Head, who shall act as chair; the Chiefs of such Zone Clinical Sections as are established; Zone Clinical Department Facility Chiefs (if any); and appropriate AHS medical and other administrative leaders relevant to the Zone Clinical Department.

2.6.7.2 The purpose of the Zone Clinical Department Executive Committee shall be to assist the Zone Clinical Department Head in fulfilling his/her responsibilities; to promote joint decision-making with AHS medical and other administrative leaders; and to coordinate the work of the Zone Clinical Department within AHS.

2.6.7.3 The responsibilities and functions of the Zone Clinical Department Executive Committee shall include, but not be limited to:

a) making recommendations, as appropriate, to the Zone Medical Director and the Zone Medical Administrative Committee with respect to the establishment of Zone Clinical Sections within the Zone Clinical Department;

b) working jointly with the Zone Clinical Department Head in recommending Medical Staff Appointments and Clinical Privileges, as well as changes to Appointments and Clinical Privileges;
c) developing and implementing Zone Clinical Departmental policies regarding quality and safety of Patient care in support of Zone Rules and policies;
d) ensuring the fulfillment of the provisions for On-Call and Service Coverage Responsibilities pursuant to section 4.2.7 of these Bylaws; and
e) working collaboratively with other Zone Clinical Departments to ensure high quality and safe Patient care, and coordinated service delivery, within all Facilities and communities of the Zone.

2.6.8 Nothing in this part of these Bylaws shall preclude a Zone Medical Director from grouping Zone Clinical Departments that provide patient care services of a related nature into clinical programs. Committees comprised of medical administrative leaders and/or Practitioners from the relevant Zone Clinical Departments, and relevant AHS operational administrative leaders and staff, may be established to lead such clinical programs.

2.6.9 **Zone Clinical Department Meetings**

2.6.9.1 Zone Clinical Department meetings shall be defined by the Zone Rules. The agenda for such meetings shall be prepared by the Zone Clinical Department Executive Committee. Active and Probationary Staff members shall attend Zone Clinical Department meetings. Community, Temporary, and Locum Tenens Staff may attend Zone Clinical Department meetings.

2.6.9.2 Zone Clinical Department meetings shall address internal organization, resource allocation, recruitment and retention strategies and plans, the facilitation of teaching, research and other pertinent Zone Clinical Departmental matters.

2.6.9.3 Quality of patient care and safety activities shall be conducted by each Zone Clinical Department in accordance with requirements established by the Zone Medical Director or Chief Medical Officer.

2.7 ZONE CLINICAL DEPARTMENT HEADS

2.7.1 **Appointment and Accountability**

2.7.1.1 Each Zone shall organize its clinical activities into Zone Clinical Departments led by a Zone Clinical Department Head.

2.7.1.2 The Zone Clinical Department Head shall be a member, or be eligible to be a member, of that Zone Clinical Department.

2.7.1.3 The Zone Clinical Department Head shall be appointed by the Zone Medical Director after consideration of the recommendation of a search committee pursuant to the process specified in the Rules.

2.7.1.4 The Zone Clinical Department Head shall be directly accountable to the Zone Medical Director.

2.7.2 **Responsibilities and Duties**

2.7.2.1 The Zone Clinical Department Head shall have responsibility of the overall function and structure of the Zone Clinical Department. The Zone Clinical Department Head shall be responsible for matters within the Zone Medical Administrative Committee's jurisdiction in relation to the Zone Clinical Department.

2.7.2.2 The Zone Clinical Department Head may delegate some of his/her responsibilities and duties to a Deputy Zone Clinical Department Head, Zone Clinical Section Chiefs and/or Clinical Department Site Chiefs.

2.7.2.3 Without limiting the authority of AHS relative to its administrative structures, the responsibilities of the Zone Clinical Department Head include, but are not limited to:

a) establishing a Zone Clinical Department Executive Committee, as specified in section 2.6.7 of these Bylaws;
b) advancing the perspective, advice and resource requirements of Zone Clinical Department members;
c) advocating for the provision of high quality and safe Patient care within the Zone Clinical Department;
d) in keeping with the objectives and goals of AHS, assigning duties and responsibilities to members of the Zone Clinical Department;
e) promoting and representing the activities of the Zone Clinical Department;
f) collaborating with other Zone Clinical Departments and the Zone Medical Administrative Committee to ensure high quality and safe patient care, and coordinated service delivery within all Facilities and communities of the Zone;
g) assisting in drafting or amending Zone Medical Staff Rules and developing province-wide privileging criteria for procedures new to AHS;
h) preparing, maintaining and promoting educational programs for Zone Clinical Department members and other staff associated with the Zone Clinical Department;
i) developing and promoting departmental research activities;
j) conducting Periodic Reviews for Practitioners in the Zone Clinical Department pursuant to Part 5 of these Bylaws;
k) performing all other duties assigned to him/her by these Bylaws and the Rules; and
l) performing other duties as may be delegated by the Zone Medical Director.

2.8 PROVINCIAL PRACTITIONER EXECUTIVE COMMITTEE

Purpose
The purpose of the Provincial Practitioner Executive Committee is to advise AHS and the Chief Medical Officer on provincial / system-wide matters pertinent to quality and safe Patient care as well as issues including but not limited to:

a) Practitioner workforce planning;
b) the development and oversight of the Medical Staff Rules and AHS-wide policies pertinent to the Medical Staff;
c) discharging responsibilities essential to maintaining appropriate accreditation of AHS; and
d) performing all other duties assigned to it by these Bylaws and the Medical Staff Rules.

The composition, duties and responsibilities of the Provincial Practitioner Executive Committee are described in the Medical Staff Rules.

2.9 MEDICAL STAFF BYLAWS AND RULES REVIEW COMMITTEE

Purpose
The purpose of the Medical Staff Bylaws and Rules Review Committee is to review the Bylaws and Rules at least once in each three year period from the date of the most recent adoption or more frequently as required, and to discharge all other duties assigned to it by these Bylaws and the Medical Staff Rules.

The composition, duties and responsibilities of the Medical Staff Bylaws and Rules Review Committee are described in the Medical Staff Rules.

2.10 ZONE MEDICAL ADMINISTRATIVE COMMITTEES

Purpose
Each Zone shall have a Zone Medical Administrative Committee. The purpose of the Zone Medical Administrative Committee is to advise the Zone Medical Director on matters pertinent to quality and safe Patient care at a Zone level and to discharge all other duties assigned to it by these Bylaws and the Medical Staff Rules.

The composition, duties and responsibilities of the Zone Medical Administrative Committee are described in the Medical Staff Rules.

2.11 ZONE APPLICATION REVIEW COMMITTEES

Purpose
Each Zone shall have a Zone Application Review Committee. The purpose of the Zone Application Review Committee is to review all initial Applications to the Medical Staff and prepare a written recommendation (to accept, deny, or amend the Application) after initial review by a Zone Clinical Department(s), and to review all Requests to Change a Medical Staff Appointment and Clinical Privileges and prepare a written recommendation (to accept, deny, or amend the Request for Change) after initial review by a Zone Clinical Department(s). The composition, duties and responsibilities of the Zone Application Review Committee are described in the Medical Staff Rules.

2.12 ZONE MEDICAL STAFF ASSOCIATIONS

The Medical Staff of each Zone shall establish a Zone Medical Staff Association to facilitate the engagement and participation of the Zone Medical Staff in Practitioner-related matters, and the fulfilment of the responsibilities and duties of Practitioners pursuant to these Bylaws and the Rules. The Zone Medical Staff Associations shall be the representative bodies for Practitioners in matters related to these Bylaws and the Medical Staff Rules. Each Zone Medical Staff Association shall be governed by its own constitution.

PART 3 - THE PROCESS FOR MEDICAL STAFF APPOINTMENTS AND CLINICAL PRIVILEGES

3.0 GENERAL

3.0.1 A Medical Staff Appointment is provincial and outlines the category of Appointment and the Practitioner's rights and responsibilities associated with that Appointment. Upon being granted an Appointment, a Practitioner must be assigned to the appropriate Zone Clinical Department(s). A Practitioner may be appointed to more than one Zone Clinical Department (within one or more Zones) but one department must be designated as the Primary Zone Clinical Department.

3.0.2 Clinical Privileges that are granted to the Practitioner define the diagnostic or therapeutic Procedures or other Patient care services a Practitioner is deemed competent to perform; the Facility(ies) and Zone(s) within which the Practitioner is eligible to provide care and services to Patients; and the specified AHS Programs and Professional Services, in addition to Universal Programs and Professional Services, that the Practitioner is eligible to access. A Practitioner is not entitled to perform Procedures or treat patients simply by virtue of being a member of the Medical Staff.

3.0.3 The granting of Clinical Privileges shall consider the needs of AHS; the Practitioner Workforce Plan; the resources available or the Facilities required for the requested Procedures and access to AHS Services and Programs; and the Practitioner's training, experience, demonstrated ability and skills, and current clinical competence. Access to AHS Programs and Professional Services and performance of Procedures will be subject to the availability of the required resources and staff.

3.0.4 The grant of a Medical Staff Appointment and Clinical Privileges to a Practitioner is exclusive to that Practitioner.

3.0.5 No Practitioner shall assign, transfer, encumber or delegate a grant of a Medical Staff Appointment and Clinical Privileges granted to that Practitioner and any purported assignment, transfer or encumbrance thereof shall be null and void.

3.0.6 A Medical Staff Appointment and Clinical Privileges granted to any Practitioner automatically terminate upon the death of that Practitioner.

3.0.7 A Medical Staff Appointment and Clinical Privileges may only be granted to an individual and will not be granted to a firm, partnership or corporation, including a professional corporation.

3.1 MEDICAL STAFF APPOINTMENTS

3.1.1 Appointment to the Medical Staff is not a right. It shall be granted only to professional and competent individuals with a license for independent practice with the relevant College, and who initially and continuously meet the qualifications, standards, and requirements set forth in these Bylaws and in such Medical Staff Rules as are adopted from time to time.

3.1.2 Practitioners shall be subject to the responsibilities, expectations and Periodic Review as outlined in these Bylaws and the Medical Staff Rules.

3.1.3 Practitioners in the Probationary Staff, Active Staff, Temporary Staff and Locum Tenens Staff categories (pursuant to sections 3.2, 3.3 and 3.4 of these Bylaws) may provide specified clinical services for Patients in Facilities and may access AHS Programs and Professional Services as defined by Clinical Privileges.

3.1.4 A Medical Staff Appointment is required to access AHS intranet/internal information technologies and systems.

3.1.5 Locum Tenens Practitioners shall require a Medical Staff Appointment and Clinical Privileges appropriate to their assignment.

3.1.6 Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists, residing and practicing outside Alberta who are requested to provide assessment and consultative advice by Telemedicine to Patients do not require specific privileges at the site.

3.1.7 Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists residing and practicing outside Alberta who are providing services that require issuing orders or directions for patient care shall require a Medical Staff Appointment and grant of Clinical Privileges appropriate to the service being provided at the site where the patient is located at the time of the service. This grant of clinical privileges for telehealth/telemedicine services may be province-wide.

3.1.8 AHS Scientist Leaders shall apply for, and hold, a Medical Staff Appointment and will be assigned to the most appropriate Primary Zone Clinical Department. Such individuals shall be exempt from the provisions of Parts 5 and 7 of these Bylaws.

3.1.9 Categories of Appointment
AHS Medical Staff Appointments shall be made to one of the categories listed below:

a) Probationary Staff
b) Active Staff
c) Temporary Staff
d) Community Staff
e) Locum Tenens Staff

3.1.10 **Probationary Staff**

3.1.10.1 Initial Medical Staff Appointments shall be to the Probationary Staff, except:
a) those in the Temporary and Community Staff category, or
b) where, in the opinion of the Chief Medical Officer or designate, after consultation with the applicable Zone Clinical Department Head(s) and Zone Application Review Committee, a direct appointment to the Active Staff or Locum Tenens Staff category is appropriate.

3.1.10.2 Applicants shall indicate the category (Active or Locum Tenens Staff) they are applying to in their application.

3.1.10.3 Members in the Probationary Staff category shall be assigned to a Primary Zone Clinical Department. There will be a performance assessment to determine eligibility for Appointment to either the Active Staff or Locum Tenens Staff category. Initial appointment to the Probationary Staff category shall be for a minimum period of twelve months and a maximum period of twenty-four months, unless otherwise extended under the provisions of 3.1.10.4, exclusive of approved leaves of absence. After a total of eighteen months in the Probationary Staff category, the Practitioner is deemed to have applied for a change in their category of Medical Staff Appointment pursuant to section 3.5 of these Bylaws.

3.1.10.4 The performance assessment pursuant to section 3.1.10.3.3 of these Bylaws shall be in accordance with the Rules. The performance assessment shall be signed by the Zone Clinical Department Head(s), and shall indicate whether the Practitioner should move to the Active or Locum Tenens Medical Staff Category, continue in the Probationary category for a further specified period of time beyond, or that their appointment should cease.

3.1.11 **Active Staff**
Members in the Active Staff category shall be Practitioners who have satisfied the requirements of the probationary period and have received an Appointment in the Active Staff category, or have been appointed directly to this category. Members of the Medical Staff transitioning to the Active Staff category from another category may be appointed to the Probationary Staff category as an interim step. In these cases, all requirements for movement out of the Probationary Staff category will apply.

3.1.12 **Temporary Staff**
AHS may grant a Medical Staff Appointment in the Temporary Staff category for a specific purpose and for a defined time, not to exceed one hundred and twenty consecutive days. This category of Appointment shall be used for short-term temporary situations and the scope of practice shall be defined according to Clinical Privileges granted.

3.1.13 **Community Staff**
3.1.13.1 A Community Physician, Podiatrist, Dentist or Oral & Maxillofacial Surgeon who does not provide specified clinical services for Patients in Facilities, and who does not require access to AHS Services and Programs, may apply for a Medical Staff Appointment in the Community Staff category in order to benefit from participating in the activities of AHS and membership in the relevant Zone Clinical Department.

3.1.13.2 If a Practitioner in the Community Staff category requests access to AHS Programs and Professional Services requiring a grant of Clinical Privileges, the Appointment must be changed to the Probationary or Active Staff category pursuant to section 3.5 of these Bylaws.

3.1.13.3 Practitioners in the Community Staff category shall be entitled to access AHS intranet/internal information technologies and systems.

3.1.14 **Locum Tenens Staff**
Members in the Locum Tenens Staff category shall be Practitioners who have satisfied the requirements of the probationary period and have received an Appointment in the Locum Tenens Staff category, or have been appointed directly to this category. AHS may grant a Medical Staff Appointment in the Locum Tenens category to physicians with appropriate expertise who do not otherwise hold an AHS Medical Staff Appointment. Physicians who hold this category of appointment provide expertise and coverage in an existing practice and/or Facility in order to facilitate the defined absence of another Practitioner, or to address a temporary shortfall in Practitioner Workforce. The scope and duration of practice of the Locum Tenens shall be defined by the Clinical Privileges granted.

3.2 CLINICAL PRIVILEGES

3.2.1 AHS grants Clinical Privileges which shall specify:

a) AHS Programs and Professional Services that the Practitioner is eligible to access
b) Procedures that the Practitioner is deemed to be competent and eligible to perform; and
c) Sites of Clinical Activity in which the Practitioner is eligible to provide Patient care and services.

3.2.2 Clinical Privileges, including AHS Programs and Professional Services and Sites of Clinical Activity that the Practitioner is eligible to access, as well as Procedures that the Practitioner is deemed competent and eligible to access, shall be recommended by the Zone Clinical Department Head(s). No Zone Clinical Department, Zone Clinical Section or speciality "owns" any Clinical Privilege, including Procedures.

3.2.3 In the case of a Practitioner in the Locum Tenens category, Clinical Privileges shall be granted in conjunction with the initial Appointment. Prior to the subsequent placement of the Locum Tenens in a new site of Clinical Activity, the relevant Zone Medical Director shall be satisfied there are sufficient physical and human resources available to allow the Locum Tenens to utilize all the Clinical Privileges granted.

3.2.4 Neither appointment to the Medical Staff nor the granting of Clinical Privileges shall confer entitlement to unrestricted use of AHS Programs and Professional Services, and Sites of Clinical Activity. Access to, and allocation of, all physical and human resources shall be subject to their availability, budgetary considerations, and the administrative allocation procedures and policies of Zone Clinical Departments and of AHS. Such procedures and policies shall be established in consultation with the Medical Staff through the processes available in these Bylaws and the Rules.

3.2.5 Different Practitioners are not eligible, per se, for the same Clinical Privileges simply by virtue of being members of the same Zone Clinical Department(s).

3.2.6 **Procedures**

3.2.6.1 AHS and the Medical Staff shall establish a list of Procedures, which shall be contained within the Rules. The process for establishing, maintaining and changing the list of Procedures shall be found in the Rules. The grant of Clinical Privileges shall delineate the Procedures which the Practitioner is entitled to perform.

3.2.6.2 Through the process defined in the Rules, AHS shall establish the need for, and the capacity of, AHS to support a new Procedure, and if deemed appropriate, privileging criteria for the new Procedure. The process will ensure that the eligibility to perform a new Procedure is determined fairly, rigorously and with regard to demonstrated competence, rather than limiting access to any particular Zone Clinical Department(s) or speciality.

3.2.6.3 The granting of Clinical Privileges for Procedures for all Practitioners is made on the basis of each Practitioner's documented training, experience, demonstrated abilities and skill, and current competence, as well as the available AHS resources.

3.2.7 **Sites of Clinical Activity**
The grant of Clinical Privileges shall delineate the Sites of Clinical Activity, including where the Practitioner is eligible to perform various Procedures. Sites of Clinical Activity will be defined by the Zone Medical Administrative Committee, and will reflect geographic restrictions, as well as access to Facilities in the Zone.

Sites of Clinical Activity shall also specify:

a) Inpatient Hospital Service - which will normally include admission and treatment of hospitalized Patients and the use of AHS Programs and Professional Services for the needs of hospitalized Patients, as described in the Clinical Privileges granted.
b) Outpatient Clinics and Services in Hospital and other Facilities - which will normally include the treatment of ambulatory Patients with access to AHS Programs and Professional Services for the needs of ambulatory Patients, as described in the Clinical Privileges granted.
c) Continuing Care Facilities - which will normally include the admission and treatment of Patients in these facilities with access to AHS Programs and Professional Services, as described in the Clinical Privileges granted.
d) Telemedicine

3.3 APPOINTMENT AND PRIVILEGES PROCEDURE

3.3.1 **General Provisions**
Applications for a Medical Staff Appointment and Clinical Privileges shall be made in the manner specified in these Medical Staff Bylaws and the Rules. The Medical Staff Bylaws and Rules, the application request forms and any applicable policies and procedures shall be available on the web site of AHS.

3.3.2 Only a complete Application shall be reviewed. The responsibility for providing all required Application information rests with the applicant. All applicants for a Medical Staff Appointment must be eligible to work in Canada.

3.3.3 Applications shall be reviewed, a decision made and the applicant informed of the decision within ninety days from the receipt of a complete Application by the Medical Affairs Office. If no decision is received by the applicant within ninety days, it shall be deemed to be a recommendation of denial and the applicant may request, within thirty days, that the application process proceed pursuant to section 3.6 of these Bylaws.

3.4 APPLICATION PROCESS

3.4.1 All Applications shall be submitted on the prescribed forms.

3.4.2 Applications are to be submitted to the Medical Affairs Office and will be reviewed for completeness on receipt. An applicant will be advised of the date of receipt and any deficiencies in the Application within fifteen days of the receipt of the Application.

3.4.3 The Medical Affairs Office will forward complete Applications to the applicable Zone Clinical Department(s) within fifteen days of receipt. The Primary Zone Clinical Department Head shall forward a written recommendation, signed by all relevant Zone Clinical Department Heads, (to accept, deny, or amend the application) to the Medical Affairs Office and to the applicant, within thirty days of receipt of the complete Application by the Zone Clinical Department(s).

3.4.4 The Medical Affairs Office will forward the recommendation of the Zone Clinical Department(s) and all information considered by the applicable Zone Clinical Department(s) to the Zone Application Review Committee for review. The Zone Application Review Committee shall return a written recommendation (to accept, deny, or amend the application) to the Medical Affairs Office within thirty days of receipt of the recommendation of the Zone Clinical Department(s) by the Zone Application Review Committee.

3.4.5 If the recommendation of the Zone Application Review Committee is favourable, the Medical Affairs Office shall forward the recommendation to the Chief Medical Officer for a decision to accept or reject the recommendation of the Zone Application Review Committee. The Chief Medical Officer shall provide the applicant with written notification of the decision within fifteen days of receipt of the recommendation by the Chief Medical Officer.

3.4.6 If the recommendation of the Zone Application Review Committee is unfavourable, the Application shall proceed pursuant to section 3.6 of these Bylaws.

3.4.7 An approved Application will result in the preparation of a Medical Staff Letter of Offer by the Medical Affairs Office. With the Medical Staff Letter of Offer, the applicant shall be provided with copies of, or access to, all documents referred to pursuant to section 3.4.7.2 of these Bylaws. The Medical Staff Letter of Offer shall:

3.4.7.1 Indicate the terms of the Appointment including the category of Medical Staff Appointment, the assignment to the appropriate Zone Clinical Department(s), the identification of the Primary Zone Clinical Department, and the Clinical Privileges granted. Where a member of the Medical Staff is subject to a return-in-service agreement (RiSA) with AHS, completion of the RiSA will also be a condition of the Appointment.

3.4.7.2 Include a statement that the Applicant:

a) has read and understands the Medical Staff Bylaws and Rules and agrees to be governed by them;
b) accepts the category of Medical Staff Appointment, the assignment to Zone Clinical Department(s), the identification of the Primary Zone Clinical Department (and Clinical Sections or programs where applicable), and the Clinical Privileges granted; and
c) has read and understands all relevant AHS policies including, but not limited to, those pertaining to confidentiality/privacy, acceptable Information Technology/Information Management usage, health record keeping, and Patient safety; and, agrees to be governed by them provided that their content does not supersede the Code of Conduct of the relevant College, or the relevant code of ethics of the profession.

3.4.7.3 In the case of a Practitioner being granted an Appointment in the Locum Tenens category, the Medical Staff Letter of Offer shall specify the requirement that prior to any subsequent placement of the Locum Tenens in a new Site of Clinical Activity, the relevant Zone Medical Director must be satisfied that there are sufficient physical and human resources available to allow the Locum Tenens to utilize the Clinical Privileges granted.

3.4.8 A Medical Staff Letter of Offer shall not take effect until a signed copy of the letter, indicating the applicant's agreement with its terms, is returned to the Medical Affairs Office within thirty days of it being forwarded to the applicant.

3.5 REQUEST TO CHANGE A MEDICAL STAFF APPOINTMENT AND CLINICAL PRIVILEGES

3.5.1 A Request to Change may include an application to terminate or change the category of a Medical Staff Appointment, including a recommendation not to continue their Probationary Appointment, or to change Clinical Privileges.

3.5.2 A Request to Change must be initiated on the prescribed form by the Practitioner, the Primary Zone Clinical Department (in the case of a Request to Change the category of Appointment), or the relevant Zone Clinical Department(s) (in the case of a Request to Change Clinical Privileges), and will not be considered until such form is completed and submitted to the Medical Affairs Office. Changes to a Medical Staff Appointment and/or Clinical Privileges arising from a Triggered Review shall be addressed pursuant to section 6.8 of these Bylaws.

3.5.3 A Request to Change initiated by the Practitioner or Zone Clinical Department(s) will be submitted to the Medical Affairs Office and must include particulars of the change requested, and reasonable support for the need or desirability of the change. The Medical Affairs Office shall forward the Request to Change to the Practitioner (if initiated by the Zone Clinical Department(s)) or to the Zone Clinical Department Head(s) (if initiated by the Practitioner).

3.5.4 The Practitioner shall provide the Zone Clinical Department Head(s) (if the Request to Change is initiated by the Zone Clinical Department(s)) with written notification of whether he/she accepts or rejects the proposed change, or wishes to amend it, within thirty days of receipt of the Request to Change by the Practitioner.

3.5.5 The Zone Clinical Department Head(s) shall provide the Practitioner (if the Request to Change is initiated by the Practitioner) with written notification of whether it accepts, rejects, or amends the proposed change within thirty days of receipt of the Request to Change by the Zone Clinical Department Head(s).

3.5.6 The Zone Clinical Department Head(s) shall forward a recommendation (to accept, deny, or amend) the Request to Change, including written notification as to whether the Practitioner and the Zone Clinical Department(s) are in agreement, to the Practitioner and to the Medical Affairs Office within sixty days of receipt of the original Request to Change by the Medical Affairs Office.

3.5.7 The Medical Affairs Office will forward the recommendation of the Zone Clinical Department(s) to the Zone Application Review Committee together with all the information considered for review. The Zone Application Review Committee shall return a written recommendation (to accept, deny, or amend the Request for Change) to the Medical Affairs Office, which shall provide a copy to the Zone Clinical Department Head(s) and the Practitioner, within thirty days of the receipt of the recommendation of the Zone Clinical Department(s) by the Zone Application Review Committee.

3.5.8 If the recommendation of the Zone Application Review Committee is favourable, the Medical Affairs Office shall forward the recommendation to the Chief Medical Officer for a decision to accept or deny the recommendation of the Zone Application Review Committee. The Chief Medical Officer shall provide the Practitioner with written notification of a decision within fifteen days of receipt of the recommendation by the Chief Medical Officer.

3.6 UNFAVOURABLE RECOMMENDATIONS

3.6.1 A recommendation of the Zone Clinical Department(s), the Zone Application Review Committee, and/or the Zone Medical Administrative Committee with respect to an Application or a Request to Change may be favourable or unfavourable. An unfavourable recommendation may be a recommendation to deny the Application or Request to Change or a recommendation to amend the Application or Request to Change, without the unanimous agreement of the applicant/Practitioner, Zone Clinical Department Head(s), and the Zone Application Review Committee.

3.6.2 **Notification of the applicant/Practitioner**
Whenever an unfavourable recommendation is made by the Zone Clinical Department(s) or Zone Application Review Committee, the Medical Affairs Office shall provide the applicant/Practitioner with the recommendation as well as the substance of the concerns and reasons leading to the recommendation.

3.6.3 **Unfavourable recommendations by the Zone Clinical Department(s)**

3.6.3.1 If an Application or Request to Change is recommended for denial by the Zone Clinical Department(s), it will be forwarded by the Medical Affairs Office to the Zone Application Review Committee as an unfavourable recommendation.

3.6.3.2 If the Zone Clinical Department(s) recommends an amendment to an Application/Request to Change, the Zone Clinical Department Head(s) and the applicant/Practitioner shall use reasonable efforts to reach agreement with respect to the proposed amendment(s) prior to the recommendation being forwarded by the Medical Affairs Office to the Zone Application Review Committee.

i. **If agreement is reached** between the Zone Clinical Department Head(s) and the applicant/Practitioner, the amended Application/Request to Change will be forwarded by the Medical Affairs Office to the Zone Application Review Committee as a favourable recommendation.

ii. **If agreement cannot be reached** between the Zone Clinical Department Head(s) and the applicant/Practitioner, the amended Application/Request to Change shall be forwarded by the Medical Affairs Office to the Zone Application Review Committee as an unfavourable recommendation.

3.6.4 **Unfavourable recommendations made by the Zone Clinical Department(s) and supported by the Zone Application Review Committee**
If the Zone Application Review Committee supports an unfavourable recommendation made by the Zone Clinical Department(s), the unfavourable recommendation shall be forwarded to the Medical Affairs Office which shall inform the applicant/Practitioner that he/she may request the Application

or Request to Change be considered by the Zone Medical Administrative Committee pursuant to section 3.6.7 of these Bylaws.

3.6.5 **Amendments recommended by the Zone Application Review Committee**
If the Zone Application Review Committee recommends an amendment to an Application/Request to Change, the Zone Application Review Committee and Zone Clinical Department Head(s) shall use reasonable efforts to reach agreement with respect to the proposed amendment(s).

3.6.5.1 **If agreement is reached** between the Zone Clinical Department Head(s) and the Zone Application Review Committee, the Application/Request to Change shall proceed pursuant to section 3.6.3.2 of these Bylaws.

3.6.5.2 **If agreement cannot be reached** between the Zone Clinical Department Head(s) and the Zone Application Review Committee, the Application/Request to Change shall proceed pursuant to section 3.6.6 of these Bylaws.

3.6.6 **Unfavourable Recommendations and Disagreement between the Zone Clinical Department(s) and the Zone Application Review Committee with respect to a recommendation**
If the Zone Application Review Committee disagrees with the recommendation of the Zone Clinical Department(s), the Zone Application Review Committee may request such further information from the Zone Clinical Department(s) and the applicant/Practitioner as may be required. The Zone Application Review Committee and the Zone Clinical Department Head(s) shall make reasonable efforts to reach agreement with respect to the recommendation.

3.6.6.1 **If agreement is reached** between the Zone Clinical Department Head(s) and the Zone Application Review Committee, and the recommendation is favourable to the applicant/Practitioner, the recommendation shall be forwarded by the Medical Affairs Office to the Chief Medical Officer as a favourable recommendation.

3.6.6.2 **If agreement is reached** between the Zone Clinical Department Head(s) and the Zone Application Review Committee, and the recommendation is unfavourable to the applicant/Practitioner, the recommendation shall be forwarded to the Medical Staff Office which shall inform the applicant/Practitioner that he/she may request the Application or Request to Change be considered by the Zone Medical Administrative Committee pursuant to section 3.6.7 of these Bylaws.

3.6.6.3 **If agreement cannot be reached** between the Zone Clinical Department Head(s) and the Zone Application Review Committee, the Medical Affairs Office shall inform the applicant/Practitioner that the Application/Request to Change shall be referred to the Zone Medical Administrative Committee for consideration and review pursuant to section 3.6.7 of these Bylaws.

3.6.7 Where the Zone Application Review Committee has made an unfavourable recommendation with respect to a Medical Staff Application or a Request to Change, the recommendation shall be forwarded to the Medical Affairs Office which shall inform the applicant/Practitioner that he/she may request that the Application or Request to Change may be considered by the Zone Medical Administrative Committee.

3.6.7.1 The applicant/Practitioner shall be entitled to attend the meeting of the Zone Medical Administrative Committee, and to make representations, orally and/or in writing, personally and/or by an Advisor, relating to the Application or Request to Change.

3.6.7.2 The Medical Affairs Office and the Zone Medical Director shall provide the applicant/Practitioner with reasonable prior notice of the time and place at which the Zone Medical Administrative Committee is scheduled to consider the Application or Request to Change.

3.6.7.3 The Zone Medical Administrative Committee shall review the recommendation(s) from the Zone Clinical Department(s) and the Zone Application Review Committee, the complete Application or Request to Change, representations from the applicant/Practitioner and any other information it considers relevant; and shall make a recommendation within thirty days to be forwarded by the Medical Affairs Office to the Chief Medical Officer.

3.7 DECISIONS OF THE CHIEF MEDICAL OFFICER

3.7.1 A decision of the Chief Medical Officer may be favourable or unfavourable. An unfavourable decision may be either a decision to deny or to amend the Application or a Request to Change.

3.7.2 The applicant/Practitioner shall be notified of the decision within fourteen days of receipt of any recommendation from a Zone Applications Review Committee or Zone Medical Administrative Committee.

3.7.3 The decision of the Chief Medical Officer relative to an Application or Request to Change is final, subject only to legal rights of appeal.

3.8 EXCEPTIONAL AND URGENT SITUATIONS

3.8.1 Under exceptional circumstances, as approved by the Chief Medical Officer, an interim grant of an Appointment and appropriate Clinical Privileges may be made to an applicant whose Application has not yet been fully completed and/or completely processed and approved as outlined in these Bylaws so long as the applicable criteria set out in section 3.8.5 pursuant to these Bylaws are met at the time of Appointment. An interim grant of an Appointment shall not exceed ninety consecutive days.

3.8.2. In urgent situations, the Chief Medical Officer or the Chief Executive Officer may make a Medical Staff Appointment to the Temporary Staff and a grant of Clinical Privileges without the benefit of some of the information listed in the application form, and without following the procedures provided in these Bylaws and the Rules.

3.8.3 In urgent situations, the Chief Medical Officer or the Chief Executive Officer may change the category of Medical Staff Appointment and/or make an addition to the Clinical Privileges of a Practitioner without the benefit of some of the information listed in the prescribed form, and without following the procedures provided in these Bylaws and the Rules.

3.8.4 The Zone Medical Affairs Office, on behalf of the Chief Medical Officer or the Chief Executive Officer shall notify the Zone Application Review Committee of the Appointment or change in Appointment or Clinical Privileges, and the nature of the urgent situation within seven days of the action. Should the Zone Application Review Committee believe it is required, it shall notify the Zone Medical Administrative Committee of the Appointment or Change in Appointment or Clinical Privileges.

3.8.5 Where a Medical Staff Appointment is made in such an urgent situation, the applicant will be required to provide to the Chief Medical Officer proof of the applicant's current registration with the relevant College and evidence of current professional liability protection acceptable to AHS.

3.8.6 A Medical Staff Appointment and grant of Clinical Privileges or a change in Appointment and/or Clinical Privileges made under exceptional circumstances or urgent situations shall be for a maximum of ninety days. During those ninety days, the applicant will be eligible to be considered for Appointment and a grant of Clinical Privileges or a change in Appointment and/or Clinical Privileges in the normal manner described in these Bylaws and the Rules.

3.9 AGREEMENTS WITH OTHER PROVIDERS

3.9.1 AHS may enter into agreements with Other Providers to allow Practitioners or other Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists to access and/or provide services to patients in the Other Providers' approved hospitals; continuing care facilities; community health, urgent care and public health centres; and/or diagnostic and treatment services and programs.

3.9.2 Such agreements may provide for one or more of the following:

3.9.2.1 The granting of appointments and clinical privileges by Other Providers to Practitioners or other Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists in order that they may access and/or provide services to patients in the Other Providers' approved hospitals; continuing care facilities; community health, urgent care and/or public health centers; and/or diagnostic and treatment services and programs;

3.9.2.2 The adoption of AHS Medical Staff Bylaws Appointment and Clinical Privilege application procedures and processes, including Requests to Change, by Other Providers to Practitioners or other Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists seeking appointments and clinical privileges in the Other Providers' approved hospitals; continuing care facilities; community health, urgent care or public health centers; and/or access to diagnostic and treatment services and programs;

3.9.2.3 The adoption of AHS Medical Staff Bylaws Periodic and Triggered Review processes by Other Providers to the Practitioners or other Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists who have appointments and clinical privileges in the Other Providers' approved hospitals, continuing care facilities, community health, urgent care or public health centers and/or diagnostic and treatment services and programs;

3.9.2.4 Acceptance, with or without amendment, of the Responsibilities and Accountabilities outlined in Part 4 of these Bylaws by the Other Providers and the Practitioners or other Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists who have appointments and clinical privileges in the Other Providers' approved hospitals; continuing care facilities; community health, urgent care or public health centers; and/or diagnostic and treatment services and programs;

3.9.2.5 The adoption or acceptance of such other provisions of these Bylaws as may be appropriate, having regard to the circumstances.

3.9.3 The adoption of these Medical Staff Bylaws' procedures or processes for the Practitioners or other Physicians, Dentists, Oral & Maxillofacial Surgeons and Podiatrists who have appointments and clinical privileges in Other Providers' approved hospitals, continuing care facilities, and community health, urgent care or public health centers; and/or who access Other Providers' diagnostic and treatment services and programs, shall involve, to the fullest extent practically possible, participation from, and implementation by, the Other Providers' administration, medical administrative leaders and/or medical staff.

3.9.4 Where, as a consequence of the adoption and application of these Medical Staff Bylaws' procedures or processes, a Practitioner or other Physician, Dentist, Oral & Maxillofacial Surgeon or Podiatrist, who has an appointment and clinical privileges in Other Providers' approved hospitals, continuing care facilities, community health, urgent care or public health centers; and/or who accesses Other Providers' diagnostic and treatment services and programs, is subject to a recommendation of a change in the appointment and/or clinical privileges granted by the Other Providers, or to remedial actions or sanctions as a result of a review, such change or remedial action or sanction shall be imposed by the appropriate body or medical administrative leader as appointed by the Other Provider.

PART 4 - RESPONSIBILITIES AND ACCOUNTABILITY OF AHS AND THE MEDICAL STAFF

4.0 GENERAL

4.0.1 The Medical Staff and AHS share joint responsibility and accountability for the provision of health services to Albertans in a Patient-centered system. This Part of the Bylaws describes the joint responsibilities and accountability of AHS and the Medical Staff, as well as the individual Practitioner's responsibilities and accountability.

4.0.2 AHS, subject to legislation and any direction provided by the Minister, has the responsibility and mandate to take appropriate actions to assess, enhance and protect the health of Albertans, through the promotion of health generally, and by ensuring reasonable access to appropriate, high quality and safe health services. In addition, AHS is responsible for appointing a Senior Medical Officer of Health to carry out the duties pursuant to the Public Health Act. AHS retains decision-making authority with respect to the distribution of resources to meet these responsibilities.

4.0.3 Within the medical governance and organizational structure jointly established by AHS and the Medical Staff, the Medical Staff are expected to provide Patient services in a professional and competent manner, and to collaborate with, and contribute expert advice to, AHS.

4.0.4 Within the medical governance and organizational structure jointly established by AHS and the Medical Staff, AHS is expected to consider the impact of decisions relating to the delivery of health care services on individual Practitioners, groups of Practitioners, and the Medical Staff generally; and shall facilitate Practitioner and Medical Staff input into the deliberation and decision processes.

4.0.5 AHS administrative leaders and the Medical Staff jointly commit to demonstrating ethical behaviour and professionalism in all interactions.

4.0.6 Practitioners shall be governed by the AHS values of respect, accountability, transparency and engagement, AHS policies and by the AHS Code of Conduct. Practitioners shall also be governed by the relevant Professional Code of Conduct, and the respective code of ethics of the relevant profession. If the content of the AHS Code of Conduct conflicts with the relevant Professional Code of Conduct or code of ethics, then the Professional Code of Conduct or code of ethics of the relevant profession shall take precedence.

4.0.7 When fulfilling the duties and responsibilities of their AHS administrative role, Practitioners who are AHS medical administrative leaders shall also be governed by the AHS values of respect, accountability, transparency and engagement, the AHS Code of Conduct, the relevant Professional Code of Conduct, and the respective code of ethics of the relevant profession. Notwithstanding section 4.0.6, if the AHS Code of Conduct conflicts with the relevant Professional Code of Conduct or code of ethics, the code(s) which prescribes the higher standard of conduct shall take precedence.

4.0.8 Notwithstanding section 4.0.6 of these Bylaws, Practitioners who are AHS Representatives or AHS Agents shall also be governed by the AHS Conflict of Interest Bylaw when fulfilling the duties and responsibilities related to their role as an AHS Representative or an AHS Agent.

4.1 JOINT RESPONSIBILITIES AND ACCOUNTABILITY

4.1.1 **Medical Staff Governance and Organizational Structure**
AHS and the Medical Staff shall jointly develop and maintain Bylaws and Rules. These shall provide a Medical Organizational Structure that fulfills statutory requirements, effectively manages Medical Staff affairs, and facilitates the meaningful and effective participation of the Medical Staff in the affairs of AHS. AHS and the Medical Staff shall jointly contribute to an effective Medical Organization Structure through:

a) the development, implementation and amendment of Bylaws and Rules governing the creation, organization and operation of the Medical Staff, including:

   i. administrative structures, committees and leadership for the governance of the Medical Staff;
   ii. granting of Appointments to Physicians, Podiatrists, Dentists or Oral & Maxillofacial Surgeons as members of the Medical Staff;

iii. granting Clinical Privileges to Practitioners;
iv. defining the responsibilities of all Practitioners who are granted Appointments and Clinical Privileges;
v. reviewing and determining Practitioner compliance with discharging the responsibilities related to Appointments and Clinical Privileges;
vi. establishing principles and process for the Periodic Review of Practitioners;
vii. establishing principles and process for the Triggered Review of a Practitioner; and
viii. establishing a transparent, consistent, and fair approach to dispute resolution; one encouraging and supporting consensual means and efforts as the preferred mechanism to resolve disputes; and thereafter, as appropriate, through more formal mechanisms in a graduated fashion.

b) the management of the AHS Practitioner Workforce Plan, as defined in the Rules.
c) the selection and evaluation of AHS medical administrative leaders. While recognizing the final authority of AHS, the Medical Staff shall have input in the process of selection and review of AHS medical administrative leaders at an appropriate level, as defined in the Bylaws and Rules.
d) the efficient communication within the Medical Staff; as well as between Practitioners and other health care professionals, the executive and administrative staff of AHS, and other health system stakeholders.

4.1.2 **Quality and Safety of Care**

AHS and the Medical Staff shall jointly participate in activities and planning that promote and support:

a) quality improvement programs and systems of evaluation to achieve the highest standard of Patient care possible.
b) the Zone Clinical Departments in the development of mechanisms that maintain the highest standards of clinical practice and professionalism.
c) Patient safety and engagement
d) Practitioner and AHS staff safety
e) evidence-based decision-making wherever applicable.
f) reasonable and effective on-call schedules.

4.1.3 **On-Call and Service Coverage Responsibilities**

4.1.3.1 AHS and the Medical Staff shall jointly establish and maintain reasonable and effective on-call schedules for safe and effective Patient care and coverage at all times.

4.1.3.2 On-call schedules shall be consistent with the clinical services provided by the Zone Clinical Department and the Clinical Privileges of the Practitioners who provide the on-call coverage.

4.1.3.3 AHS and the Medical Staff shall work jointly to ensure on-call schedules do not place work demands on individual Practitioners that prevent the Practitioner from providing safe Patient care and coverage. AHS medical administrative leaders shall work collaboratively with Practitioners to resolve such situations when they arise.

4.1.4 **Documentation of Care**

AHS and the Medical Staff share the responsibility to create and maintain an accurate health record of the care provided to every Patient in AHS Facilities or other AHS Sites of Clinical Activity. To accomplish this:

a) AHS will provide and maintain the appropriate infrastructure and information management systems to create a health record, and shall be the custodian of all such health records pursuant to applicable legislation except where a Practitioner or Practitioners and AHS have otherwise entered into a written agreement addressing custodianship of the health record.
b) AHS will ensure the proper and timely completion of the health record by all staff including documentation of their role, the care provided, and the relevant events during the Patient's interaction with AHS.
c) The Rules shall describe the requirements for the proper and timely completion of health records, and shall be compliant with all applicable legislation, professional and ethical obligations, and AHS policies.

4.1.5 **Utilization of AHS Resources**
AHS and the Medical Staff shall jointly participate in activities that promote and support the effective and efficient use of AHS resources.

4.1.6 **Administrative, Research and Education Activities**
AHS and the Medical Staff shall jointly participate in activities and planning that promote and support:

a) administrative, research and education activities of AHS and/or the Zone Clinical Department.
b) the safest and highest quality care.
c) an environment that facilitates continuous improvement in the delivery of health care through biomedical, clinical, health services and outcomes research.
d) the establishment, maintenance, and continual improvement of the educational, clinical and professional standards for all Practitioners.
e) the education of all health care staff, with the objective of creating and sustaining an environment that supports excellence in undergraduate, graduate, and postgraduate

4.2 INDIVIDUAL PRACTITIONER RESPONSIBILITIES AND ACCOUNTABILITY

4.2.1 **Medical Staff Governance**
Individual Members of the he Medical Staff shall:

a) comply with these Bylaws and Rules and such approved amendments as may from time to time be made, and with applicable AHS policies, the AHS Code of Conduct, and the Professional Code of Conduct of the relevant College and/or the respective code of ethics of the relevant profession.
b) comply with all requirements or expectations in the Medical Staff Letter of Offer, provided that if the Medical Staff Letter of Offer conflicts with these Bylaws and the Rules, these Bylaws and the Rules shall take precedence.
c) comply with all obligations contained in contracts for service between a member of the Medical Staff and AHS, provided that if the contract for service conflicts with these Bylaws and the Rules, these Bylaws and the Rules shall take precedence.
d) follow reasonable direction on matters pertaining to Practitioner responsibilities and accountabilities pursuant to these Bylaws and the Rules, issued by anyone having the authority to do so under these Bylaws and the Rules, provided that the content of such direction does not supersede the respective code of ethics of the relevant profession.

4.2.2 **Professional Qualifications and Liability Protection**
Individual members of the Medical Staff shall obtain, provide proof of, and maintain:

a) licensure from an appropriate College
b) specialty or sub-speciality certification where applicable
c) membership in the Canadian Medical Protective Association or suitable malpractice insurance to the satisfaction of AHS.

4.2.3 **Patient Advocacy**
Individual members of the Medical Staff have the right and the responsibility to advocate on behalf of their Patients. In doing so, Practitioners should advocate in a manner that is consistent with the values and principles of their regulatory College, their professional association and AHS. When advocating as individuals, Practitioners who hold medical administrative leadership roles within AHS shall articulate clearly that they are not speaking as representatives of AHS. Advocacy should reflect the principles of honesty, fairness, transparency, accountability and professionalism. Practitioners are encouraged to first advocate or enquire about the matter internally within AHS before making public statements.

4.2.4 A Practitioner who believes that he or she has been targeted with a retaliatory Concern for advocating on behalf of his/her Patient, or for reporting an act or omission that creates either a specific danger to the life, health or safety of another person, interferes with the performance of the duties or functions of that Practitioner or another person, or points out management of public funds or assets, may submit a Concern pursuant to Article 6.1.3 of these Bylaws.

4.2.5 A Concern initiated pursuant to Article 4.2.4 shall be assessed and reviewed by an AHS Medical Administrative leader who is not involved in the initial review of the report of the act or omission,

and who has no specific supervisory roles in relation to the individual initiating the retaliatory Concern.

4.2.6 The fact that a Practitioner has initiated a Concern does not limit the Practitioner's right to seek injunctive or other relief from the Courts.

4.2.7 **Quality and Safety of Care**
Individual members of the Medical Staff shall:

a) demonstrate and maintain clinical skills and judgment to provide Patient care that meets established professional standards.
b) perform the activities and responsibilities expressed in the Medical Staff Appointment and Clinical Privileges granted.
c) provide information, expertise, and advice to AHS in assessing health needs, planning service delivery and programs, and AHS resource utilization and management, through the Medical Organizational Structures as set out in these Bylaws.
d) complete health records in a proper, comprehensive, and timely manner that accurately reflects their role in the Patient's interaction with AHS.

4.2.5 **Accountability and Compliance**
Individual members of the Medical Staff shall demonstrate their accountability and compliance with these Bylaws, AHS Policies, the AHS Code of Conduct, the relevant Professional Code of Conduct and the respective code of ethics of the relevant profession by:

a) reporting to their Zone Clinical Department Head(s) the presence of any physical or mental health issues that impair the Practitioner's ability to care safely for a Patient. Such information shall be kept strictly confidential unless disclosure to a specified party(ies) is required by law or is deemed necessary to ensure public or Patient safety or is agreed to, in writing, by the Practitioner.
b) being subject to Periodic Review pursuant to Part 5 of these Bylaws (only for Practitioners in the Active and Locum Tenens categories of Appointment);
c) being subject to Triggered Initial Assessment and/or Triggered Review of Concerns, if required, pursuant to Part 6 of these Bylaws (for Practitioners in all categories of Appointment);
d) choosing processes that are contained in these Bylaws and the Medical Staff Rules to resolve disputes provided however that in doing so the Practitioner does not waive any legal rights otherwise available should the processes in these Bylaws and the Rules not succeed in resolving the dispute;
e) contributing to the functioning of the Zone Clinical Department(s) to which they are assigned;
f) using best efforts to attend Zone Clinical Department meetings.

4.2.6 **Professional Conduct**
Individual members of the Medical Staff shall meet the expectations for professional conduct and behaviour as defined in the AHS Code of Conduct and the relevant Professional Code of Conduct, and/or the respective codes of ethics of the relevant profession.

4.2.7 **On-Call and Service Coverage Responsibilities**
Practitioners shall provide safe and effective on-call and service coverage. The individual Practitioner shall:

a) participate equitably and fairly in an on-call schedule(s) consistent with his/her Clinical Privileges and as established within his/her Zone Clinical Department(s);
b) manage his/her other concurrent clinical activities in order to ensure that he/she can safely and appropriately fulfill his/her on-call duties and responsibilities.
c) ensure on-call coverage by another Practitioner(s) with appropriate skills and Clinical Privileges if he/she is unable to provide the coverage assigned to him/her in a previously established on-call schedule. If urgent circumstances limit or prevent the Practitioner from fulfilling this responsibility, the Zone Clinical Department Head or designate(s) and/or Facility or Community Medical Director shall provide reasonable assistance to make alternative arrangements for coverage of the on-call period in question.
d) ensure service coverage of his/her Patients by another Practitioner(s) with appropriate skills and Clinical Privileges whenever the Practitioner is unavailable for any reason to provide such coverage. If urgent circumstances limit or prevent the Practitioner from fulfilling this responsibility, the Zone Clinical Department Head or designate(s) and/or Facility or Community Medical Director shall provide reasonable assistance to make alternative arrangements for service coverage.

PART 5 – PERIODIC REVIEW

5.0.1 This Part of the Bylaws establishes the processes for Periodic Reviews of Practitioners.

5.0.2 Periodic Reviews provide the Practitioner and the Zone Clinical Department Head(s) or designate(s) with an opportunity to review professional performance, identify goals and to exchange information regarding health care issues, in the context of the Practitioner's Appointment and Clinical Privileges.

5.0.3 Members of the Medical Staff with an Appointment in the Active Staff category shall participate in Periodic Reviews every three years or more often if specified in the Medical Staff Letter of Offer. Members of the Medical Staff with an Appointment in the Locum Tenens Staff category shall have an initial Periodic Review undertaken at the conclusion of their first year in this category, and every three years thereafter. All Practitioners other than those in the Community Staff category shall be subject to an annual Periodic Review after attaining the age of 65 years.

5.0.4 The Rules shall describe the procedure for Periodic Reviews. The review must include all matters relevant to the category of Appointment and Clinical Privileges granted to the Practitioner. These include, but are not limited to:

a) the terms, conditions and major responsibilities contained in his/her Medical Staff Letter of Offer, and any amendments subsequently made to its terms and conditions;
b) actions arising from the previous Periodic Review;
c) the Individual Practitioner Responsibilities and Accountability contained in Section 4.2 of the Bylaws;
d) the professionalism, competence, training, experience, judgment, physical and mental health of the Practitioner, as they relate to the fulfillment of his/her responsibilities as defined by these Bylaws and the Rules.
e) continuing professional development and maintenance of competence activities;
f) in the case of Practitioners in the Locum Tenens category, or Practitioners in the Active category who take Locum Tenens assignments in other Zones, assessments completed by the requesting Practitioner(s) at the conclusion of the Locum Tenens assignment(s); and
g) assessment of the Practitioner by the relevant health care team(s) and Patients. The Rules shall specify the methods and tools to be used in these assessment processes.

5.0.5 The Practitioner and the Zone Clinical Department Head(s) or designate(s) shall meet to discuss the Periodic Review. Both the Practitioner and the Zone Clinical Department Head(s) or designate(s) shall identify and be responsible for further action arising from the Periodic Review. A written summary of the Practitioner's Periodic Review, including any recommendations or plans for further action, and the Practitioner's written comments, if any, will be placed on the Practitioner's Zone Clinical Department file(s), and a copy shall be provided to the Practitioner.

5.0.6 Except as required by law or permitted by these Bylaws, the written summary of the Periodic Review prepared by the Zone Clinical Department Head(s) or designate(s), together with recommendations, plans and/or Practitioner's comments shall be confidential and shall not be disclosed to any person or entity without the express consent of the Practitioner.

5.0.7 Where the Zone Clinical Department Head(s) or designate(s) has concern(s) arising from the Periodic Review that are consistent with the matters identified in sections 4.2 and 6.1.3 of these Bylaws, the Primary Zone Clinical Department Head shall forward a report outlining the concern(s) and the substantive reasons for it to the Zone Medical Director, and shall provide a copy of the written report to the Practitioner. The Zone Medical Director may direct that a Triggered Review be conducted.

PART 6 - TRIGGERED INITIAL ASSESSMENT AND TRIGGERED REVIEW

6.0 GENERAL

This part of these Bylaws establishes the processes for conducting a Triggered Initial Assessment of a Concern or other information/complaints, and a Triggered Review of a Concern. This part of these Bylaws applies to all Practitioners, including medical administrative leaders, and to all categories of Appointment.

6.0.1 A Triggered Initial Assessment:

a) shall be initiated upon receipt of a Concern
b) may be initiated upon receipt of other information / complaints regarding any aspect of a Practitioner's responsibilities and accountability pursuant to sections 4.2 and 6.1.3 of these Bylaws.

6.0.2 A Triggered Review may be initiated when recommended:

a) as a result of a Periodic Review pursuant to Part 5 of these Bylaws; or
b) by the Zone Medical Director at the conclusion of a Triggered Initial Assessment pursuant to section 6.3 of these Bylaws.

6.0.3 A Triggered Review may include:

a) Consensual Resolution pursuant to section 6.4 of these Bylaws;
b) a Hearing pursuant to section 6.5 of these Bylaws; and/or
c) an Appeal pursuant to section 6.6 of these Bylaws.

6.0.4 The timeframes for completion of a Triggered Initial Assessment and a Triggered Review, as described in this part of these Bylaws, are guidelines, and are meant to balance expediency in resolving Concerns with ensuring appropriate time for thorough investigation, a fair process, and best decisions. Unnecessary delays shall be avoided.

6.0.5 If the Affected Practitioner is a medical administrative leader with functions required of him/her pursuant to this part of these Bylaws, then such functions will be assumed by a more senior medical administrative leader selected by the Zone Medical Director.

6.0.5.1 If the Zone Medical Director is the Affected Practitioner, the functions required of him/her pursuant to this part of these Bylaws shall be fulfilled by an Associate Chief Medical Officer.

6.0.5.2 If an Associate Chief Medical Officer is the Affected Practitioner and the Concern or other information/complaints involve his/her professional performance and/or conduct related to his/her Appointment, rather than his/her role as Associate Chief Medical Officer, the Concern or other information/complaints shall be addressed pursuant to this part of these Bylaws, and the functions required of the Associate Chief Medical Officer shall be fulfilled by the Chief Medical Officer.

6.0.5.3 If an Associate Chief Medical Officer is the Affected Practitioner and the Concern or other information/complaints pertain to his/her role as Associate Chief Medical Officer, the Concern or other information/complaints shall be forwarded directly to the Chief Medical Officer.

6.0.5.4 If the Chief Medical Officer is the Affected Practitioner and the Concern or other information / complaints involve his/her professional performance and/or conduct related to his/her Appointment, rather than his/her role as Chief Medical Officer, the Concern or other information/complaints shall be addressed pursuant to this part of these Bylaws; and the functions required of the Chief Medical Officer pursuant to this part of these Bylaws shall be fulfilled by the Chief Executive Officer of AHS.

6.0.5.5 If the Chief Medical Officer is the Affected Practitioner and the Concern or other information/complaints pertain to his/her role and performance as the Chief Medical Officer, the Concern or other information/complaints shall be forwarded directly to the CEO.

6.0.6 A Concern or other information/complaints of a clinical/Patient care nature involving a member of the Medical Staff who is also an Academic Physician shall be addressed through the provisions of these Bylaws. A Concern or other information/complaints of an academic (research or teaching) nature shall normally be addressed through the processes and procedures of the relevant Faculty of Medicine (University of Calgary)/ Faculty of Medicine & Dentistry (University of Alberta). In cases involving issues of both a clinical and an academic nature, or where the academic activities in question are undertaken in AHS Facilities and impact Patient care or clinical services in AHS Facilities, AHS and the relevant Faculty of Medicine/Medicine & Dentistry shall collaborate in addressing the Concern or other information/complaints and in determining which party's processes and procedures shall be followed.

6.0.7 A Triggered Initial Assessment or Triggered Review may, at the discretion of the Zone Medical Director, proceed notwithstanding that the Affected Practitioner has resigned from the Medical Staff.

6.0.8 A Triggered Initial Assessment or Triggered Review may, at the discretion of the Zone Medical Director, proceed notwithstanding that a Complainant has withdrawn the Concern.

6.1 CONCERNS

The complainant must acknowledge that the process used will follow that laid out in the AHS Medical Staff Bylaws.

6.1.1 A Concern must be:

a) in writing;
b) signed by either the Complainant or by the individual(s) conveying the Concern involving the Affected Practitioner; and
c) supported by a reasonable degree of relevant detail forming the basis of the Concern.

6.1.2 A Concern may be received from a Complainant or may be initiated by AHS.

6.1.3 Matters which form the basis of a Concern include, but are not limited to:

a) quality and safety of patient care;
b) clinical performance;
c) participation in continuing professional development and maintenance of competence activities relevant to the Practitioner;
d) contribution to Zone Clinical Department objectives;
e) issues related to leadership as raised by a member(s) of the Medical Staff;
f) ethical conduct;
g) professional behaviour and conduct including interactions with patients, families, visitors, professional colleagues, and AHS clinical and non-clinical staff;
h) breach of the responsibilities and expectations pursuant to these Bylaws, the Medical Staff Rules, the Practitioner's Medical Staff Letter of Offer (or any subsequent amendments to the letter), applicable AHS policies and the AHS Code of Conduct, the Professional Code of Conduct of the relevant College and/or the respective code of ethics of the relevant profession. If AHS policies and/or the AHS Code of Conduct conflict with the Professional Code of Conduct of the relevant College and/or the respective code of ethics of the relevant profession, then the Professional Code of Conduct and the code of ethics of the relevant profession shall take precedence;
i) breach of any formal agreement with AHS; and,
j) any health problem that significantly affects the Practitioner's ability to carry out his/her AHS professional responsibilities.
k) retaliatory actions as described in Article 4.2.4 of these Bylaws

6.1.4 A Concern initiated by a Complainant:

6.1.4.1 The Complainant will be notified by the AHS Patient Concerns Office, AHS Human Resources or the Medical Affairs Office that the Concern has been received and has been forwarded to the Zone Medical Director or designate.

6.1.4.2 The Zone Medical Director or designate, subject to any legal requirements, will contact the Complainant to:

a) explain the Triggered Initial Assessment and the Triggered Review processes;
b) inform the Complainant(s) that a Triggered Initial Assessment or Triggered Review, if recommended or required, cannot proceed without the Affected Practitioner being provided with a copy of the Concern, which shall include the identity of the Complainant(s);
c) confirm that the Complainant(s) wishes to have the complaint addressed as a Concern, and thus comply with the requirements specified in sections 6.1.1 of these Bylaws;
d) obtain from the Complainant(s) written acknowledgement that the nature and implications of the processes pursuant to section 6.1.4.2 a) and b) are understood.

6.1.4.3 The Affected Practitioner shall not communicate directly, in writing or verbally, about the Concern with the Complainant unless given permission to do so by the Zone Medical Director; there is mutual agreement to do so as part of Consensual Resolution; and/or if recommended as part of the resolution of the Concern.

6.1.5 A Concern initiated by AHS:

The Zone Clinical Department Head(s) or designate(s) or the Zone Medical Director or designate(s) may initiate a Concern on behalf of AHS when:

a) there are reasonable grounds to believe that one or more of the matters specified in section 6.1.3 of these Bylaws exists; and
b) those with direct knowledge are unwilling or unable to submit a Concern; and/or
c) a complaint fails to meet the requirements specified in section 6.1.1 of these Bylaws; and/or
d) the Complainant(s) does not agree or comply with the requirements specified in section 6.1.4.2 of these Bylaws.

6.2 PROCEDURAL FAIRNESS

6.2.1 The Affected Practitioner is entitled to procedural fairness including, but not limited to:

a) the opportunity at any time to initiate, or participate in, Consensual Resolution, if mutually agreeable to the Affected Practitioner and AHS;
b) confidentiality consistent with the nature of the proceeding, and to the extent permitted by law, provided that the Affected Practitioner does not present a risk to Patients or the public;
c) being provided with a copy of the Concern, including the identity of the person(s) bringing the Concern forward;
d) the right to respond to the Concern;
e) full disclosure, to the extent permitted by law, of all information considered in the Triggered Initial Assessment and/or Triggered Review;
f) the assistance of an Advisor;
g) timely disposition of the Triggered Initial Assessment and/or Triggered Review consistent with the nature of the Concern;
h) being provided with a copy of any recommendations, decisions and the reasons leading to them;
i) being provided with a copy of any documentation sent to the relevant College, to the extent permitted by law; and
j) if a Hearing is required, to:

I. have a Hearing free of bias;
II. have the opportunity to object to the composition of the Hearing Committee provided that prior knowledge of the subject matter of the Hearing does not automatically disqualify a person from being a member of the Hearing Committee;
III. be represented by legal counsel, give evidence, examine and cross examine witnesses;
IV. request a review by the Zone Medical Administrative Committee of the report and/or recommendations of the Hearing Committee pursuant to section 6.6.1 of these Bylaws; and
V. be provided, to the extent permitted by law, with a copy of any documents, placed in the Affected Practitioner's file at the conclusion of the Triggered Initial Investigation and/or Triggered Review.

6.2.2 AHS is entitled to procedural fairness including, but not limited to:

a) the opportunity at any time to initiate, or participate in, Consensual Resolution, if mutually agreeable to the Affected Practitioner and AHS;
b) exclude documents or information from full disclosure if required by applicable legislation;
c) be represented by legal counsel, give evidence, examine and cross examine witnesses before the Hearing Committee (if a Hearing is required);
d) timely disposition of the Triggered Initial Assessment and/or Triggered Review consistent with the nature of the Concern;
e) make recommendations and decisions affecting the Medical Staff Appointment and/or the Clinical Privileges of the Affected Practitioner; and
f) request a review by the Zone Medical Administrative Committee of the report and/or recommendations of the Hearing Committee pursuant to section 6.6.1 of these Bylaws.

6.2.3 Any recommendations approved or decisions made by the Chief Medical Officer shall be final, subject only to legal rights of appeal.

6.3 TRIGGERED INITIAL ASSESSMENT

6.3.1 The Zone Medical Director or designate(s) shall, upon receipt of a Concern, or may, upon receipt of other information/complaints:

a) conduct a Triggered Initial Assessment; or
b) direct that a Triggered Initial Assessment be conducted by the relevant AHS medical administrative leader(s), including the Affected Practitioner's Zone Clinical Department Head(s) or designate(s), Facility or Community Medical Director(s), and/or Senior Medical Director, or by another investigator.

6.3.2 A Triggered Initial Assessment initiated upon receipt of:

6.3.2.1 a Concern shall be completed within ninety days of receipt of the Concern by the Zone Medical Director.

6.3.2.2 other information/complaints shall be completed within ninety days, and shall either be dismissed or become a Concern to be addressed pursuant to this part of these Bylaws. If the result of the Triggered Initial Assessment is not to proceed to the status of a Concern, the Affected Practitioner shall be notified and such noted in the Affected Practitioner's file.

6.3.3 The AHS medical administrative leader(s) conducting the Triggered Initial Assessment on the basis of a Concern or on the basis of other information/complaints that have become a Concern pursuant to section 6.3.2.2 of these Bylaws shall provide a copy of the Concern to the Affected Practitioner within seven days of initiating the Triggered Initial Assessment. The Affected Practitioner's response, if any, shall be considered by the Zone Medical Director when deciding on the disposition of the Concern.

6.3.4 Within twenty-eight days of completing the Triggered Initial Assessment initiated upon receipt of a Concern, the Zone Medical Director may:

a) dismiss the Concern as being unfounded;
b) determine that further action is not required or will not contribute further to investigation and resolution of the Concern;
c) refer the Complainant to an appropriate body or agency internal or external to AHS if the Concern does not pertain to the responsibilities and expectations of the AHS Medical Staff Appointment of the Affected Practitioner;
d) request further investigation and/or appoint another investigator if he/she determines the Triggered Initial Assessment to be incomplete;
e) refer the matter to an Associate Chief Medical Officer, pursuant to section 6.3.5 of these Bylaws, if the Affected Practitioner is an AHS medical administrative leader and the Concern is determined to pertain primarily to his/her role as a medical administrative leader;
f) refer the Concern, or a portion thereof, for internal or external expert opinion;
g) request that the Affected Practitioner engage in Consensual Resolution pursuant to section 6.4 of these Bylaws;
h) refer the Concern for a Hearing if the Affected Practitioner declines to participate in Consensual Resolution;
i) refer for a Hearing pursuant to section 6.5 of these Bylaws if he/she determines that the Concern is not amenable to Consensual Resolution pursuant to section 6.4 of these Bylaws;

j) refer the Concern to the relevant College if the Practitioner agrees, in writing; or if the Zone Medical Director, after consultation with the Associate Chief Medical Officer, determines that:

I. the referral is required by law; or
II. the referral is necessary to ensure public or Patient safety; or
III. the Concern will not be amenable to resolution pursuant to this part of these Bylaws but only if the Concern is within the scope of authority of the College to receive and act upon, and only after considering all reasonable alternatives and meeting with the Affected Practitioner to review the determination to refer and the reasons for it. If referral to the relevant College is planned under these circumstances, it shall not be made earlier than seven days following the meeting between the Affected Practitioner and the Zone Medical Director, and the Practitioner shall be provided with a copy of all materials intended to be sent to the relevant College.

6.3.5 If the Affected Practitioner is an AHS medical administrative leader and it is determined that the Concern or other information/complaints pertains primarily to his/her role and function as an AHS medical administrative leader, the Zone Medical Director shall refer the matter to an Associate Chief Medical Officer.

6.3.5.1 The Associate Chief Medical Officer shall decide if the Concern or other information/complaints is most appropriately addressed through a Triggered Initial Assessment and/or Triggered Review pursuant to this part of these Bylaws, or through internal AHS processes, and in consideration of the Affected Practitioner's contractual arrangement with AHS.

6.3.5.2 If internal AHS processes are to be followed, the Associate Chief Medical Officer shall designate an appropriate AHS medical administrative leader to explain the process to the Complainant(s), conduct an investigation of the Concern or other information/complaints and periodically inform the Complainant(s) of the progress of the internal AHS process.

6.3.5.3 Pursuant to section 6.9 of these Bylaws, at the conclusion of the AHS process, the Complainant(s) shall only be informed that the matter has been investigated and either dismissed or has resulted in appropriate action.

6.3.5.4 If the Concern or other information/complaints has been dismissed, the Complainant(s) may be provided with other options to pursue the matter should he/she be dissatisfied with the outcome of the internal AHS process.

6.3.6 The Affected Practitioner shall disclose to the Zone Medical Director If the relevant College is independently in receipt of the Concern, or investigating the Concern, and shall authorize the relevant College to confirm to the Zone Medical Director that this is the case.

6.3.7 A copy of any documentation placed in a Practitioner's file regarding the disposition of a Concern shall be provided to the Practitioner.

6.4 CONSENSUAL RESOLUTION PROCESS

6.4.1 At any time throughout the processes specified in Part 6 of these Bylaws, the Affected Practitioner and/or the relevant AHS medical administrative leader(s) may recommend Consensual Resolution to address the matter. This shall be a consensual process between the Affected Practitioner and the relevant AHS medical administrative leader(s), and may also include any other relevant persons including the Complainant(s).

6.4.2 The relevant AHS medical administrative leader(s) shall be selected by the Zone Medical Director and may include the Affected Practitioner's Zone Clinical Department Head(s) or designate(s), Facility or Community Medical Director(s), and/or Senior Medical Director; The Zone Medical Director may also request that an Associate Zone Medical Director participate in Consensual Resolution. The process may include mediation.

6.4.3 The Affected Practitioner and the relevant AHS administrative leader(s) shall meet and consider the Concern; the Affected Practitioner's response, if any; the Triggered Initial Assessment; and any other information they consider relevant, provided however that the Affected Practitioner is entitled to review and respond to all such information to the extent permitted by law.

6.4.4 Consensual Resolution shall result in a report and recommendation(s) from the relevant AHS medical administrative leader(s) to the Zone Medical Director, and shall conclude within fifty-six days unless otherwise agreed between the Zone Medical Director and Practitioner

6.4.4.1 Discussions and communications that occur during Consensual Resolution are strictly confidential and shall not be disclosed, except in accordance with section 6.8.5 of these Bylaws, or used in any process or proceeding outside Consensual Resolution without the written consent of the Affected Practitioner and all others who participated in Consensual Resolution.

6.4.4.2 No information or documents arising from Consensual Resolution shall be shared with a Hearing Committee other than that Consensual Resolution was attempted but was unsuccessful.

6.4.5 The Zone Medical Director shall review the report and the recommendation(s) arising from Consensual Resolution.

6.4.6 The Zone Medical Director may accept the report and recommendation(s) or may request clarification of the report and/or recommendation(s). In the latter case, the Zone Medical Director may meet with the relevant medical administrative leader(s) and/or the Affected Practitioner to discuss the report and/or recommendations.

6.4.7 The Zone Medical Director shall forward a written final report and recommendation(s), including any amendments, to the Affected Practitioner within fourteen days of receipt of the initial report and recommendation(s) from the relevant AHS medical administrative leader(s).

6.4.8 If the Affected Practitioner accepts the report and recommendation(s), he/she and the relevant medical administrative leader(s) shall be accountable for implementation of the recommendation(s).

6.4.9 If the Affected Practitioner rejects the report and/or recommendation(s), the Zone Medical Director and the Affected Practitioner shall meet to ensure a common understanding of the report and recommendations, and to determine if agreement can be reached, failing which the matter shall proceed to a Hearing pursuant to section 6.5 of these Bylaws.

6.4.10 The Affected Practitioner shall have fourteen days to provide a written response to the final report and recommendation(s) arising from Consensual Resolution.

6.5 HEARING

6.5.1 A Hearing before a Hearing Committee is required when:

a) the Zone Medical Director determines that a Concern is not amenable to Consensual Resolution;
b) the Affected Practitioner declines participation in Consensual Resolution; or
c) the Affected Practitioner rejects the final report and/or recommendation(s) of Consensual Resolution.

6.5.2 Following the decision to refer a Concern to a Hearing Committee, the Zone Medical Director shall:
a) notify the Practitioner as soon as possible of the decision to refer the matter to a Hearing and the anticipated timeframes.
b) make best efforts to convene the Hearing Committee within 42 days of the decision to refer.

6.5.3 The composition and procedures of a Hearing Committee shall be described in the Rules.

6.5.4 Mandate and Functions of the Hearing Committee

6.5.4.1 The Hearing Committee shall receive information, hear evidence, consider the Concern, and prepare a report and make recommendations.

6.5.4.2 The Hearing Committee is entitled to retain independent legal counsel to advise it on process and procedure in conducting the Hearing.

6.5.4.3 AHS shall present, and the Hearing Committee shall consider, the Concern and any evidence (either oral or written) that is relevant to the matters in issue, provided however that in advance of the hearing the Affected Practitioner is entitled to reasonable notice of evidence to be produced in order to allow for a fair response.

6.5.4.4 At any time during the Hearing, the Hearing Committee may ask the relevant AHS medical administrative leader(s) to provide further information.

6.5.4.5 The Hearing Committee may receive and consider relevant expert opinion(s) from within AHS, or external to AHS.

6.5.4.6 The Affected Practitioner shall appear before the Hearing Committee and is a compellable witness. In addition, the Committee may request that the Complainant(s) or any other person who may have knowledge or information relevant to the matters at issue give evidence.

6.5.4.7 Evidence may be given before a Hearing Committee in any manner that the Hearing Committee considers appropriate. The Hearing Committee is not bound by the rules of law respecting evidence that are applicable to judicial hearings.

6.5.5 After receiving and considering all relevant information and evidence, the Hearing Committee shall prepare a report and recommendation to either:

a) dismiss the Concern as being unfounded; or
b) if the Concern or the issues raised in the report are well-founded, prepare recommendations regarding remedial action or sanctions to be imposed upon the Affected Practitioner. Such action or sanctions may include but are not limited to:

i. no further action
ii. placing a caution or reprimand in the Affected Practitioner's file;
iii. requiring the Affected Practitioner to undergo counselling or treatment;
iv. requiring upgrading or further education;
v. requiring the Affected Practitioner to undertake a period of clinical supervision with prospective review of cases with or without special requirements of concurrent consultation or direct supervision;
vi. in the case of conduct which is unprofessional, unethical, unbecoming, improper, or deemed to be disruptive workplace behaviour, requiring the Affected Practitioner to undertake remedial measures to address the behaviour that gave rise to the Concern;
vii. temporary suspension of all or specified Clinical Privileges;
viii. permanent change of specified Clinical Privileges;
ix. a change in the category of Appointment;
x. termination of the Affected Practitioner's Appointment; and/or
xi. any other recommendation considered appropriate to ensure public or Patient safety.

6.5.6 The Hearing Committee report and recommendation(s) shall be forwarded to the Zone Medical Director within thirty days. The Zone Medical Director shall review the report of the Hearing Committee, and provide a copy to the Affected Practitioner.

6.5.6.1 Within thirty days of receiving the report of the Hearing Committee, the Affected Practitioner shall provide written notification to the Zone Medical Director as to whether he/she accepts or rejects the findings and/or recommendation(s) of the report.

a) If the Affected Practitioner accepts the report and/or recommendation(s) of the Hearing Committee, the report and the Affected Practitioner's response are sent by the Zone Medical Director to the Chief Medical Officer for a decision pursuant to section 6.8 of these Bylaws.
b) If the Affected Practitioner does not accept the report and/or recommendation(s) of the Hearing Committee, he/she may request a review by his/her Zone Medical Administrative Committee of the procedure of the Hearing Committee but only if he/she contends that:

i. the findings are materially inconsistent with the evidence; or
ii. breaches of process and fairness occurred and may have affected the findings and/or recommendations;
iii. the Hearing Committee erred in law; or
iv. there is new evidence that could not have been produced through reasonable efforts at the time of the Hearing, and that may have affected the findings and/or recommendation(s).

c) The Zone Medical Director shall inform the Zone Medical Administrative Committee Chair within seven days of receipt of the request from the Affected Practitioner.
d) If the Affected Practitioner does not provide written notification to the Zone Medical Director as to whether he/she accepts or rejects the report and/or recommendation(s) of the Hearing Committee within thirty days, the Zone Medical Director shall forward the report and recommendation(s) of the Hearing Committee to the Chief Medical Officer for a decision.

6.6 APPEAL OF THE HEARING COMMITTEE PROCESS

6.6.1 The Affected Practitioner or AHS may request that the Zone Medical Administrative Committee review the report and/or recommendations of the Hearing Committee. The appeal will only consider whether:

a) the findings are materially inconsistent with the evidence; or
b) breaches of process and fairness occurred and affected the findings and/or recommendations of the Hearing Committee;
c) the Hearing Committee erred in law; or
d) there is new evidence that could not have been produced through reasonable efforts at the time of the original Hearing and may have affected the findings and/or recommendation(s).

6.6.2 The Zone Medical Administrative Committee will not repeat the investigation or Hearing. The review will only consider the appeal items outlined in Section 6.6.1 a), b) or c) above, and will only refer to the documented record of evidence to the extent necessary to determine whether the process was fair.

6.6.3 Where the Zone Medical Administrative Committee determines that the findings are materially inconsistent with the evidence, or that there have been breaches of process and/or fairness that affected the findings and/or recommendations, it shall remit the matter to the Zone Medical Director for a further Hearing by a differently composed Hearing Committee.

6.6.4 Where the Zone Medical Administrative Committee determines that the Hearing Committee has erred in law, the Zone Medical Administrative Committee may remit the matter to the Zone Medical Director for a further Hearing by a differently composed Hearing Committee, or may, based on the documented record of evidence provided to it, vary or remove the relevant finding(s) or recommendation(s), and submit its report to the Zone Medical Director to forward to the Chief Medical Officer for decision.

6.6.5 Should the Zone Medical Administrative Committee determine that new evidence exists that may have affected the findings and/or recommendations of the initial Hearing, the Zone Medical Administrative Committee shall refer the matter to the original Hearing Committee for further consideration and recommendation to the Zone Medical Director.

6.6.6 Within sixty days of notification of the request to review the Hearing Committee proceedings and process, the Zone Medical Administrative Committee shall deliver a report of their findings and recommendations to the Zone Medical Director (pursuant to section 6.6.3 or 6.6.4), or the original Hearing Committee (pursuant to section 6.6.5).

6.7 IMMEDIATE ACTION

6.7.1 For the purposes of this section, Immediate Action means immediate suspension or restriction of a Medical Staff Appointment and/or Clinical Privileges without first conducting a Triggered Initial Assessment or Triggered Review as described in these Bylaws. Curtailment of Clinical Privileges for incomplete health records (as described in the Medical Staff Rules) shall not constitute an Immediate Action.

6.7.2 Immediate Action may be taken by the Zone Medical Director or designate, the Chief Medical Officer or designate or the CEO if there are reasonable grounds to believe that the Practitioner's professional performance and/or conduct requires steps be taken to protect the health or safety of any person, including the Practitioner, so long as no lesser measures will suffice, and the Affected Practitioner does not agree in writing to voluntarily restrict their relevant clinical activities. The Zone Medical Director or the CEO shall consult the Chief Medical Officer or designate before notifying the Affected Practitioner.

6.7.3 The Affected Practitioner will immediately be notified of the Immediate Action and the reasons for it by the Zone Medical Director, the Chief Medical Officer, or CEO who authorized the Immediate Action following consultation pursuant to section 6.7.2 above.

6.7.4 As soon as practical after the Affected Practitioner has been notified, the relevant College shall also be notified of such Immediate Action by the Zone Medical Director, the Chief Medical Officer or the CEO who authorized the Immediate Action.

6.7.5 The Zone Medical Director, the Chief Medical Officer or the CEO who authorized the Immediate Action shall request, within three days of the Immediate Action being taken, a review of the Immediate Action by the Immediate Action Review Committee. Should the Affected Practitioner agree in writing with the Immediate Action prior to the commencement of the review, the Immediate Action Review Committee shall be adjourned. The composition, duties and responsibilities of the Immediate Action Review Committee are described in the Medical Staff Rules.

6.7.6 After receiving and considering all relevant information and evidence, the Immediate Action Review Committee shall prepare a report and recommendation regarding the disposition of the Immediate Action to the Chief Medical Officer, and to the Zone Medical Director or the CEO if the one of the latter authorized the Immediate Action, within seven days of receipt of the request to do so.

6.7.7 The Immediate Action Review Committee may recommend:

a) discontinuing the Immediate Action pending a complete review by a Hearing Committee of the Concern or reasons leading to the Immediate Action; or
b) continuing the Immediate Action pending a complete review by the Hearing Committee of the Concern or reasons leading to the Immediate Action; or
c) modifying the Immediate Action (including, but not limited to, specific restrictions on Clinical Privileges) pending a complete review by a Hearing Committee of the Concern or reasons leading to the Immediate Action.

6.7.8 The Chief Medical Officer shall make a final decision relating to the report and recommendation of the Immediate Action Review Committee pursuant to section 6.7.7 above, and shall communicate the decision in writing to the Affected Practitioner, within four days. This decision shall also be provided to the Zone Medical Director or CEO if one of these two persons authorized the Immediate Action, the Zone Medical Administrative Committee, and the Complainant, if any. The relevant College shall also be notified of the decision. The decision of the Chief Medical Officer is final, subject only to legal rights of appeal.

6.7.9 After a decision is made with respect to continuing, modifying or discontinuing the Immediate Action pursuant to sections 6.7.7 and 6.7.8 of these Bylaws, a Hearing Committee shall conduct a complete review, pursuant to section 6.5 of these Bylaws, of the Concern or reasons leading to the Immediate Action, and shall prepare and forward a report and recommendations to the Chief Medical Officer.

6.7.10 The Immediate Action will be limited to fourteen days unless extended within that fourteen day period by the Zone Medical Director, the Chief Medical Officer or the CEO, who authorized the Immediate Action, or the Immediate Action Review Committee. The Immediate Action shall continue until a decision is rendered by the Chief Medical Officer.

6.8 DECISIONS OF THE CHIEF MEDICAL OFFICER

6.8.1 All final reports and recommendation(s) of a Hearing Committee and the Zone Medical Administrative Committees with respect to an appeal of a Hearing Committee process shall be sent to the Chief Medical Officer for a decision.

6.8.2 The Chief Medical Officer will render a decision within fourteen days of receipt of the report and recommendation(s) from a Hearing Committee and, if applicable from a Zone Medical Administrative Committee, and within seven days of receipt of the report and recommendation(s) from the Immediate Action Review Committee. The Chief Medical Officer may:

a) dismiss the Concern and/or the Immediate Action as being unfounded;
b) determine that no further action is required; or
c) determine appropriate remedial actions or sanctions. These may include, but are not limited to, a temporary or permanent change to the Appointment or Clinical Privileges, or termination of the Appointment of the Affected Practitioner. The Affected Practitioner may choose to

voluntarily submit to such actions or sanctions. If he/she does not, the actions or sanctions shall be imposed.

6.8.3 The decision of the Chief Medical Officer may be the same as, or different from, up to and including rejecting, the recommendations of a Hearing Committee or the Zone Medical Administrative Committee. If the decision of the Chief Medical Officer differs from the recommendations of the Hearing Committee or the Zone Medical Administrative Committee, written reasons for the difference shall be provided to the Hearing Committee and/or Zone Medical Administrative Committee, the Zone Medical Director and the Affected Practitioner.

6.8.4 The Affected Practitioner, Zone Medical Administrative Committee, Zone Medical Director and relevant Zone Clinical Department Head(s) shall be notified in writing of the decision of the Chief Medical Officer and the rationale for the decision.

6.8.5 If, in the decision of the Chief Medical Officer, a substantive change in the Appointment or Clinical Privileges of the Affected Practitioner is authorized, the Chief Medical Officer will inform the relevant College.

6.8.6 The decision of the Chief Medical Officer is final, subject only to legal rights of appeal.

6.9 NOTIFICATION OF THE COMPLAINANT

The Zone Medical Director, or if applicable, the Associate Chief Medical Officer pursuant to section 6.3.5 of these Bylaws, or the Chief Medical Officer shall periodically inform the Complainant(s), if any, of the progress of Triggered Initial Assessment or Triggered Review. At its conclusion, the Complainant(s) shall only be informed that the matter has been investigated and either dismissed or has resulted in appropriate action. If the Concern has been dismissed, the Complainant(s) may be provided with other options to pursue the matter should they be dissatisfied with the outcome of the Triggered Initial Assessment and/or Triggered Review.

6.10 PRACTITIONER-INITIATED REVIEWS

6.10.1 A Practitioner may voluntarily self-report a Concern about his/her own professional performance and/or conduct to the AHS medical administrative leader(s) who is his/her immediate supervisor, or to a more senior leader if warranted by the nature and significance of the Concern.

6.10.2 By voluntarily self-reporting a Concern, the Practitioner is entitled and expected to work collaboratively with the relevant medical administrative leader(s) to review and resolve the Concern.

6.10.3 The Practitioner and the relevant medical administrative leader(s) shall develop, in writing, a mutually agreed upon plan to review and resolve the Concern. The proposed plan must be approved by the Zone Medical Director and, if appropriate, may include temporary or permanent changes to the Practitioner's Medical Staff Appointment or Clinical Privileges. The Practitioner shall receive a copy of the approved plan.

6.10.4 The Practitioner shall be compliant with the conditions and terms of the plan, including any periodic monitoring, review, or reporting that has been agreed upon.

6.10.5 If the Practitioner and the relevant medical administrative leader(s) are unable to reach agreement upon a plan, or if, during the implementation of the plan, the Practitioner is unable or unwilling to comply with the conditions and terms of the plan, then review and resolution of the Concern shall immediately proceed to a Hearing pursuant to section 6.5 of these Bylaws.

6.10.6 Upon conclusion of the plan and resolution of the Concern, or if the process is unsuccessful in resolving the Concern, a written report shall be placed in his/her file(s), and a copy provided to the Practitioner.

6.11 DISPOSITION OF RECORDS

All information obtained, reviewed, discussed and otherwise used or developed in any process related to this part of these Bylaws, and that is not otherwise publicly known, publicly available, or part of the public domain, is considered to be privileged and strictly confidential information of AHS. It shall not to be disclosed to anyone outside of the process related to this part of these Bylaws except if agreed to, in writing by the Affected Practitioner or where determined by the Chief Medical Officer as required by law or necessary to

ensure public or Patient safety. Records of the proceedings outlined in this section (e-mails, correspondence, reports, and notes) will be retained in a manner consistent with the AHS record retention policy.

PART 7 – TRANSITION PROVISIONS

7.0 GENERAL

7.0.1 A Practitioner who has a Medical Staff Appointment with a former health region or with the former Alberta Cancer Board as of the effective date of these Bylaws will automatically receive an AHS Medical Staff Appointment and a grant of Clinical Privileges under these Medical Staff Bylaws and Rules unless the Practitioner advises AHS that he/she or she does not wish the Medical Staff Appointment and/or Clinical Privileges to continue.

7.0.2 Practitioners will be granted an Appointment in an equivalent category, and Clinical Privileges equivalent to those held as of the effective date of these Bylaws or those considered most appropriate or equivalent by the Zone Medical Director or designate.

7.0.3 If a Practitioner does not agree with the category of Appointment or Clinical Privileges granted the Practitioner may, within ninety days of the effective date of these Bylaws, initiate a Request to Change in accordance with Article 3.5.

7.0.4 Clinical Privileges granted under this Part will be deemed held at AHS Sites of Clinical Activities where the Practitioner previously held equivalent privileges as of the effective date of these Bylaws.

7.0.5 As of the effective date of these Bylaws, a Physician, Podiatrist, Dentist or Oral & Maxillofacial Surgeon who did not hold a Medical Staff or Dental Staff Appointment with a former health region or with the former Alberta Cancer Board may apply for an AHS Medical Staff Appointment and Clinical Privileges pursuant to these Medical Staff Bylaws and Rules.

7.0.6 All applications for a Medical Staff Appointment and privileges initiated in a former health region or the former Alberta Cancer Board prior to the effective date of these Medical Staff Bylaws will be continued to their conclusion under the provisions of these AHS Medical Staff Bylaws. The Zone Medical Director (or designate) shall confirm the status of the application and continue the process utilizing the decision making bodies or organizational positions identified in these Bylaws, and as well shall identify the appropriate Medical Staff category and Clinical Privileges that may be required.

7.0.7 Should an applicant disagree with the Zone Medical Director (or designate)'s continuation of the application(s) for an Appointment and Clinical Privileges under these AHS Medical Staff Bylaws, then within thirty days of receipt of the written notice of continuation, the applicant may withdraw the applications(s) and submit new application(s) for an Appointment and Clinical Privileges in accordance with Article 3.4, failing which the applicant shall be deemed to have accepted the continuation.

7.0.8 All performance reviews, disciplinary proceedings or disciplinary actions initiated or underway in a former health region or the former Alberta Cancer Board prior to the effective date of these Bylaws may continue to their conclusion under the provisions of these AHS Medical Staff Bylaws and Rules with such adjustments in decision making bodies or processes as may be required to be determined by the Chief Medical Officer or designate.

7.0.9 Should an Affected Practitioner disagree with the continuance of the performance review, disciplinary proceeding or disciplinary action under these AHS Medical Staff Bylaws and Rules, then within thirty days of the effective date of these Bylaws, the Affected Practitioner shall give written notice to that effect to the Zone Medical Director, and the performance review, disciplinary proceeding or disciplinary action shall then be re-initiated under the provision of Parts 5 or 6 of these Bylaws.

Alberta Health Services

POLICY

TITLE
IMMUNIZATION OF WORKERS FOR COVID-19

SCOPE
Provincial

DOCUMENT #
1189

APPROVAL AUTHORITY
Alberta Health Services President and Chief Executive Officer

INITIAL EFFECTIVE DATE
September 14, 2021

SPONSOR
Workplace Health and Safety

REVISION EFFECTIVE DATE
November 29, 2021

PARENT DOCUMENT TITLE, TYPE, AND NUMBER
Not applicable

SCHEDULED REVIEW DATE
March 31, 2022

NOTE: The first appearance of terms in bold in the body of this document (except titles) are defined terms – please refer to the Definitions section.

If you have any questions or comments regarding the information in this document, please contact Policy Services at policy@ahs.ca. The Policy Services website is the official source of current approved policies, procedures, directives, standards, protocols, and guidelines. Only the electronic version of this document, as hosted on the Policy Services website or www.ahs.ca, is valid.

OBJECTIVES

- To set out **worker** immunization requirements for COVID-19 to protect the health and safety of workers, patients, and the communities that Alberta Health Services (AHS) serves.

PRINCIPLES

AHS is committed to protecting the health and safety of its workers, patients, visitors, and others accessing AHS sites. Immunization against COVID-19 is the most effective means to prevent the spread of COVID-19, to prevent outbreaks in AHS facilities, to preserve workforce capacity to support the health care system, and to protect our workers, patients, visitors, and others accessing AHS sites. Immunization against COVID-19 also supports the AHS Values of Compassion, Accountability, Respect, Excellence, and Safety.

This Policy is in addition to other AHS policy documents supporting worker and patient safety during the COVID-19 pandemic including, but not limited to, the AHS *Use of Masks During COVID-19* Directive, *Attending Work with COVID-19 Symptoms, Positive Test, or Close Contact* Directive, and the *Fit for Work Screening (COVID-19)* Protocol.

This Policy shall be reviewed regularly, and at least prior to March 31, 2022, to ensure alignment with public health measures and regulations, and to confirm it adequately covers the health and safety risks that it addresses.

APPLICABILITY

Compliance with this document is required by Alberta Health Services, Alberta Precision Laboratories, Carewest, CapitalCare, and Covenant Health employees, members of the medical and midwifery staffs, students, volunteers, and other persons acting on their behalf. Compliance requirements for other contracted service providers, such as continuing care, will be

communicated directly to the contracted service providers. This document does not apply to physicians with community appointments.

ELEMENTS

1. Immunization Requirements

1.1 Effective December 13, 2021, all workers must be **fully immunized** against COVID-19.

1.2 A worker on an approved Leave of Absence must be fully immunized prior to returning to work.

1.3 A worker hired after November 30, 2021 must be fully immunized prior to commencing work.

2. Proof of Immunization Records

2.1 No later than November 28, 2021, workers shall disclose accurate proof of their immunization status to:

a) AHS or an AHS subsidiary, if the worker is an AHS employee, medical staff, midwifery staff, or volunteer;

b) Covenant Health, if the worker is a Covenant Health employee, medical staff, or volunteer;

c) their educational institution, if the worker is a student or instructor; or

d) their employer, if the worker is a contracted service provider.

2.2 Proof of immunization is being collected to protect the health and safety of workers, patients, and other persons accessing AHS sites and to preserve AHS' workforce capacity to support the health care system.

2.3 Proof of immunization records collected under this Policy shall be securely and confidentially retained, accessed, and used as necessary to determine fit for work status of workers, to manage and administer employment and other working relationships with workers, to address accommodation requests, and to comply with all applicable laws, such as the *Occupational Health and Safety Act* (Alberta) and *Regional Health Authorities Act* (Alberta).

2.4 Proof of immunization records are collected under the authority of Section 33(c) of the *Freedom of Information and Protection of Privacy Act* (Alberta) and shall be used, accessed, and disclosed in accordance with the legislation and the AHS *Collection, Access, Use, and Disclosure of Information* Policy.

3. Workplace Accommodation

3.1 Any AHS employee who is unable to be immunized due to a medical reason, or for another protected ground under the *Alberta Human Rights Act*, will be reasonably accommodated, up to the point of undue hardship, in accordance with the AHS *Workplace Accommodation* Policy. An AHS employee will not be permitted to undergo rapid testing as a reasonable accommodation unless Section 4 of this Policy applies.

3.2 Employees of AHS subsidiaries, Covenant Health, and applicable contracted service providers, who are unable to be immunized due to a medical reason, or for another protected ground under the *Alberta Human Rights Act,* will be reasonably accommodated, up to the point of undue hardship, in accordance with their applicable workplace accommodation policies. An employee of AHS subsidiaries, Covenant Health and applicable contracted service provider, will not be permitted to undergo rapid testing as a reasonable accommodation unless Section 4 of this Policy applies.

3.3 Any current AHS employee requesting workplace accommodation shall make a request for the accommodation as soon as reasonably possible, and no later than October 16, 2021, and provide required information in accordance with the AHS *Workplace Accommodation* Policy (or the appropriate accommodation policy of an AHS subsidiary or Covenant Health, if applicable).

3.4 Any current AHS member of the medical or midwifery staff who is not an employee of AHS, an AHS subsidiary, or Covenant Health, and who is unable to be immunized due to a medical reason, may request an exception as soon as reasonably possible and no later than October 16, 2021. A request for an exception shall be made on the *Medical or Midwifery Staff Request for Exception COVID-19 Mandatory Immunization for Workers* form and shall be submitted as directed on the form. The lack of immunization may affect the safe exercise of their Clinical Privileges as described in the *Medical Staff Bylaws* and *Rules* (Rule 3.4.4.2), or may directly impact their ability to practice and patient safety as described in the *Midwifery Staff Bylaws* and *Rules,* as applicable.

4. Rapid Testing at Facilities at Significant Risk of Service Disruption

4.1 Section 4.2 of this Policy only applies to current workers in facilities that are at a significant risk of service disruption.

a) Section 4.2 of this Policy does not apply to a worker hired after November 30, 2021 or to any worker in a facility that is not at significant risk of service disruption.

b) Facilities at significant risk of service disruption are determined by the Vice President and Chief Operating Officer, Clinical Operations and will be communicated to affected workers at these facilities.

4.2 Workers who are not fully immunized and are working in a facility that is at a significant risk of service disruption will be required to undergo regular rapid testing. The following conditions apply:

a) The worker must be tested using a Health Canada-approved COVID-19 test.

b) The test must be conducted at an existing private testing location (e.g., a pharmacy). Publicly-funded COVID-19 testing (e.g., through AHS) shall not be accepted.

c) The worker must have a negative test completed no more than 48 hours prior to the start of their shift.

d) The cost of the tests are at the worker's expense, unless an approved workplace accommodation or exception (for medical or midwifery staffs) applies.

e) The testing must be completed on the worker's own time.

f) The worker must retain proof (paper or electronic) of a negative test result and show that proof to their leader before the start of their next scheduled shift and if asked during their shift.

(i) If the worker tests positive for COVID-19, the worker must be tested for COVID-19 using a polymerase chain reaction (PCR) test. If the PCR test is positive, the worker must isolate in accordance with applicable Chief Medical Officer of Health Orders and the AHS *Attending Work with COVID-19 Symptoms, Positive Test, or Close Contact* Directive.

g) Workers who refuse to be tested or fail to comply with these conditions shall be considered non-compliant with this Policy and subject to Section 5 of this Policy until they are fully immunized.

5. Non-Compliance

5.1 A worker is considered to be in non-compliance with this Policy if they are:

a) not working in a facility that is at a significant risk of service disruption and have not met the requirements of Sections 1-3 of this Policy; or

b) working in a facility that is at a significant risk of service disruption and have not met the requirements of Sections 1-4 of this Policy.

5.2 With respect to students, instructors, and applicable contracted service providers, failure to comply with this Policy shall result in AHS reviewing the applicable contract or other relevant circumstances and initiating further discussions with the applicable educational institution or contracted service provider and, in this

respect, AHS reserves all rights it has at law, equity, or pursuant to any applicable agreement to address such non-compliance.

5.3 In all other cases not outlined in Section 5.2 above, except where a workplace accommodation or exception (for medical or midwifery staff) applies, failure to comply with this Policy shall result in:

a) a meeting being held with the worker to discuss their concerns with vaccination against COVID-19 and provide educational materials on the COVID-19 vaccines; and

b) if the worker remains non-compliant with this Policy, the worker being placed on an unpaid leave of absence for the period of time required to become fully immunized or, in the case of medical or midwifery staff, Immediate Action being taken as set out in Part 6 of the *Medical Staff* Bylaws or *Midwifery Staff* Bylaws.

DEFINITIONS

Fully immunized means a worker:

a) who has received two doses of a vaccine considered valid by Alberta Health in a two-dose COVID-19 vaccine series or one dose of a vaccine considered valid by Alberta Health in a one-dose COVID-19 vaccine series; and
b) for whom fourteen days have elapsed since the date on which the person received the second dose of the COVID-19 vaccine considered valid by Alberta Health of a two-dose series or one dose of the COVID-19 vaccine considered valid by Alberta Health in a one-dose vaccine series.

Worker means AHS, its subsidiaries and Covenant Health employees, members of the medical and midwifery staffs, students and instructors, volunteers, and applicable contracted service providers (including anyone providing services for AHS on behalf of an applicable contracted service provider).

REFERENCES

- Alberta Health Services Governance Documents:
  - *Attending Work with COVID-19 Symptoms, Positive Test, or Close Contact* Directive (#1188)
  - *Collection, Access, Use, and Disclosure of Information* Policy (#1112)
  - *Fit for Work Screening (COVID-19)* Protocol (#1184-01)
  - *Medical Staff Bylaws* and *Rules*
  - *Midwifery Staff* Bylaws and *Rules*
  - *Use of Masks During COVID-19* Directive (#HCS-267)
  - *Workplace Accommodation* Policy (#1156)
- Alberta Health Services Forms:
  - *Employee Request for Accommodation* Form (#19566)
  - *Got My COVID-19 Immunization* Form

  - *Medical or Midwifery Staff Request for Exception COVID-19 Mandatory Immunization for Workers* Form
- Alberta Health Services Resources:
  - AHS Immunization Information Insite Page
  - AHS Values
- Non-Alberta Health Services Documents:
  - *Alberta Human Rights Act*
  - *Freedom of Information and Protection of Privacy Act* (Alberta)
  - *Occupational Health and Safety Act* (Alberta)
  - *Regional Health Authorities Act* (Alberta)

Exhibit "K"

Biodistribution and Spike Protein Safety of mRNA Vaccines: An Update

It's easy to misinterpret science, and it takes more effort to understand the true narrative.

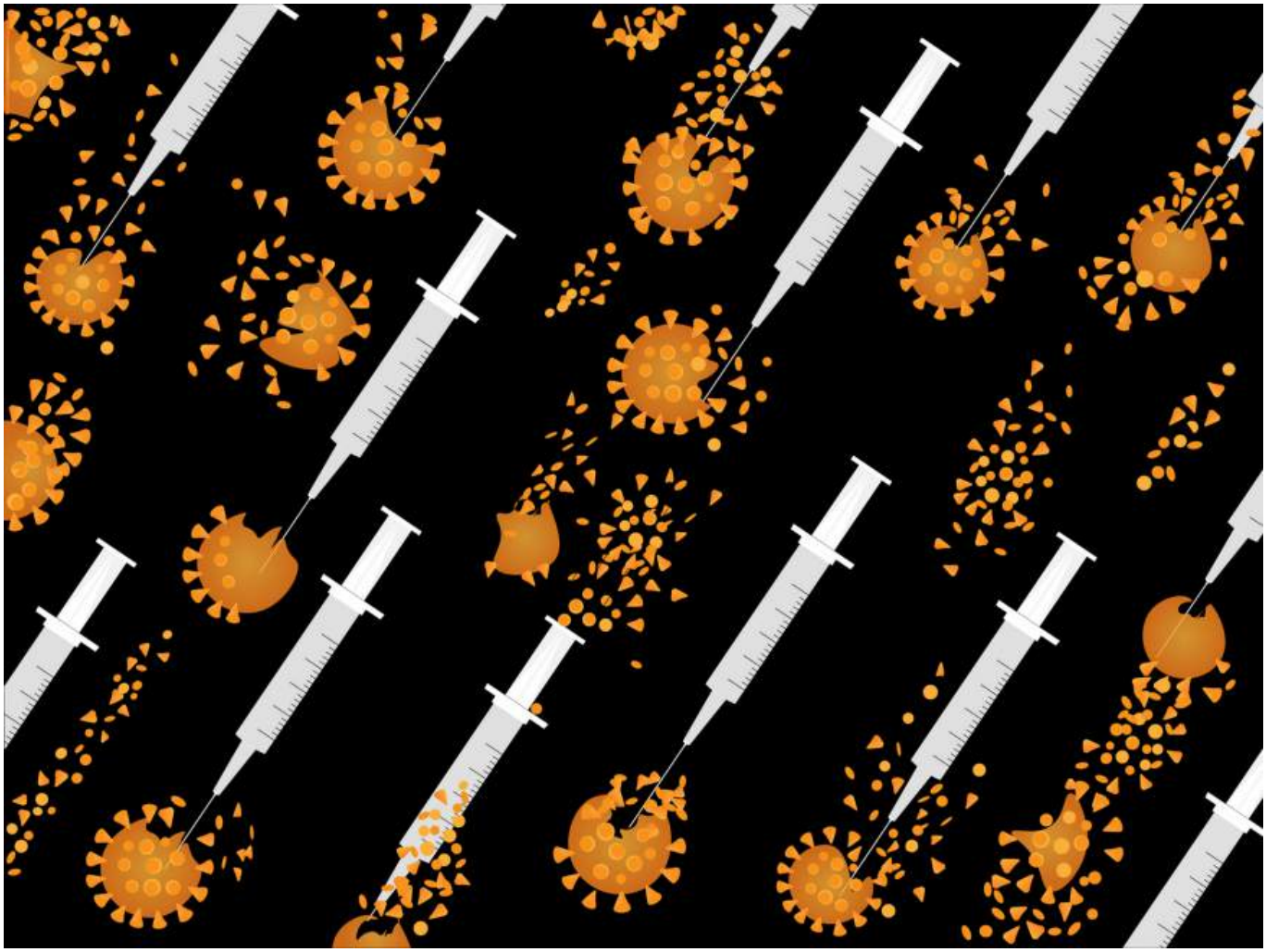
Shin Jie Yong Follow

Jul 7 · 11 min read ★

[redacted]

This is Exhibit K referred to
in the affidavit of Dr. Geert Grdadolnov
Sworn before me herein this 9
day of December, 2021

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor



Source: iStock

In the past few months, there has been a push for the idea that the spike proteins related to mRNA vaccines are toxic to our bodies. The vaccine can cause spike protein deposition in the ovaries, for example, but is this really true? I wish there's a yes or no answer to this question, but the science behind it isn't so straightforward. Rest assured, however, that the mRNA vaccines aren't toxic to the ovaries or any other tissues.

This article will explain why, as objectively as possible, and also serve as an update to a related article about spike protein safety I wrote back in December 2020 and another one about mRNA vaccine biodistribution I wrote four months ago.

How Covid-19 vaccines work in brief

Nearly all the vaccines against Covid-19 use the SARS-CoV-2's spike protein to induce immunity in some way or another. (SARS-CoV-2 is the coronavirus that causes Covid-19.)

The mRNA vaccine, for example, uses lipid nanoparticles (LNPs) to deliver mRNA into cells. This mRNA instructs the cell to make the spike proteins of SARS-CoV-2 that provoke immune reactions. The DNA vaccine acts similarly, using adenovirus to carry spike protein-encoding DNA into cells. The protein subunit vaccine, on the other hand, directly administers purified spike proteins into the body. In contrast, inactivated vaccine uses dead virions with intact spike proteins to induce immunity.

SARS-CoV-2 has spike proteins on its surface that latch on the ACE2 receptor on human cells. The spike protein-ACE2 binding allows SARS-CoV-2 to infect cells to replicate itself. Thus, vaccines aim to train our immune system to neutralize the spike proteins, preventing SARS-CoV-2 from infecting cells.

The biodistribution and toxicity concern

In an interview on 28 May 2021 that went viral, Byram W. Bridle, Ph.D., an associate professor specializing in virology and immunology, claimed that he and collaborators had obtained a 'biodistribution study' of the mRNA vaccine from the Japanese regulatory agency.

Prof. Bridle then said spike protein is a known toxin, which will harm the tissue it accumulates in. He speculates that this could be the culprit behind the blood clots (in the brain and other organs) and heart inflammation cases that are associated with Covid-19 vaccines.

Basically, Prof. Bridle said:

> *It's the first time ever scientists have been privy to seeing where these [mRNA] vaccines go after vaccination. Is it a safe assumption that it stays in the shoulder muscle? The short answer is: absolutely not. It's very disconcerting. The spike protein gets into the blood, circulates through the blood in individuals over several days post-vaccination…It accumulates in a number of tissues, such as the spleen, the bone marrow, the liver, the adrenal glands [and particularly] the ovaries…The conclusion is we made a big mistake. We didn't realize it until now. We thought the spike protein was a great target antigen. We*

> *never knew the spike protein itself was a toxin and was a pathogenic protein. So by vaccinating people, we are inadvertently inoculating them with a toxin."*

J. Patrick Whelan, MD, Ph.D., a pediatric rheumatologist, shared the same concern, warning the Food and Drug Administration (FDA) via a public submission in December 2020 that:

> *I am concerned about the possibility that the new [mRNA] vaccines aimed at creating immunity against the SARS-CoV-2 spike protein have the potential to cause microvascular [small blood vessels] injury to the brain, heart, liver, and kidneys in a way that does not currently appear to be assessed in safety trials of these potential drugs.*

In June 2021, Robert W. Malone, MD, MS, one of the pioneers of mRNA and DNA vaccine technology, also said that spike proteins are 'cytotoxic' (toxic to living cells) in a podcast and tweet:

> *The SARS-CoV-2 spike protein is cytotoxic. That is a fact. Who says so? Multiple peer reviewed references. The Salk Institue. It is the responsibility of the vaccine developers to demonstrate that their expressed version is not toxic. Show us.*

Therefore, the overall cause for worry is that spike protein-based vaccines could distribute cytotoxic spike proteins throughout the body, beyond the injection site, and harm the host.

Addressing the biodistribution concern

Prof. Bridle mentioned that the vaccine-derived spike proteins could enter the bloodstream and settle on various tissues, particularly the ovaries, based on the Japanese biodistribution study of the Pfizer mRNA vaccine.

Japan insisted on completing its own preclinical and clinical trials before authorizing the vaccine for use for Japanese people. Although this action has delayed vaccine roll-out, we also get more data on the Pfizer mRNA vaccine in addition to other governmental reports.

In this Japanese study, a substantial amount of the Pfizer mRNA vaccine settled in the injection site, liver, spleen, adrenal glands, and ovaries of rats at 48 hours following intramuscular injection (see yellow highlights below). But these numbers alone can be misleading.

As Abraham Al-Ahmad, Ph.D., an associate professor of pharmacology, who specializes in drug biodistribution in the brain, expertly explained:

> *That person is providing us with amount of the radiolabeled tracer detected in the tissue (e.g. ug/g tissue), with the approximation of total lipids amount in tissue. This assumes that the nanoparticles made it through the tissue complete, but we cannot exclude that we are maybe measuring only the 08-A01-C0 compound accumulation. In practice, we usually focus our attention on the percentage of injected dose (% ID) when it comes to appreciate the distribution and the delivery of a drug into an organ/tissue.*

Basically, the numbers highlighted in yellow refer to total lipid content, including both the mRNA vaccine's LNPs (lipid nanoparticles) and lipid tracer (i.e., 08-A01-C0 compound). Thus, the more appropriate numbers to look at should be the "% of administered dose" highlighted in cyan.

Now, the numbers are no longer nerve-racking: Only <1% of the injected mRNA vaccine got into the ovaries, adrenal glands, heart, brain, and other tissues at 48-hour. Most of the vaccine remained in the injection site and went into the liver, "suggesting these LNPs may be eliminated mostly via hepatic [liver] clearance route," Prof. Al-Ahmad wrote.

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Species (Strain):	Rat (Wistar Han)
Sex/Number of Animals:	Male and female/3 animals/sex/timepoint (21 animals/sex total for the 50 µg dose)
Feeding Condition:	Fed ad libitum
Method of Administration:	Intramuscular injection
Dose:	50 µg [^{3}H]-08-A01-C0 (lot # NC-0552-1)
Number of Doses:	1
Detection:	Radioactivity quantitation using liquid scintillation counting
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, and 48 hours post-injection

Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL) (males and females combined)							% of administered dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	--	--	--	--	--	--	--
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2	0.001	0.007	0.010	0.015	0.035	0.066	0.106
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	--	--	--	--	--	--	--
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77	--	--	--	--	--	--	--
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030

Injection site	128	394	311	338	213	195	165	19.9	52.6	31.6	28.4	21.9	29.1	24.6
Kidneys	0.391	1.16	2.05	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34	0.008	0.025	0.065	0.192	0.405	0.692	0.762
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3	0.602	2.87	7.33	11.9	18.1	15.4	16.2
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09	0.052	0.101	0.178	0.169	0.122	0.101	0.101

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Sample	Total Lipid concentration (µg lipid equivalent/g [or mL]) (males and females combined)							% of Administered Dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	--	--	--	--	--	--	--
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37	--	--	--	--	--	--	--
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	--	--	--	--	--	--	--
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	--	--	--	--	--	--	--
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4	0.013	0.093	0.325	0.385	0.982	0.821	1.03
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420	--	--	--	--	--	--	--
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805	--	--	--	--	--	--	--
Blood:Plasma ratio[a]	0.815	0.515	0.550	0.510	0.555	0.530	0.540	--	--	--	--	--	--	--

Source: Japanese government report. Page 6–7 of 'Pharmacokinetics Overview' section (or pdf page 16–17).

Even the dose the Japanese study used is very high when controlled for weight; that is, 18–35-times higher than what is injected into humans. As David H. Gorski, MD, Ph.D., a professor of surgery and blogger, explained:

> *The human vaccine contains…~0.46 mg lipids or 460 µg. Let's just round it up to 500 µg (0.5 mg). That's approximately 10x the dose given to the rats. However, for the typical '70 kg' male, 0.5 mg represents a per-weight dose of 0.0071 mg/kg, or 7.1 µg/kg. Let's compare to the rats, which generally weigh around 200 g (0.2 kg)…That would translate to a per-weight dose of ~250 µg/kg. Even if you used much older rats, who can weigh as much as twice as much, that would still translate to a dose of 125 µg/kg. So we're looking at a lipid nanoparticle [dose] of ~18–35 times higher (as a rough estimate) than the typical adult human dose.*

The Japanese biodistribution study results are consistent with Pfizer's that was submitted to the European Medicines Agency (EMA) in February 2021. Pfizer also found that the LNP-encapsulated mRNA vaccine was mainly metabolized in the liver and did not enter other tissues easily. They also noted no effects on fertility or ovarian functions.

As the EMA report stated:

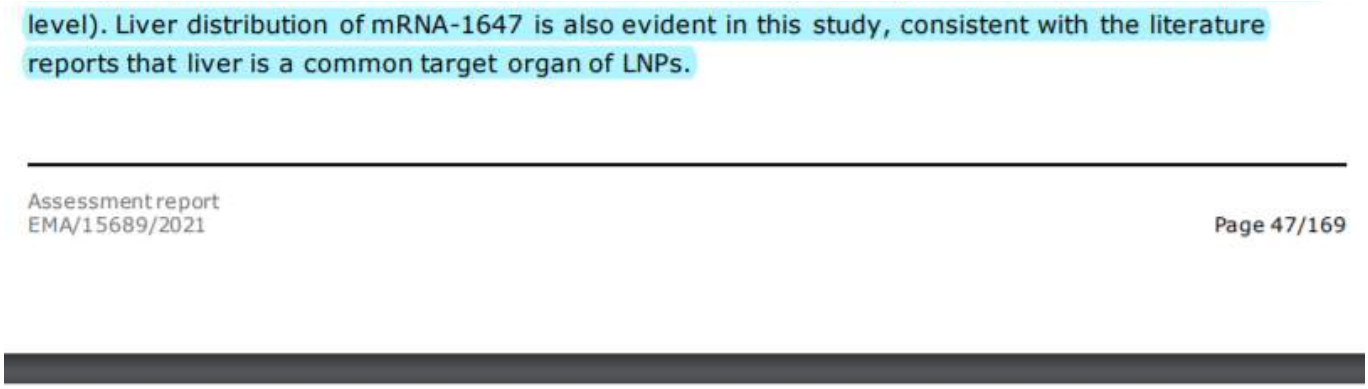
> The biodistribution was also studied in rats using radiolabeled LNP and luciferase modRNA (study 185350). The radiolabeling data, measuring distribution to blood, plasma and selected tissues, of IM injection of a single dose of 50 µg mRNA over a 48-hour period is considered more sensitive than the bioluminescence method and indicate a broader biodistribution pattern than was observed with bioluminescence. Over 48 hours, distribution from the injection site to most tissues occurred, with the majority of tissues exhibiting low levels of radioactivity.
>
> Radioactivity was detected in most tissues from the first time point (0.25 h) and results support that injections site and the liver are the major sites of distribution. The greatest mean concentration was found remaining in the injection site at each time point in both sexes. Low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, distribution was mainly observed to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of radiolabeled LNP+modRNA outside the injection site was greatest in the liver (up to 21.5%) and was much less in spleen (≤1.1%), adrenal glands (≤0.1%) and ovaries (≤0.1%). The mean concentrations and tissue distribution pattern were broadly similar between the sexes. No evidence of vaccine-related macroscopic or microscopic findings were found in the ovaries in the repeat-dose toxicity studies (Study 38166 and Study 20GR142) and no effects on fertility were identified in the DART study.

Source: EMA assessment report on the Pfizer mRNA vaccine; page 47 out of 140. Note: DART stands for Development and Reproductive Toxicology (in rats).

For the Moderna mRNA vaccine, the EMA assessment report has previously released its biodistribution data that also finds no cause for concern. Although the Moderna LNP-encapsulated mRNA vaccine entered various tissues at low amounts, they are mostly gone by the third day.

As stated in the EMA report :

> Concentrations of mRNA-1647 were quantifiable in the majority of tissues examined at the first time point collected (2 hours post-dose) and peak concentrations were reached between 2- and 24-hours post-dose in tissues with exposures above that of plasma. Besides injection site [muscle] and lymph nodes [proximal and distal], increased mRNA concentrations (compared to plasma levels) were found in the spleen and eye. Both tissues were examined in the frame of the toxicological studies conducted with mRNA-1273 final vaccine formulation. Low levels of mRNA could be detected in all examined tissues except the kidney. This included heart, lung, testis and also brain tissues, indicating that the mRNA/LNP platform crossed the blood/brain barrier, although to very low levels (2-4% of the plasma



level). Liver distribution of mRNA-1647 is also evident in this study, consistent with the literature reports that liver is a common target organ of LNPs.

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EMA/15689/2021

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The $T_{1/2}$ of mRNA-1647 was reliably estimated in muscle (site of injection), proximal popliteal and axillary distal lymph nodes and spleen with average $T_{1/2}$ values for all vaccine components of 14.9, 34.8, 31.1 and 63.0 hours, respectively. mRNA-1647 was rapidly cleared from plasma during the first 24 hours with the $T_{1/2}$ estimated in a range of 2.7 - 3.8 hours. The mean concentrations of all vaccine components became undetectable after 24 hours, except for gH, which was detectable up to the last time point of 120 hours but which was also detectable in 2 pre-dose plasma samples. The mRNA constructs were not measurable after maximum 3 days in tissues other than the muscle, lymph nodes, and spleen (~25 hours in brain).

Reference with regards to the mRNA biodistribution is made to the respective adverse findings observed in rat spleens in toxicological studies. No adverse findings were detected in the ophthalmological examinations or the brain/CNS.

Source: EMA assessment report on the Moderna mRNA vaccine; page 47–48 out of 169.

Overall, these biodistribution studies show that the Pfizer and Moderna mRNA vaccines do not enter other tissues or organs easily.

Even if the mRNA vaccines did enter the ovaries in tiny amounts, there's no evidence that ovarian cells can translate the mRNA into spike proteins. Even if ovarian cells somehow managed to manufacture some spike proteins, there's no evidence that this can harm the ovaries. Maybe the spike proteins expressed on ovarian cells degrade within hours or days and disappear in a few days. Animal studies have shown that cells that take up the mRNA vaccine only express the mRNA-encoded proteins on its surface for about 48 hours, which then quickly decline to zero in a few days.

Thus, multiple stringent biochemical conditions and steps must be met to even allow for the tiniest possibility of mRNA vaccine harming the ovaries or other tissues. (I discussed this in-depth for the brain here.)

Addressing the biodistribution concern part II

But critics will question three things: (1) such studies are done in rats; (2) such studies used luciferase-encoding mRNA rather than the spike protein-encoding mRNA; and (3) such studies do not measure the spike proteins. All these critics are, honestly, valid limitations of the biodistribution studies.

- For (1): While rats are mammals like humans, the more convincing animal model is non-human primates like monkeys.
- For (2): Luciferase is a type of protein that lights up under imaging scans, enabling researchers to see where the LNPs had carried the mRNA (that encodes luciferase) into. So, luciferase-based studies only show biodistribution of LNPs, not spike proteins.
- For (3): Since luciferase-based studies don't inform spike protein biodistribution, we still don't know where the manufactured spike proteins go after vaccination. For instance: when the mRNA vaccine instructs muscle cells (at the injection site) to make spike proteins, where will these spike proteins go?

As points (1) and (2) are not really major issues, point (3) needs to be taken more seriously. Thankfully, the mRNA vaccines are designed in such a way that the vaccine-derived spike proteins are anchored onto the cell surface. This means that the manufactured spike proteins (at the instruction of the mRNA vaccine) get stuck on the cell. Hence, spike proteins made by muscle cells at the injection site will stay at the injection site.

"A mutation where amino acids 986 and 987 are replaced with prolines (S-2P), stabilizing the transmembrane-anchored S glycoprotein in the prefusion conformation but still allowing for cleavage of the S1 and S2 subunits, is the approach used in the licensed vaccines mRNA-1273 [Moderna] and BNT162b2 [Pfizer]," immunologists wrote. The keyword is transmembrane-anchored, where the vaccine-derived S glycoprotein (or spike protein) is anchored on the cell membrane.

But some will question that maybe some of the spike proteins get unstuck from the cells. As a result, spike proteins made at the injection site might go and wreak havoc elsewhere. To this end, during the interview, Prof. Bridle cited a study from Harvard Medical School that detected spike proteins in the bloodstream of 11 out of 13 recipients of the Moderna mRNA vaccine on day-1.

Besides the small sample size, this study actually detected very tiny amounts of spike proteins with an ultrasensitive technology that's not often used. Plus, the Harvard study found that spike protein amount in the blood declined after day-1 and was no longer detectable on day-14.

However, this study has been used to push the notion that authorities and experts lied about the vaccine-derived spike proteins being anchored on the cell surface. But all assays (or tools) have a limit of detection. It's just that the Harvard study used a special assay called Simoa that reached the picograms (a trillionth of a gram) level of detection.

Deplatform Disease, a science blog many experts have cited, calculated that the detected levels of spike proteins in the Harvard study were 100,000-times lower than the amount that might cause harm.

While the root cause is unclear, the detected spike proteins in the blood of vaccinated persons in this study might be due to (1) too many anchored spike proteins on the cell surface that a few got released or (2) usual day-to-day cell death that release some of the anchored spike proteins.

Addressing the spike protein toxicity concern

…100,000-times lower than the amount that might cause harm? Yes, many studies using cultured cells and animals have found that the spike protein of SARS-CoV-2 alone — without its genome — is sufficient to harm blood vessels at a certain concentration. (Such concentrations are 100,000-times higher than the amount detected in the Harvard study.)

But all of such studies have one thing in common: they use the spike protein of SARS-CoV-2, not vaccine-derived ones. The one Dr. Malone particularly pushed is from Salk Institute, where researchers injected SARS-CoV-2 spike proteins into hamsters, which injured the lungs and blood vessels due to angiotensin-converting enzyme 2 (ACE2) dysregulation.

This ACE2 dysregulation finding is very crucial. ACE2 is the receptor that the spike protein of SARS-CoV-2 binds to in order to infect human cells. Too much binding and activation of ACE2 throws off the balance in the renin-angiotensin system (RAS). RAS regulates blood pressure and the vascular system, so its dysregulation will upset blood vessel functions.

But Carolyn Machamer, Ph.D., a professor of cell biology, explained:

> *There are changes that were made on purpose that would prevent the spike protein from being able to undergo binding to the [ACE2] receptor and fusion. And so, all this business about toxicity that has been shown for the real spike protein, the one that doesn't have that block, is totally irrelevant for the vaccine.*

Deplatform Disease further added:

> *…the spike protein in the Pfizer and Moderna vaccines is not quite the same as the wild-type spike protein found on the virus. This protein has been prefusion stabilized which means it lacks the ability to change conformation into its postfusion state (via a double proline substitution). This change is thought to significantly enhance the ability of the spike protein to elicit neutralizing antibodies from the immune system, but it also has another functional consequence: the spike protein has drastically less ability to cause syncytium formation… [that may] play a direct role in the disease process of COVID-19.*

All these mean that the vaccine-derived spike proteins, at least for the mRNA ones, are modified so that they won't bind to the ACE2 receptor. No binding means no activation, and there won't be any problems in ACE2 or RAS in vaccinated persons.

A real SARS-CoV-2 infection, in contrast, floods the body with infectious virus particles, each with its own spike proteins that can bind to the ACE2 receptor and dysregulate RAS. One can only imagine the countless amount of spike proteins that Covid-19

deposits in its victims. No wonder blood vessel injury and blood clots are so common in Covid-19 patients.

Closing remarks

I must admit that this article can be heavy to read. Even I would not be able to comprehend all of this without the written explanations of other experts. No wonder it's easy to misinterpret science, and it takes effort to understand the true narrative. And I hope this article provides a coherent read on this complicated matter.

In brief, while it's true that the mRNA vaccine has a broad biodistribution in our body and that the spike proteins of SARS-CoV-2 are dangerous, the narrative doesn't end there. Minuscule amounts of mRNA vaccine entering other tissues or organs are only of minuscule significance, and membrane-anchored spike proteins from the vaccines are not dangerous. Although there will always be people and even experts who insist otherwise, let's stay informed to differentiate between a good and bad scientific argument.

For another article discussing the claims of Covid-19 vaccines being unsafe based on what has been reported to surveillance systems like VAERS, kindly see here: *Underreporting and Post-Vaccine Deaths in the Vaccine Adverse Event Reporting System (VAERS) Explained*.

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An Update on COVID-19 Vaccine Induced Thrombotic Thrombocytopenia Syndrome and Some Management Recommendations

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Abstract

The thrombotic thrombocytopenia syndrome (TTS), a complication of COVID-19 vaccines, involves thrombosis (often cerebral venous sinus thrombosis) and thrombocytopenia with occasional pulmonary embolism and arterial ischemia. TTS appears to mostly affect females aged between 20 and 50 years old, with no predisposing risk factors conclusively identified so far. Cases are characterized by thrombocytopenia, higher levels of D-dimers than commonly observed in venous thromboembolic events, inexplicably low fibrinogen levels and worsening thrombosis. Hyper fibrinolysis associated

with bleeding can also occur. Antibodies that bind platelet factor 4, similar to those associated with heparin-induced thrombocytopenia, have also been identified but in the absence of patient exposure to heparin treatment. A number of countries have now suspended the use of adenovirus-vectored vaccines for younger individuals. The prevailing opinion of most experts is that the risk of developing COVID-19 disease, including thrombosis, far exceeds the extremely low risk of TTS associated with highly efficacious vaccines. Mass vaccination should continue but with caution. Vaccines that are more likely to cause TTS (e.g., Vaxzevria manufactured by AstraZeneca) should be avoided in younger patients for whom an alternative vaccine is available.

Keywords: COVID-19, COVID-19 vaccine, disseminated intravascular coagulation, heparin induced thrombocytopenia, platelet factor 4, thrombosis, thrombotic thrombo-cytopenic purpura, vaccine induced thrombocytopenia and thrombosis

1. Background

A new deadly virus of the coronavirus family was first identified in December 2019 and named SARS-2-CoV-2; this virus caused severe acute respiratory syndrome and is now known as COVID-19. Patients presented with variable symptoms, ranging from asymptomatic carriers to life-threatening/changing consequences. Several vaccines have been developed and are currently being used to reduce disease incidence and mortality in many countries. Lately, rare but life-threatening events such as thrombosis with thrombocytopenia syndrome (TTS) (also called VITT—vaccine induced thrombocytopenia and thrombosis) have been reported with some COVID-19 vaccines. Recent reviews of TTS following COVID-19 vaccinations have not included clinical management guidelines [1,2]. To this end, this review summarizes the available data on the pathophysiology of COVID-19 and thrombosis, the different types of vaccines used to prevent COVID-19, the proposed mechanisms of TTS and some clinical management recommendations.

2. COVID-19 and Thrombosis

Approximately 40–45% of SARS-2-CoV-2 infected individuals are asymptomatic [3], while 14% develop severe illness, and 5% are critically unwell [4]. The clinical course of COVID-19 can be severe and sometimes associated with complications such as venous thromboembolism events (VTEs), severe inflammatory response syndrome, acute respiratory distress syndrome and multi-organ dysfunction syndromes, particularly in the elderly or those with co-morbidities such as diabetes mellitus, renal disease and cardiovascular conditions [5]. More than one-fifth of all patients with COVID-19 develop VTEs [6].

The pathophysiology of COVID-19 associated thrombosis is not completely understood. The associated hyper-inflammatory response produced by COVID-19 is inter-woven with other pathways, involving pro-inflammatory mediators, endothelial damage and direct invasion of cells such as type 2 pneumocytes, and coagulopathies such as disseminated intravascular coagulation (DIC) [7].

Platelets contain chemokines, chemotactic factors, various adhesion molecules, co-stimulatory molecules in their membranes and granules to support their role in haemostasis and immunomodulation. Platelets trigger blood coagulation and inflammation and initiate innate immune responses through the expression of Toll-like receptors (TLRs) to release inflammatory cytokines, trigger adaptive immune responses and activate T cells through the expression of key costimulatory molecules and major histocompatibility complex (MHC) molecules. Platelets release large amounts of

extracellular vesicles which can interact with multiple immune mediators. Therefore, the function of platelets extends beyond aggregation, and the interaction with haemostasis, inflammation and the immune response results in the amplification of the body's defence mechanisms [8].

An abnormal viral coagulopathy typically results in a pro-thrombotic phenotype that can cause micro-thrombi and macro-thrombi, resulting in both venous and arterial occlusions [9]. There have also been rare isolated cases of thrombotic thrombocytopenic purpura (TTP) [10]. Thrombotic complications were reported early in our understanding of viral induced clinical syndromes of COVID-19 infection, and they are now a leading cause of death during the COVID-19 pandemic.

Early research identified various laboratory parameters to help stratify thrombotic risk, resulting in many hospitals in the United Kingdom (UK) adopting a COVID-19 test panel consisting of D-dimer tests, clotting screen, fibrinogen, serum ferritin, lactate dehydrogenase and troponin levels. This enabled VTE prophylaxis to be adapted to individual patient risk, with low molecular weight heparin used as an anticoagulant for inpatients and continued post discharge for periods of up to 12 weeks. Oral anticoagulants are also useful in some patients post discharge [11].

Thrombocytopenia occurred in almost one in three COVID-19 (31.6%) infected inpatients and at a greater rate in individuals with severe COVID-19 (57.7%) [12]. The majority of patients presented with mild thrombocytopenia, with some cases of severe thrombocytopenia requiring a careful balance between bleeding and thrombotic risk. Several pathophysiological mechanisms have been postulated for thrombocytopenia in such cases. These include bone marrow suppression that is somewhat similar to that observed in sepsis; there is likely direct infection of the marrow by SARS-2-CoV-2, affecting megakaryocytic and haematopoietic precursor cell function and synthesis. Other mechanisms include reduced thrombopoietin synthesis in the liver, generation of micro-thrombi with subsequent platelet consumption and, finally, immune thrombocytopenia (ITP) resulting in peripheral platelet destruction [13]. Infection with COVID-19 and injury to the type II alveolar cells results in increased expression of p53, suppression of uPA and uPAR and increases in PAI-1. In addition, the type II alveolar cells are also the source of surfactant; viral infection diminishes the release of surfactant. There is a temporal relationship between COVID-19 infection and fibrinolysis. In the acute phase of the infection, the inflow of fibrinogen and coagulation factors result in fibrin deposition and hyaline membrane formation. Acute inflammatory cytokines consisting of IL-1, IL-6 and IL-17A upregulates plasminogen activator inhibitor-1 (PAI-1) and suppresses the expression of urokinase-type plasminogen activator (uPA) and urokinase-type plasminogen activator receptor (uPAR). Reduced surfactant levels activate the p53 pathway, resulting in increases in PAI-1 and decreases in uPA and uPAR. The fibrinolytic balance is then shifted to a hypofibrinolytic state, which stimulates fibrin deposition, hyaline membrane formation and microvascular thrombosis [14,15,16].

3. Vaccinations

The World Health Organization (WHO) estimates that over 200 million people have so far been diagnosed with COVID-19, with over 4 million deaths worldwide [17]. The identification of this virus stimulated a global race to develop a vaccine. The UK was the first country to start a mass vaccination campaign with Comirnaty (the Pfizer-BioNTech vaccine, Mainz, Germany) for COVID-19 in December 2020; this was then quickly followed by approval of Vaxzevria (AstraZeneca, Oxford, UK). The Moderna COVID-19 vaccine was approved in January 2021 [18]; other vaccines include Sputnik V (Gamaleya Institute, Moscow, Russia), BBBP-CorV (SinoPharm, Shanghai, China), Janssen COVID-19 vaccine (Johnson & Johnson, New Brunswick, NJ, USA) and Covovax (Novavax, Gaithersburg, MD, USA).

There are currently at least nine different technology platforms used to create vaccines against COVID-19. Most vaccine candidates undergoing clinical trials focus on the coronavirus spike protein and its variants as the primary antigen of COVID-19 infection. These methods involve nucleic acid technologies (nucleoside-modified messenger RNA and DNA), non-replicating viral vectors, peptides, recombinant proteins, live attenuated viruses and inactivated viruses [19].

The vaccine types are listed as follows:

- **RNA vaccines**: An RNA vaccine contains RNA which, when introduced into a tissue, acts as messenger RNA (mRNA) in order to cause cells to synthesize spike proteins and stimulate an adaptive immune response. RNA vaccines often, but not always, use the nucleoside-modified messenger RNA. The delivery of mRNA is achieved by using lipid nanoparticles to protect the RNA strands and to facilitate their absorption into cells. The best-known examples are the Comirnaty and the Moderna COVID-19 vaccines [20].
- **Adenovirus vector vaccines:** These vaccines are examples of non-replicating viral vector vaccines that use an adenovirus shell containing DNA encoding a SARS-CoV-2 protein. These vaccines are non-replicating and produce only the antigens that elicit a systemic immune response [21]. Examples of this group include Vaxzevria, Sputnik V [22], Convidecia (CanSino Biologics, Tianjin, China) and Janssen COVID-19 vaccines [23].
- **Inactivated viral vaccines:** These vaccines include viral particles grown in culture and subsequently inactivated toward non-pathogenic particles with immunogenic properties. Vaccines of this type include CoronaVac (Sinovac Biotech, Beijing, China); BBIBP-CorV and WIBP-CorV (Sinopharm, Beijing, China); Covaxin (Bharat Biotech, Hyderabad, India); and CoviVac (Chumakov Centre, Moscow, Russia) [24].

Despite recent surges of COVID-19 in some countries (e.g., Israel, UK) that have been fueled by more transmissible variants, mass vaccination programs have nonetheless been generally successful with fewer deaths reported after implementation of the vaccination program. A single inoculation with Comirnaty or Vaxzevria in the UK resulted in an 85% reduction in hospitalization from COVID-19 infections [13]. It is estimated that programs in the UK (Comirnaty and Vaxzevria inoculations) have prevented at least 10,400 deaths as of March 2021 [25]. The number of deaths in the UK within 28 days of a positive COVID-19 test has been steadily falling since mid-January 2021.

Data from the official UK government dashboard suggests that deaths from coronavirus in those who are 80 years or older in England fell by 62% between 24 January and 12 February 2021 [26]. This compares to a drop of 47% in those aged between 20 and 64 years old and of 51% in those between aged 65 and 79 years old. Further evidence comes from Scotland which has seen deaths from COVID-19 falling in all locations, with the fastest decreases occurring in long-term care homes where deaths fell by 62% in the three weeks leading to 14 February 2021, approaching a level last observed near the end of October 2020. Older residents in care homes were prioritized when the vaccination program began. The report from the National Records of Scotland shows that the number of deaths in those aged 85 and over has fallen by 45%, which is steeper than in younger age groups [27].

4. Vaccines and Serious Adverse Events

Adverse events have been reported with most of the COVID-19 vaccines; these are typically mild (pain at the injection site, myalgia, headaches, fatigue and tiredness) and usually resolved within a few days. The most frequent adverse reactions in adolescents 12 to 15 years of age were injection site pain

(>90%), fatigue and headache (>70%), myalgia and chills (>40%) and arthralgia and pyrexia (>20%). These are the data published and regularly updated on UK government central adverse drugs reactions reporting systems [28].

However, some patients experienced rare side-effects that sometimes were fatal. The early adoption of Comirnaty as frequently associated with reports of anaphylaxis type reactions and some safety concerns were raised, resulting in some recommendations for increased monitoring of patients after receiving the injection and even avoiding Comirnaty in those with a history of allergic reactions. These measures substantially reduced the rates of serious adverse events.

Attention has now centred on VTEs that occur 5 to 24 days after the first inoculation with Vaxzevria. It is important to note that VTE is not an uncommon event and can occur naturally at any age. Even as new waves of COVID-19 emerge in many countries, apprehension remains relative to the safety and efficacy of Vaxzevria, with several countries in the European Union either entirely suspending inoculations or restricting its use to selected age groups [20,21]. For example, Austria suspended the use of a single batch (ABV5300) of vaccines pending further investigation [29], while the UK has advised that an alternative should be sought for those aged below 30 years, and Germany has suspended its use in those aged 60 years and under [30]. At the same time, these concerns led France and Germany to consider using Sputnik V [31]. The marketing authorization holder report concluded in its observed-to-expected analysis that the number of deep vein thrombosis (DVT) or pulmonary embolisms (PE) cases observed was in fact significantly lower than expected, suggesting no causal association between VTEs and Vaxzevria [32]. However, the pharmacovigilance risk assessment committee stressed caution in this interpretation due to concerns related to quality, sensitivity and appropriate stratification in the marketing authorization holder report. The recently approved Janssen COVID-19 vaccine (which also uses an adenovirus vector) includes VTEs in its risk management plan [33].

5. Thrombosis with Thrombocytopenia Syndrome

TTS is an extremely rare but increasingly recognized serious adverse event related to unusual sites of thromboembolism, such as cerebral venous sinus thrombosis (CVST) or abdominal thromboses (splanchnic, mesenteric or portal vein), all of which are associated with thrombocytopenia. ‘CVST with thrombocytopenia’ is a rare subtype of cerebrovascular accident, with an incidence of 5.0 per million in those receiving Vaxzevria and 4.1 per million in those receiving mRNA based vaccines, and the prevalence is three times greater in younger to middle aged women (mean age 35) [34,35,36,37]. An international study on cerebral venous and dural sinus thrombosis, as one of the largest prospective cohort studies on CVST, confirmed this gender bias for CVST. The presentation of CVST was initially described in case-controlled studies, but later confirmed in a meta-analysis (pooled odds ratio: 5.59) that proposed gender-specific risk factors such as oral contraceptives [38], hormone replacement therapies and pregnancy (including the post-partum period) [39]. This is further supported by epidemiological studies demonstrating a correlation between the use of oral contraceptive and CVST in younger to middle aged females [40]. The epidemiology of CVST has not been carefully studied, making it difficult to comprehend and compare the data in the context of the COVID-19 era.

At least 12 cases of CVST with thrombocytopenia have been reported in the USA from 2 March to 21 April 2021 [41], and case reports were also published from European countries [42,43]; starting in the first week of April 2021, with a total of 169 cases of CVST with thrombocytopenia reported among 34 million people vaccinated Vaxzevria in the European Economic Area (EEA) and the UK [44].

Recent estimates suggest a 100-fold increased risk of developing a CVST after being infected with COVID-19, with a third of cases occurring in those aged less than 30 years old [37]. A non-peer reviewed report identified a 30-fold increased risk of splanchnic vein thrombosis in recipients of mRNA based vaccines such as the Comirnaty or Moderna COVID-19 vaccines (1 per 1.6 million for Vaxzevria recipients vs. 1 per 44.9 million for mRNA vaccines) [37]. It is important to note that the report focusses on cases of CVST and splanchnic thrombosis without associated thrombocytopenia.

A Danish population study of mostly female healthcare workers who received Vaxzevria identified no clear causal association between the vaccine and blood clots [45]. Records on the time course of VTEs in relation to the vaccine administration are unknown. It is also unclear if the patients who developed VTE were infected with COVID-19 (asymptomatic or otherwise) prior to or immediately before immunity developed [45]. It is difficult to apply data from this Danish study to other regions or to gauge the prevalence of different COVID-19 strains or to determine the viral pathogenicity and associated secondary complications. The underlying co-morbidities or pre-existing risk factors such as a history of previous VTEs or thrombophilia were also not considered. The rapid spread of the COVID-19 pandemic limited the Danish study to only pre-COVID-19 era data for the comparisons of VTEs. Importantly, the study reinforced early concerns about the unusual sites of thrombosis with thrombocytopenia shortly after receiving Vaxzevria.

The overall interim recommendation and shared agreement between the WHO, European Medicines Agency (EMA) and MHRA is that the intended benefits of receiving a vaccine for COVID-19 still far outweighs its rare side-effects. More recently, TTS was reported in six patients receiving the Janssen vaccine [46]. Vaxzevria and the Janssen vaccine both consist of recombinant adenoviral vectors based on a chimpanzee adenovirus (Vaxzevria) or a human adenovirus (Janssen vaccine) that encodes the SARS-CoV-2 spike protein immunogen. While a few individuals receiving the Moderna COVID-19 vaccine lipid nanoparticle encapsulated mRNA vaccine were diagnosed with CVST, the FDA reports that there are currently no reports of patients who developed TTS after being vaccinated with Comirnaty or the Moderna COVID-19 vaccine. The striking clinical similarities of TTS and heparin-induced thrombocytopenia (HIT) and the uniformly positive platelet factor 4 (PF4)-heparin enzyme-linked immunosorbent assays (ELISAs) in these cases may be due to circulating PF4-reactive antibodies that can directly activate platelets in the absence of heparin. It is important to note that non-ELISA-based commercial assays (e.g., HemosIL AcuStar HIT-IgG, HemosIL HIT-Ab, Diamed PaGIA gel and STic Expert assays) are weakly sensitive for anti-PF4 antibodies in samples from patients with suspected TTS [47]. Intravenous immune globulin and a monoclonal antibody to the Fc receptor can block platelet activation by these antibodies, at least in vitro. These clinical and laboratory features are similar to rare cases of an HIT-like syndrome previously described after some medications or infections in patients not receiving heparin [48].

6. Possible Pathophysiology of TTS

Antibody-mediated thrombotic thrombocytopenia during COVID-19 is presumed to be an autoimmune reaction induced by SARS-CoV-2. The high incidence of thrombotic thromboembolic events during severe COVID-19 results in the frequent administration of heparin in affected patients [49]. HITT is a possible cause when thrombocytopenia is associated with thrombosis in this setting [50]. Several studies report the presence of anti-PF4/heparin antibodies in COVID-19 patients, these antibodies can also be found without any history of heparin administration [51]. Furthermore, these antibodies do not always activate platelets in the presence of heparin/PF4 complexes [52], although they can do so in presence of PF4 alone [53], suggesting that their production is likely unrelated to HIT [54]. Related to this notion is that IgG antibodies in the serum of severe cases of COVID-19 infections induce platelet

apoptosis and procoagulant activity via FcγRIIA (CD32) receptor-dependent mechanisms [55]. The antigenic specificity of these antibodies is unclear, although it is likely that at least some of them are directed against PF4.

The model we support is based on the hyperactivation of platelets during COVID-19, which results in the release of PF4 into the circulation [56]. Circulating PF4 forms complexes with endogenous polyanionic proteoglycans released by damaged endothelial cells. Syndecan-1 and endocan are potential proteoglycans candidates as their serum levels are increased in severely ill COVID-19 patients in association with other markers of endothelial injury [57]. Complexes formed between PF4 and endothelial cell-derived polyanionic proteoglycans can then stimulate extra follicular B cells that produce anti-PF4 antibodies, as suggested by previous reports that autoimmune responses elicited by extra follicular B cells may be involved in the pathophysiology of severe COVID-19 [58].

A recent study by Kowarz and colleagues suggested a different slicing mechanism for spike open reading frame in adeno vector vaccines, which results in soluble spike variants that can initiate severe side effects when binding to ACE2-expressing vascular endothelial cells. They compared this phenomenon to thromboembolic events caused by spike protein encoded by the SARS-CoV-2 virus and termed this possible mechanism as the “Vaccine-Induced COVID-19 Mimicry” syndrome (VIC19M syndrome) [59].

Anti-phospholipid antibodies could also additionally contribute to platelet activation, as suggested by increases in anti-SARS-CoV-2 antibodies in other viral diseases [60]. The rare prothrombotic thrombocytopenic events following vaccination with Vaxzevria (~1 in 100 000 recipients) has a clinical presentation similar to HIT, suggesting that a vaccine-induced autoimmune response to PF4 may be plausible. Supporting this hypothesis is a recent study identifying platelet-activating anti-PF4 antibodies in the sera of patients suffering from unusual thrombotic events associated with thrombocytopenia within 4 to 16 days after receiving Vaxzevria [61]. The progression of this possible vaccine-induced anti-PF4 autoimmune response could be related to mechanisms similar to those for prothrombotic thrombocytopenia induced by the SARS-CoV-2 virus itself. Other possible mechanisms include adenoviral vector entry in megakaryocytes and the subsequent expression of spike protein on platelet surfaces and also direct platelet activation by the vector [62].

7. Heparin Induced Thrombocytopenia with Thrombosis

HIT with thrombosis is a severe prothrombotic condition that occurs in less than five percent of patients receiving intravenous unfractionated heparin, less commonly with low molecular weight heparin and usually between 4 and 10 days after initiation of treatment [63]. Thrombocytopenia is a hallmark of HIT with thrombosis, with platelet counts decreased by more than half in most patients. After exclusion of other causes of thrombocytopenia and HIT, a clinical diagnosis of HIT with thrombosis is established by immune enzymatic detection of circulating antibodies to PF4/heparin complexes, followed by a functional assay demonstrating platelet activation by the patient’s serum in the presence of heparin [63]. Risk factors for HIT with thrombosis include the following: (1) the duration of heparin therapy (>5 days); (2) the type (unfractionated heparin > low molecular weight heparin > fondaparinux) and dosage of heparin; (3) the indication for treatment (surgical and trauma patients at highest risk); and (4) gender (female > male) [64]. Thrombotic complications can develop in unusual locations such as cerebral venous sinuses [65].

The specificity of PF4 autoantibodies causing HIT with thrombosis was confirmed in studies demonstrating that the epitope recognized on PF4 tetramers was exposed after interaction with heparin or other long polyanions [54]. The injection of heparin releases PF4 [66], resulting in the assembly of

PF4/heparin complexes which activate complement and bind circulating B lymphocytes in a complement-dependent manner [67]. B cells responsible for the synthesis of PF4 autoantibodies rapidly mount an IgG immune response following their first exposure to heparin [68]. B cells that produce anti-PF4 antibodies are present in healthy individuals in an anergic state in which there is an absence of an immune response to an antigen such as PF4. This B cell tolerance could be disturbed after exposure to heparin and also in some inflammatory conditions [69], where anti-PF4 IgG antibodies elicit thrombus formation and thrombocytopenia via multiple mechanisms (Figure 1).

Open in a separate window

Figure 1

Diagrammatic representation of the mechanism by which HIT can cause thrombosis. (HIT: heparin induced thrombocytopenia.)

Immune complexes assembled with PF4 bound to heparin induce platelet activation and aggregation by crosslinking with FcγRIIa receptors [63]. The pathogenesis of HIT is shown in the schematic Figure 1. Anti-PF4 antibodies also activate the pro-coagulant activity of monocytes by cross-linking their FcγR1 receptors and increase the thrombotic activity of endothelial cells via recognition of PF4 firmly attached to surface proteoglycans [70]. Thrombocytopenia results from enhanced apoptosis and clearance of antibody-decorated platelets [71]. The similarities and differences between HIT with thrombosis and TTS are highlighted in Table 1.

Table 1

Comparison between HIT with thrombosis and TTS.

	HIT with Thrombosis	TTS
Responsible Agent	Heparin, more likely with unfractionated rather than low molecular weight heparin. Acidic glycosaminoglycan 10–15 kilodaltons.	Vaxzevria. Adenovirus vector (approximately 150 megadaltons) or other vaccine constituent.
Onset	5–14 days following administration of heparin [63].	4–28 days following Vaxzevria vaccination [72], although majority of reported cases occurred 5–16 days following administration [61].
Presentation	Thrombosis and thrombocytopenia. Usually venous thrombosis, which can extend to unusual sites (e.g., cerebral venous sinus thrombosis, splanchnic vein thrombosis) [63].	Thrombosis and thrombocytopenia. Preponderance of unusual sites of venous thrombosis in the currently reported cases [61].
Pathophysiology	Conformational change of PF4 upon binding heparin known to be crucial to the generation of HIT antibodies and the subsequent activation of platelets [63].	Unknown.
Investigations	HIT antibodies detected with ELISA. Functional platelet assays used to confirm diagnosis [63].	HIT antibodies detected with ELISA [61].

HIT: heparin induced thrombocytopenia; TTS: thrombosis with thrombocytopenia syndrome; ELISA: enzyme-linked immunosorbent assay; PF4: platelet factor 4.

8. Prevalence of Platelet Factor 4 Antibody in the General Population

An assessment of immunoassay results (11 studies; 860 subjects) on the prevalence of PF4/heparin antibody (IgG/M/A) in healthy subjects concluded that commercial immunoassays are able to detect PF4/heparin antibodies in 1.0–4.3% of healthy subjects [73]. Another prospective study measured PF4/heparin antibody levels in approximately 4000 blood donors by using a commercial enzyme-linked immunosorbent assay for initial findings and then repeated for confirmatory testing. Antibody levels were initially detected in 249 of 3795 donors (6.6%; 95% confidence interval [CI], 5.8–7.4%) and then confirmed in 163 of 3789 evaluable donors (4.3%; 95% CI, 3.7–5.0%). Of the 163 repeated positive samples, 116 (71.2%) were low positives, and 124 (76.1%) exhibited heparin-dependent binding. Predominant isotypes of intermediate to high seropositive samples (OD > 0.6) were IgG (20/39 (51%)), IgM (9/39 (23%)) and indeterminate (10/39 (26%)). The high background seroprevalence of PF4/heparin antibody (4.3–6.6%) with the preponderance of low (and frequently nonreproducible) positives in blood donors suggests the need for greater assay calibration, categorization of antibody levels and evaluation of the clinical relevance of “naturally occurring” PF4/heparin antibodies [74].

However, although anti-PF4–polyanion antibodies are common—for example, they are detected in 25 to 50% of patients after cardiovascular surgery—HIT is uncommon. Cerebral venous sinus thrombosis or thrombi in abdominal vessels rarely develop in patients with HIT. The prevalence of thrombocytopenia and anti-PF4 antibodies was studied in 492 Norwegian health care workers 11 to 35 days after Vaxzevria vaccination; anti-PF4 antibodies with optical density values over a cutoff of ≥0.4 were detected in six (1.2%) vaccines [75]. This suggests that our understanding of the pathogenesis of TTS is incomplete, and the usefulness of measuring pathogenic anti-PF4-related antibodies in all vaccine recipients is unclear. Data are needed to confirm that the anti-PF4 antibodies described here can cause thrombosis and thrombocytopenia in vivo [76].

9. Other Differential Diagnoses to Consider

The unusual clinical presentation of simultaneous thrombosis with thrombocytopenia, while appearing to be contradictory, is not a medical curiosity. There are a number of serious medical conditions where this can occur, as described below.

9.1. Microangiopathic Haemolytic Anaemia

Microangiopathic haemolytic anaemia describes non-immune (negative Coomb's Test) haemolysis (schistocytes) and red blood cell fragmentation on a peripheral blood film and can occur in many conditions such as prosthetic heart valves and primary thrombotic microangiopathies (TMAs), including thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome, complement mediated-TMA and also drug-induced-TMA [77].

Although both TTP and hemolytic uremic syndrome have many similarities, they have different aetiologies. TTP is more common in adults and is caused by severe ADAMTS13 (a Von Willebrand factor cleaving protease) deficiency, thereby invoking potent systemic thrombotic activity [78]. Only 40% of all TTP cases present with the classical 'pentad' of thrombosis, thrombocytopenia, fever, renal impairment and neurological symptoms [79]. By contrast, haemolytic uremic syndrome is caused by the Shiga-like toxin and mostly affects children. Renal function is invariably always impaired with less than one-third of all patients developing a fever or having neurological symptoms [79]. Primary TMA is a medical emergency with high mortality and morbidity and, as such, requires astute recognition and prompt treatment. The PLASMIC score is a validated tool using easily testable blood markers to predict the likelihood of TTP [80]. In the absence of other explainable causes whilst awaiting ADAMTS13 results, a PLASMIC score >5 warrants urgent empirical treatment such as using plasma exchange and corticosteroids. Other treatments include rituximab and anti-von Willebrand factor (caplacizumab) [81,82], usually at a specialized tertiary medical center. Other systemic disorders can also present as microangiopathic hemolytic anemia; the examples include preeclampsia and HELLP syndrome (a complication of pregnancy accompanied by hemolysis, increased liver enzymes, low platelet counts and severe hypertension), infection, solid or stem cell transplant recipients, systemic rheumatic diseases and catastrophic antiphospholipid syndrome (a rare hypercoagulative state caused by a catastrophic complement activation resulting in widespread production of microthrombi). Management of these cases requires the treatment of the underlying disorders and do not usually require TMA-specific interventions [83].

9.2. Disseminated Intravascular Coagulopathy

There have been unusual case reports of COVID-19 patients with 'DIC like' coagulopathies [84]. The mechanisms are not clearly understood but current hypotheses suggest endothelial injury related to SARS-CoV-2 invasion. DIC is a consumptive coagulopathy resulting from unregulated and abnormally

activated coagulation and fibrinolysis and can range from acute to subclinical presentations. DIC always occurs in secondary underlying disorders such as infections, malignancies and severe intravascular hemolysis, as observed in an acute hemolytic transfusion reaction [85]. The generation of thrombin and the consumption of coagulation factors including platelets results in variable phenotypic expression of bleeding and/or clotting. Thus, while acute management is challenging, it is usually guided by the dominating phenotype. Unlike in TMA where the clotting profile is almost universally normal, patients with DIC present with prolonged prothrombin time and activated partial thromboplastin time with low fibrinogen levels. The severity of microangiopathic hemolysis is generally lower than TMA's [86].

10. Thrombocytopenia following Vaccine Administration in Children

Thrombocytopenia is an adverse event associated with vaccine administration and can limit vaccine use due to several factors such as uncertainly about which vaccines are likely causative triggers, its incidence and severity, the risk of chronic disease and the possibility of recurrences after additional doses of the same vaccine. Vaccine-related thrombocytopenia is considered to be of immune origin because antibodies can be detected on platelets in about 79% of cases, making it a part of secondary ITPs in the subgroup of drug-induced ITPs. Thrombocytopenia following vaccine administration depends on the development of autoantibodies that cross-react with naturally present antigenic targets on platelets [87]. A comprehensive review on vaccine administrations and very rare development of ITP in children concluded that it can occur after the administration of vaccines. The only vaccine that is currently known to cause ITP is the mumps, measles and rubella (MMR) vaccine, but again the incidence of ITP is significantly lower than caused by mumps, measles and rubella, which are the diseases for which the vaccine provides 99% protection. Thus, ITP, regardless of its association with vaccination, should not limit the use of MMR vaccines, and a careful risk-benefit analysis performed particularly in children with persistent or chronic ITP should be performed. It is possible that newer technologies such as reverse vaccinology could prepare protein vaccines with a lower risk of causing ITP [88].

The role of adenoviral vectors in the development of thrombocytopenia has been described early in the pandemic. Adenoviral vectors remain ideal candidates as vaccine carriers and in cancer gene therapy due to their ability to effectively activate CD8+ T cells [89]. Early innate immune responses related to adenoviral vectors are associated with the activation of vascular endothelial cells, resulting in the release of ultra-large-molecular-weight multimers of the von Willebrand factor, a blood protein that is critical for platelet adhesion. This also activates platelets and induces the exposure of the adhesion molecule P-selectin and formation of platelet-leukocyte aggregates, ultimately causing thrombocytopenia and, thus, a risk for bleeding [90].

11. Post COVID-19 Syndrome and Risk of Thrombosis

Scientific and clinical evidence is evolving on the subacute and long-term effects of COVID-19, which can affect multiple organ systems [91]. Early reports suggest residual effects of SARS-CoV-2 infection, such as fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia and decline in quality of life [92]. Cellular damage, a robust innate immune response with inflammatory cytokine production, and a pro-coagulant state induced by SARS-CoV-2 infection may contribute to these sequelae [93]. Long-term outcomes of patients with COVID-19 and VTE are unknown. A recent prospective study evaluated long-term bleeding, recurrence and death of COVID-19-associated VTE reported high rates of mortality (24%) and major bleeding (11%) in the first 30 days. ICU admission, thrombocytopenia and cancer indicated a poor prognosis [94].

12. Current Management Recommendations

The most recent updated recommendations from the Expert Hematology Panel (UK) and the American Society of Hematology suggest careful assessment of patients who present with symptoms of thrombosis 4–30 days after receiving Vaxzevria or Janssen COVID-19 vaccine [48,72]. The four diagnostic criteria below must be met:

1. Receipt of a COVID vaccine (Janssen/Vaxzevria) 4 to 30 days previously;
2. Thrombosis (often cerebral or abdominal);
3. Thrombocytopenia;
4. Positive PF4-HIT test using ELISA.

While the incidence of this thrombotic complication remains very rare, the risk of death and serious effects including thrombosis due to contracting COVID-19 nonetheless remains high. Current recommendations from both the UK and American regulators are for urgent medical evaluation for TTS if any of the following symptoms develop 4 to 30 days after vaccination: severe headache, visual changes, abdominal pain, nausea and/or vomiting, backache, shortness of breath, leg pain or swelling, petechiae or easy bruising.

If TTS is suspected, urgent diagnostic workup should be arranged, including a complete blood count with a platelet count and peripheral blood smear, imaging for thrombosis based on signs/symptoms, PF4-ELISA (HIT assay) using blood drawn prior to any therapies and fibrinogen level.

The Expert Hematology Panel (UK) classifies clinical presentations as follows:

> **Possible case:** Any patient presenting with acute thrombosis and new onset thrombocytopenia within 28 days of receiving COVID-19 vaccination;
>
> **Unlikely case:** Patients with either a reduced platelet count without thrombosis or with a D-dimer count at or near normal levels (<2000 µg/L) but with and normal fibrinogen (2–4 g/L) levels;
>
> **Probable case:** Elevated D-dimers (>4000 µg/L > 2000 with a strong clinical suspicion);
>
> **Definite case:** Cases usually present 5–28 days after vaccination and are characterized by thrombocytopenia, raised D-dimers and thrombosis, which often rapidly deteriorate.

There is a high preponderance of cerebral venous sinus thrombosis. Portal vein and splanchnic vein thrombosis, pulmonary embolism and arterial ischaemia are also common, as are adrenal infarction and hemorrhage. Intracranial hemorrhage can be significant and unexpected. Typical laboratory features include a low platelet count ($<150 \times 10^9$/L) and greatly increased D-dimer levels (above those usually expected for VTE) and many develop low fibrinogen levels contrary to hyper-fibrinogenemia observed in the acute stages of COVID-19 [95]. Antibodies associated with PF4 have been identified as in HIT but without exposure to heparin treatment. Antibodies associated with PF4 are detected by ELISA HIT assays but rarely by other HIT assay methods. The platelet count at which it is safe to initiate anticoagulation therapy is made on a case-by-case basis. The Expert Hematology Panel (UK) and American Society of Hematology revise their guidance on a regular basis as evidence emerges, with the following general recommendations: (1) Low fibrinogen or bleeding associated with TTS should not preclude anticoagulation, particularly if the platelet count is >20,000/µL or increasing following intravenous immunoglobulin initiation; (2) concurrent replacement of fibrinogen in patients with

bleeding and/or very low values should be considered; (3) avoid platelet transfusions due to the similarities with HIT where platelets transfusion is relatively contraindicated unless bleeding and associated with paradoxical thrombosis. However, risk/benefit assessment in individual patients with serious bleeding and/or the need for surgical intervention may favour platelet transfusion following the initiation of intravenous immunoglobulin (IvIG), non-heparin anti-coagulation and fibrinogen replacement if level < 1.5 g/L. Platelet transfusion is an option to support therapeutic anticoagulation. However there is insufficient evidence to state that this is superior to critical care argatroban (low dose) without platelet transfusion. If urgent neurosurgery is required, then transfuse the platelets to >100 × 10^9/L and cryoprecipitate to maintain fibrinogen >1.5 g/L [48,72].

Management involves all of the following, including probable cases while awaiting confirmatory tests:

- **Intravenous immunoglobulin**: Initiate urgently as this could most likely influence the disease process, using 1 g/kg (over two days if needed) irrespective of the degree of thrombocytopenia, and continue to review the clinical course. Steroids can also be helpful although it is unclear if its benefits outweigh potential harm.
- **Anticoagulants**: Use non-heparin-based therapies such as direct acting oral anticoagulants, fondaparinux, danaparoid or argatroban depending on the clinical presentation. Bleeding and thrombotic risk needs to be carefully assessed; low dose treatment with fondaparinux or critical illness dose argatroban may be appropriate when platelet count is <30 × 10^9/L.
- **Plasma exchange**: May be considered in cases of severe or resistant disease. This may be required daily for up to 5 days if recovery is delayed.
- **Transfer patients with cerebral venous thrombosis**: Transfer to a neurosurgical unit and consider early recourse to neuroradiology and/or neurosurgery in cases of further deterioration/ bleeding. If urgent neurosurgery is required then transfuse platelets (to >100 × 10^9/L) and cryoprecipitate to maintain fibrinogen levels at >1.5g/L.
- While it is unclear if platelet transfusion will exacerbate cerebral venous thrombosis, the risks/benefits are unknown in patients with platelets <50 × 10^9/L on anticoagulation treatment and who have secondary cerebral bleeding not requiring procedures; therefore, clear advice cannot be given at present. Consider platelet transfusion in life threatening bleeding situations.
- It is unknown whether heparin exacerbates the condition but until further evidence is available, heparin is best avoided (including line flushes) as the syndrome mimics HIT with thrombosis.
- Replace fibrinogen to ensure levels do not drop below 1.5 g/L (using fibrinogen concentrate or cryoprecipitate where fibrinogen concentrates are not readily available).
- For patients who are refractory relative to repeated doses of intravenous immune globulin treatment and plasma exchange, treatment with rituximab can be considered although there is currently no evidence of its efficacy in TTS.

Further management, including intravenous immune globulin and subsequent immunomodulation, hinges on the diagnosis of thrombotic complications in the presence of thrombocytopenia driven by a positive PF4 test. TTS should also be considered in the absence of signs, symptoms or imaging documenting thrombosis with a low platelet count and greatly increased or progressively increasing D-dimer counts or a positive PF4-ELISA test. If the PF4-ELISA produces a negative result and if there is

no thrombocytopenia, then TTS is ruled out. The advice is to treat for standard VTEs in such cases. Thrombocytopenia with negative PF4-ELISA in the absence of thrombosis should be managed as possible ITP.

Patients presenting with thrombosis and a normal platelet count post-vaccination might be in an early stage of TTS. These patients should be continuously assessed for tbe development of thrombocytopenia. The use of non-heparin anticoagulant may be indicated 4 to 30 days after receiving either the Vaxzevria or Janssen COVID-19 vaccine [48,72].

13. Evolving Clinical and Laboratories Studies

As this continues to be an evolving condition, additional data collection is underway, including serial PF4 testing, serum sample for COVID-19 antibody testing and whole genome sequencing used in tandem with standard diagnostic criteria. The addition of antiplatelet therapy to standard anticoagulation treatment may add some clinical benefits for young patients presenting with premature coronary artery disease or other arterial thrombotic conditions. As more clinical cases are being managed in the UK, argatroban monitoring has proved to be logistically cumbersome as activated partial thromboplastin time correlates poorly with benefits of argatroban (a small molecule direct thrombin inhibitor) due to high levels of Factor VIII [72]. Using argatroban can also provide false low fibrinogen levels when using some Clauss fibrinogen assays. Thus, it is recommended to use fondaparinux or another direct oral anticoagulant once bleeding risks are reduced [72].

14. Some Unanswered Questions about Vaccine Induced Thrombocytopenia and Thrombosis

- It appears that these clots are primarily caused by autoantibodies against PF4 (currently, it is unclear why these form). These are probably IgG and can cross the blood–brain barrier, causing platelets to aggregate and collect in specific locations such as the cerebral sinus vein. ‘HIT with thrombosis’ is another rare disorder with the same constellation of findings (low platelet counts and thrombosis) that is caused by treatment with heparin but at a much higher frequency (1–5%) than TTS. Whereas HIT with thrombosis has clear risk factors, no clear risk factors have so far been identified for TTS. Heparin complexes with PF4 during HIT with thrombosis, which then attaches to platelets to trigger Fc receptor mediated platelet activation. Much about TTS still remains unclear. It appears that the mechanisms of TTS and HIT with thrombosis are quite similar in being mediated by PF4 antibodies, but clots in the brain are uncommon in HIT with thrombosis for reasons that are not clear. One possibility is that there may be differences in blood flow patterns and the size of the platelet aggregates in the two conditions.
- It is unclear if there is a relationship between the new variants of COVID-19 and TTS when using adenovirus vector derived recombinant vaccines.
- Any genetic predisposition to develop TTS has not been reported yet. Next generation sequencing may be useful in addressing this important issue.
- It is not clear why the cerebral circulation may be a preferred site for the formation of blood clots with some vaccines for COVID-19.

15. Conclusions

TTS is a dynamic target requiring urgent medical attention. Autoantibodies appear to play a critical role in the prothrombotic thrombocytopenic events that can occur during the treatment of COVID-19, particularly when using Vaxzevria and Janssen COVID-19 vaccines. National and international regulatory bodies strongly advocate for mass vaccination programs but with careful selection of patients and the avoidance of the use of Vaxzevria in patients less than 30 years of age, which may be a reasonable approach provided that alternative vaccines are available. It must be emphasized that mortality and morbidity from COVID-19 are much higher than the rare risk of developing TTS or other immune mediated complications related to the vaccines. A rapid assessment of patients presenting with the symptoms of TTS is advised, and management should be initiated without delay. It is important to report confirmed and suspected cases to regulatory bodies so a clearer picture of risk factors and vulnerable populations will emerge.

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Author Contributions

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Footnotes

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Exhibit "M"

Alberta Health Services

COVID-19 Info: For Albertans | For Health Professionals | Vaccine | Testing | Results | Family Support & Visitation

A CMOH order remains in effect that requires continuous masking at all AHS and Covenant facilities provincewide.

AHS Facilities Temporary Bed / Space Reductions - News

News Releases

No physician coverage in local ED for 12 hours Tuesday

Tuesday, November 9, 2021

The Fairview Health Complex emergency department (ED) will be without physician coverage for 12 hour... Read more

Extension of temporary closure of Elk Point Emergency Department

Tuesday, November 2, 2021

The Elk Point Healthcare Centre Emergency Department will continue to be temporarily without on site... Read more

Temporary closure of weekend outpatient clinics in Manning extended

Thursday, October 28, 2021

The Manning Community Health Centre weekend outpatient clinics, which have been closed since Oct. 1,... Read more

Community lab service changes in Lethbridge

Thursday, October 28, 2021
Effective Monday November 1 community laboratory service from the Bigelow Fowler South Medical Clini...
Read more

Lab and x-ray service temporarily closed in Magrath Nov. 1

Tuesday, October 26, 2021
Community laboratory and x-ray service at the Magrath Health Centre will be temporarily closed due t...
Read more

Temporary closure of Sylvan Lake Advanced Ambulatory Care Service

Tuesday, October 26, 2021
Due to sudden physician unavailability Sylvan Lake Advanced Ambulatory Care Service will be temp clo...
Read more

No physician coverage in local Daysland ED on Monday

Friday, October 22, 2021
The Daysland Health Centre Emergency Department (ED) will temporarily be without on-site physician c...
Read more

Hours temporarily reduced at La Crete ambulatory care centre

Thursday, October 21, 2021
Operating hours reduced... Read more

No physician coverage in Daysland ED next week

Friday, October 15, 2021
The Daysland Health Centre Emergency Department (ED) will temporarily be without on-site physician c...
Read more

No physician coverage in Fairview Health Complex ED for 24 hours Oct 5

Monday, October 4, 2021
The Fairview Health Complex emergency department will be temporarily without physician coverage for ...
Read more

Changes to Outpatient Laboratory at Lacombe Hospital and Care Centre

Monday, October 4, 2021
Due to staffing challenges, Alberta Precision Laboratories is undertaking some temporary service cha...
Read more

Extension of temporary closure of Elk Point Emergency Department

Friday, October 1, 2021

The Elk Point Healthcare Centre Emergency Department will be temporarily without on-site physician c... Read more

Weekend outpatient clinics closed throughout October in Manning

Thursday, September 30, 2021
The Manning Community Health Centre will close its weekend outpatient clinics from Oct. 1 to Oct. 31... Read more

No physician coverage in local ED Sept. 20, 22, 23, 30

Friday, September 17, 2021
The Sacred Heart Community Health Centre emergency department (ED) will be without on-site physician... Read more

AHS continues to schedule prioritized cancer surgeries

Thursday, September 9, 2021
EDMONTON – There have been some social media posts suggesting that emergent or urgent cancer surgeri... Read more

Temporary closure of the Fort Macleod Emergency Department

Wednesday, September 8, 2021
The Fort Macleod Health Centre Emergency Department will be temporarily closed... Read more

AHS postpones scheduled surgeries due to COVID-19

Friday, September 3, 2021
EDMONTON – The rise in COVID-19 cases in the community and the resulting demand on hospital resource... Read more

No physician coverage in Wabasca-Desmarais emergency department for 48 hours

Friday, August 27, 2021
The Wabasca-Desmarais Health Care Centre Emergency Department (ED) will be temporarily without on-si... Read more

AHS postpones some non-urgent surgeries to create additional hospital capacity

Friday, August 27, 2021
EDMONTON - With the rise in COVID-19 cases in the community and the increasing demand on hospital re... Read more

No physician coverage at McLennan Emergency Department Thursday

Wednesday, August 25, 2021

McLENNAN - The Sacred Heart Community Health Centre Emergency Department (ED) will be temporarily wi... Read more

Operating Room services temporarily paused at Westlock healthcare centre

Friday, August 20, 2021
Full surgical services to resume at local hospital Aug 23... Read more

Temporary closure of Advanced Ambulatory Care (Sylvan Lake)

Wednesday, August 18, 2021
SYLVAN LAKE - The Sylvan Lake Advanced Ambulatory Care Service (SLAACS) will be temporarily closed t... Read more

No physician coverage in Boyle for 48 hours this week

Tuesday, August 17, 2021
The Boyle Healthcare Centre emergency department (ED) will be temporarily without on-site physician ... Read more

Temporary closure of Advanced Ambulatory Care Service (Sylvan Lake)

Friday, August 13, 2021
The Sylvan Lake Advanced Ambulatory Care Service (SLAACS) will be temporarily closed at various time... Read more

Local Spirit River ED resumes normal operations at 8 p.m.

Thursday, August 12, 2021
The Central Peace Health Complex emergency department has secured on-site physician coverage and wil... Read more

No physician coverage in Spirit River for 24 hours

Thursday, August 12, 2021
The Central Peace Health Complex emergency department will be temporarily without on-site physician ... Read more

Consort emergency department to close temporarily beginning August 12

Wednesday, August 11, 2021
The Consort Hospital and Care Centre emergency department will be temporarily without physician cove... Read more

Sylvan Lake: Temporary change in hours on August 10 for Advanced Ambulatory Care Service

Monday, August 9, 2021

The Sylvan Lake Advanced Ambulatory Care Service will operate on temporarily reduced hours August 10... Read more

Full emergency and inpatient services returning to Devon General Hospital

Friday, August 6, 2021
Emergency department services will return to 24-7 effective September 7... Read more

Bed numbers temporarily reduced at McLennan health centre

Thursday, August 5, 2021
Alberta Health Services (AHS) is temporarily reducing the number of acute care beds at the Sacred He... Read more

Edson hospital pauses surgical services this weekend

Wednesday, August 4, 2021
Edson Healthcare Centre is pausing surgical services this weekend including C-sections due to a lack... Read more

New AHS webpage provides information on bed reductions

Friday, July 30, 2021
Alberta Health Services (AHS) has launched a new webpage that provides information regarding short-t... Read more

Rocky Mountain House emergency department remains open today

Thursday, July 29, 2021
The emergency department at the Rocky Mountain House Health Centre will remain open and operational ... Read more

Temporary bed closure at Westlock Healthcare Centre

Wednesday, July 28, 2021
As a result of a staffing shortage AHS has made the decision to reduce the number of acute care beds... Read more

University of Alberta Hospital temporarily closing two of 14 operating rooms

Wednesday, July 28, 2021
Two of 14 operating rooms (ORs) at the University of Alberta Hospital (UAH) will be temporarily clos... Read more

Temporary closure of beds in Red Deer Regional Hospital Centre’s Emergency Department

Friday, July 23, 2021

RED DEER – As a result of a staffing shortage AHS is temporarily closing seven treatment spaces in t... Read more

No physician coverage in McLennan ED Saturday, Sunday

Friday, July 16, 2021
The Sacred Heart Community Health Centre emergency department (ED) will be temporarily without on-si... Read more

No physician coverage overnight in Fort Vermilion ED for two weeks

Friday, July 16, 2021
The St. Theresa General Hospital emergency department (ED) will be temporarily without physician cov... Read more

No physician coverage overnight Friday in Fairview ED

Friday, July 9, 2021
The Fairview Health Complex emergency department will be temporarily without physician coverage over... Read more

Temporary reduction in acute care beds at Rocky Mountain House Health Centre, beginning July 5

Sunday, July 4, 2021
ROCKY MOUNTAIN HOUSE – A temporary shortage of Registered Nurses (RNs) and Licensed Practical Nurses... Read more

No physician coverage in Consort ED the week of June 28

Tuesday, June 29, 2021
Emergency department resumes usual hours of operation starting July 5... Read more

No overnight physician coverage in Boyle ED June 28 - July 2

Monday, June 28, 2021
BOYLE — The Boyle Healthcare Centre emergency department (ED) will be temporarily without on-site ph... Read more

No physician coverage overnight June 28-29 in Fairview ED

Monday, June 28, 2021
The Fairview Health Complex emergency department (ED) will be temporarily without physician coverage... Read more

No physician coverage this weekend in Boyle ED

Friday, June 25, 2021

BOYLE — The Boyle Healthcare Centre emergency department (ED) will be temporarily without on-site ph... Read more

Temporary ED closures scheduled for this week in Boyle

Monday, June 21, 2021
BOYLE - The Boyle Healthcare Centre Emergency Department (ED) will be temporarily without on-site ph... Read more

No physician coverage in Boyle Healthcare Centre ED for 25-hour period

Sunday, June 13, 2021
BOYLE — The Boyle Healthcare Centre emergency department (ED) will be temporarily without on-site ph... Read more

Temporary closure of Fairview Emergency Department

Tuesday, June 8, 2021
The Fairview Health Complex Emergency Department (ED) will be temporarily without physician coverage... Read more

Temporary Boyle ED closures scheduled for this week

Tuesday, June 8, 2021
The Boyle Healthcare Centre emergency department (ED) will be temporarily without on-site physician ... Read more

No on-site ED physician coverage Tuesdays, Thursdays (Elk Point)

Monday, May 31, 2021
The Elk Point Healthcare Centre emergency department will be temporarily without on-site physician c... Read more

No on-site physician coverage in emergency for 24 hours (Elk Point)

The Elk Point Healthcare Centre emergency department (ED) will be temporarily without on-site physic... Read more

Surgical services temporarily paused at St. Paul hospital

Thursday, May 20, 2021
St. Paul Healthcare Centre is temporarily pausing surgical services, including C-sections, as a resu... Read more

Elk Point emergency department to close over 24-hour period

Wednesday, May 19, 2021

The Elk Point Healthcare Centre emergency department will be temporarily closed as it will be withou... Read more

Obstetrics service temporarily paused at Westlock hospital

Wednesday, May 19, 2021
The Westlock Healthcare Centre will be temporarily unable to provide C-sections as part of its obste... Read more

Elk Point Healthcare Centre emergency department to close over over 24-hour period

Wednesday, May 12, 2021
The Elk Point Healthcare Centre emergency department will be without on-site physician coverage for ... Read more

Rocky Mountain House Health Centre emergency department to close over 16-hour period

Wednesday, May 12, 2021
The Rocky Mountain House Health Centre emergency department (ED) will be temporarily without physici... Read more

Fairview Health Complex emergency department to close over 12-hour period

Tuesday, May 11, 2021
The Fairview Health Complex emergency department (ED) will be temporarily without on-site physician ... Read more

New family physician practising in McLennan, Falher

Friday, May 7, 2021
A new family physician is now practising in McLennan and Falher improving access to primary for loca... Read more

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Chloroquine is a potent inhibitor of SARS coronavirus infection and spread

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This is Exhibit N referred to in the affidavit of Dr. Gert Gruber Sworn before me herein this 9 day of December, 2021

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Abstract

Background: Severe acute respiratory syndrome (SARS) is caused by a newly discovered coronavirus (SARS-CoV). No effective prophylactic or post-exposure therapy is currently available.

Results: We report, however, that chloroquine has strong antiviral effects on SARS-CoV infection of primate cells. These inhibitory effects are observed when the cells are treated with the drug either before or after exposure to the virus, suggesting both prophylactic and therapeutic advantage. In addition to the well-known functions of chloroquine such as elevations of endosomal pH, the drug appears to interfere with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2. This may negatively influence the virus-receptor binding and abrogate the infection, with further ramifications by the elevation of vesicular pH, resulting in the inhibition of infection and spread of SARS CoV at clinically admissible concentrations.

Conclusion: Chloroquine is effective in preventing the spread of SARS CoV in cell culture. Favorable inhibition of virus spread was observed when the cells were either treated with chloroquine prior to or after SARS CoV infection. In addition, the indirect immunofluorescence assay described herein represents a simple and rapid method for screening SARS-CoV antiviral compounds.

Background

Severe acute respiratory syndrome (SARS) is an emerging disease that was first reported in Guangdong Province, China, in late 2002. The disease rapidly spread to at least 30 countries within months of its first appearance, and concerted worldwide efforts led to the identification of the etiological agent as SARS coronavirus (SARS-CoV), a novel member of the family *Coronaviridae* [1]. Complete genome sequencing of SARS-CoV [2,3] confirmed that this pathogen is not closely related to any of the

previously established coronavirus groups. Budding of the SARS-CoV occurs in the Golgi apparatus [4] and results in the incorporation of the envelope spike glycoprotein into the virion. The spike glycoprotein is a type I membrane protein that facilitates viral attachment to the cellular receptor and initiation of infection, and angiotensin-converting enzyme-2 (ACE2) has been identified as a functional cellular receptor of SARS-CoV [5]. We have recently shown that the processing of the spike protein was effected by furin-like convertases and that inhibition of this cleavage by a specific inhibitor abrogated cytopathicity and significantly reduced the virus titer of SARS-CoV [6].

Due to the severity of SARS-CoV infection, the potential for rapid spread of the disease, and the absence of proven effective and safe *in vivo* inhibitors of the virus, it is important to identify drugs that can effectively be used to treat or prevent potential SARS-CoV infections. Many novel therapeutic approaches have been evaluated in laboratory studies of SARS-CoV: notable among these approaches are those using siRNA [7], passive antibody transfer [8], DNA vaccination [9], vaccinia or parainfluenza virus expressing the spike protein [10,11], interferons [12,13], and monoclonal antibody to the S1-subunit of the spike glycoprotein that blocks receptor binding [14]. In this report, we describe the identification of chloroquine as an effective pre- and post-infection antiviral agent for SARS-CoV. Chloroquine, a 9-aminoquinoline that was identified in 1934, is a weak base that increases the pH of acidic vesicles. When added extracellularly, the non-protonated portion of chloroquine enters the cell, where it becomes protonated and concentrated in acidic, low-pH organelles, such as endosomes, Golgi vesicles, and lysosomes. Chloroquine can affect virus infection in many ways, and the antiviral effect depends in part on the extent to which the virus utilizes endosomes for entry. Chloroquine has been widely used to treat human diseases, such as malaria, amoebiosis, HIV, and autoimmune diseases, without significant detrimental side effects [15]. Together with data presented here, showing virus inhibition in cell culture by chloroquine doses compatible with patient treatment, these features suggest that further evaluation of chloroquine in animal models of SARS-CoV infection would be warranted as we progress toward finding effective antivirals for prevention or treatment of the disease.

Results

Preinfection chloroquine treatment renders Vero E6 cells refractory to SARS-CoV infection

In order to investigate if chloroquine might prevent SARS-CoV infection, permissive Vero E6 cells [1] were pretreated with various concentrations of chloroquine (0.1–10 μM) for 20–24 h prior to virus infection. Cells were then infected with SARS-CoV, and virus antigens were visualized by indirect immunofluorescence as described in Materials and Methods. Microscopic examination (Fig. 1A) of the control cells (untreated, infected) revealed extensive SARS-CoV-specific immunostaining of the monolayer. A dose-dependant decrease in virus antigen-positive cells was observed starting at 0.1 μM chloroquine, and concentrations of 10 μM completely abolished SARS-CoV infection. For quantitative purposes, we counted the number of cells stained positive from three random locations on a slide. The average number of positively stained control cells was scored as 100% and was compared with the number of positive cells observed under various chloroquine concentrations (Fig. 1B). Pretreatment with 0.1, 1, and 10 μM chloroquine reduced infectivity by 28%, 53%, and 100%, respectively. Reproducible results were obtained from three independent experiments. These data demonstrated that pretreatment of Vero E6 cells with chloroquine rendered these cells refractory to SARS-CoV infection.

Postinfection chloroquine treatment is effective in preventing the spread of SARS-CoV infection

In order to investigate the antiviral properties of chloroquine on SARS-CoV after the initiation of infection, Vero E6 cells were infected with the virus and fresh medium supplemented with various concentrations of chloroquine was added immediately after virus adsorption. Infected cells were incubated for an additional 16–18 h, after which the presence of virus antigens was analyzed by indirect immunofluorescence analysis. When chloroquine was added after the initiation of infection, there was a dramatic dose-dependant decrease in the number of virus antigen-positive cells (Fig. 2A). As little as 0.1–1 μM chloroquine reduced the infection by 50% and up to 90–94% inhibition was observed with 33–100 μM concentrations (Fig. 2B). At concentrations of chloroquine in excess of 1 μM, only a small number of individual cells were initially infected, and the spread of the infection to adjacent cells was all but eliminated. A half-maximal inhibitory effect was estimated to occur at 4.4 ± 1.0 μM chloroquine (Fig. 2C). These data clearly show that addition of chloroquine can effectively reduce the establishment of infection and spread of SARS-CoV if the drug is added immediately following virus adsorption.

Electron microscopic analysis indicated the appearance of significant amounts of extracellular virus particles 5–6 h after infection [16]. Since we observed antiviral effects by chloroquine immediately after virus adsorption, we further extended the analysis by adding chloroquine 3 and 5 h after virus adsorption and examined for the presence of virus antigens after 20 h. We found that chloroquine was still significantly effective even when added 5 h after infection (Fig. 3); however, to obtain equivalent antiviral

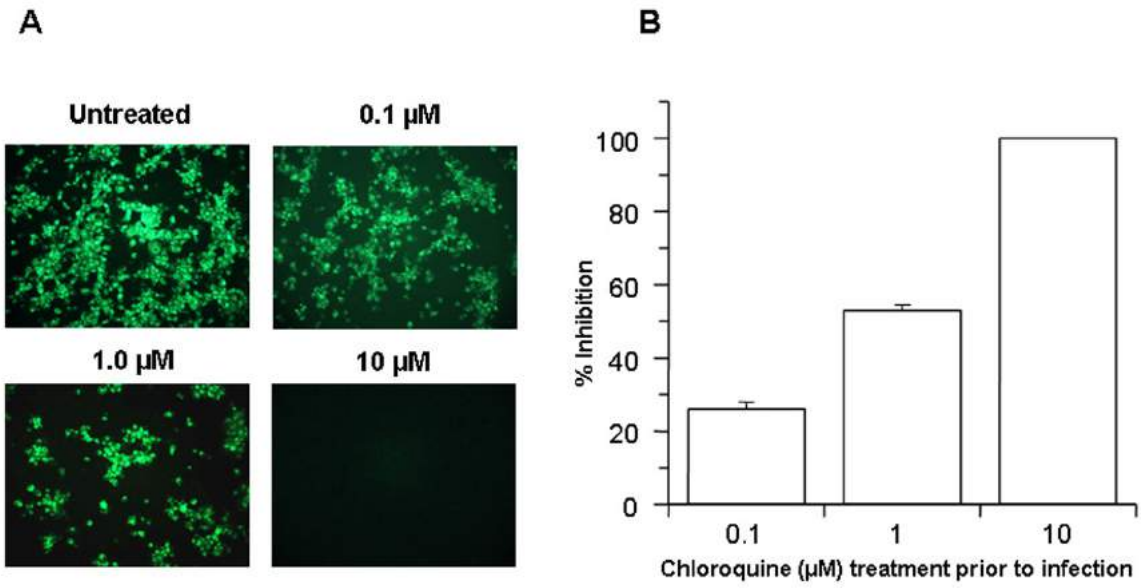

Figure 1

Prophylactic effect of chloroquine. Vero E6 cells pre-treated with chloroquine for 20 hrs. Chloroquine-containing media were removed and the cells were washed with phosphate buffered saline before they were infected with SARS-CoV (0.5 multiplicity of infection) for 1 h. in the absence of chloroquine. Virus was then removed and the cells were maintained in Opti-MEM (Invitrogen) for 16–18 h in the absence of chloroquine. SARS-CoV antigens were stained with virus-specific HMAF, followed by FITC-conjugated secondary antibodies. **(A)** The concentration of chloroquine used is indicated on the top of each panel. **(B)** SARS-CoV antigen-positive cells at three random locations were captured by using a digital camera, the number of antigen-positive cells was determined, and the average inhibition was calculated. Percent inhibition was obtained by considering the untreated control as 0% inhibition. The vertical bars represent the range of SEM.

effect, a higher concentration of chloroquine was required if the drug was added 3 or 5 h after adsorption.

Ammonium chloride inhibits SARS-CoV infection of Vero E6 cells

Since chloroquine inhibited SARS-CoV infection when added before or after infection, we hypothesized that another common lysosomotropic agent, NH_4Cl, might also function in a similar manner. Ammonium chloride has been widely used in studies addressing endosome-mediated virus entry. Coincidently, NH_4Cl was recently shown to reduce the transduction of pseudotype viruses decorated with SARS-CoV spike protein [17,18]. In an attempt to examine if NH_4Cl functions similarly to chloroquine, we performed infection analyses in Vero E6 cells before (Fig. 4A) and after (Fig. 4B) they were treated with various concentrations of NH_4Cl. In both cases, we observed a 93–99% inhibition with NH_4Cl at ≥ 5 mM. These data indicated that NH_4Cl (≥ 5 mM) and chloroquine (≥ 10 μM) are very effective in reducing SARS-CoV infection. These results suggest that effects of chloroquine and NH_4Cl in controlling SARS CoV infection and spread might be mediated by similar mechanism(s).

Effect of chloroquine and NH_4Cl on cell surface expression of ACE2

We performed additional experiments to elucidate the mechanism of SARS-CoV inhibition by chloroquine and NH_4Cl. Since intra-vesicular acidic pH regulates cellular functions, including N-glycosylation trimming, cellular trafficking, and various enzymatic activities, it was of interest to characterize the effect of both drugs on the processing, glycosylation, and cellular sorting of SARS-CoV spike glycoprotein and its receptor, ACE2. Flow cytometry analysis was performed on Vero E6 cells that were either untreated or treated with highly effective anti-SARS-CoV concentrations of chloroquine or NH_4Cl. The results revealed that neither drug caused a significant change in the levels of cell-surface ACE2, indicating that the observed inhibitory effects on SARS-CoV infection are not due to the lack of available cell-surface ACE2 (Fig. 5A). We next analyzed the molecular forms of endog-

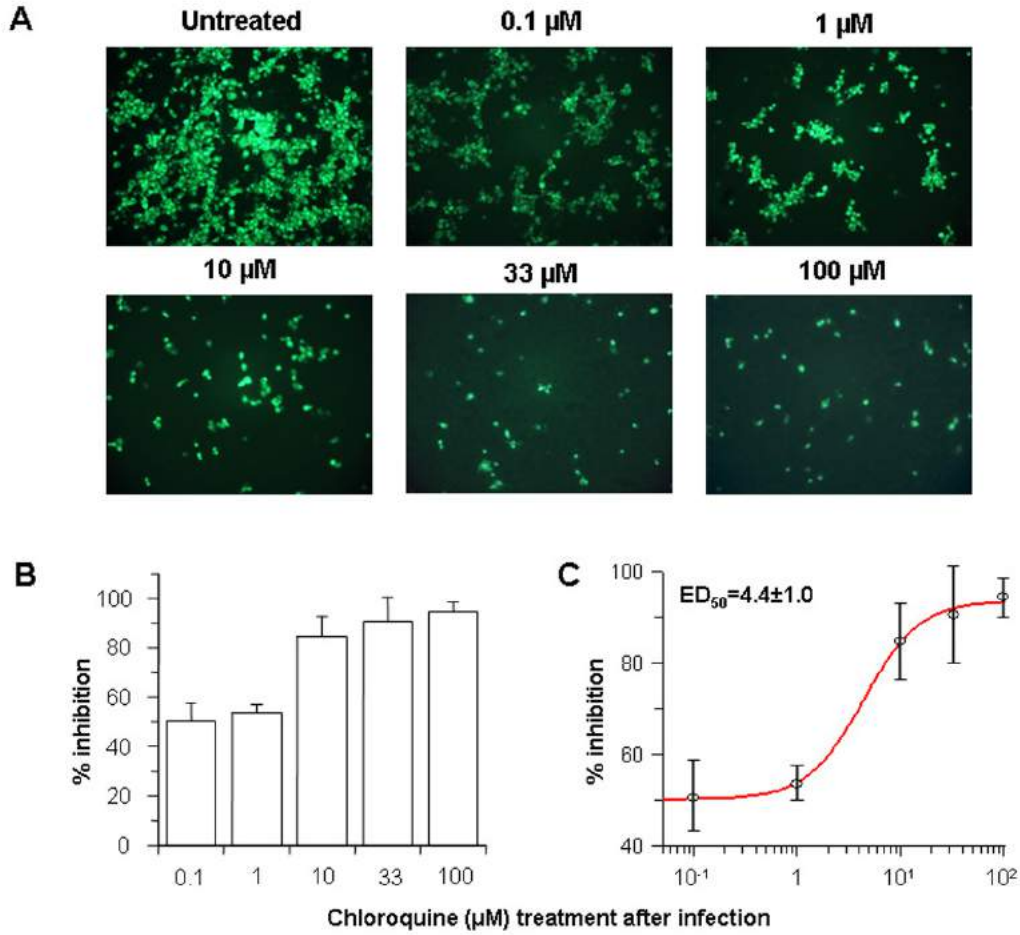

Figure 2

Post-infection chloroquine treatment reduces SARS-CoV infection and spread. Vero E6 cells were seeded and infected as described for Fig. 1 except that chloroquine was added only after virus adsorption. Cells were maintained in Opti-MEM (Invitrogen) containing chloroquine for 16–18 h, after which they were processed for immunofluorescence. **(A)** The concentration of chloroquine is indicated on the top. **(B)** Percent inhibition and SEM were calculated as in Fig. 1B. **(C)** The effective dose (ED_{50}) was calculated using commercially available software (Grafit, version 4, Erithacus Software).

enous ACE2 in untreated Vero E6 cells and in cells that were pre-incubated for 1 h with various concentrations of either NH_4Cl (2.5–10 mM) or chloroquine (1 and 10 μM) and labeled with ^{35}S-(Met) for 3 h in the presence or absence of the drugs (Fig. 5B and 5C). Under normal conditions, we observed two immunoreactive ACE2 forms, migrating at ~105 and ~113 kDa, respectively (Fig. 5B, lane 1). The ~105-kDa protein is endoglycosidase H sensitive, suggesting that it represents the endoplasmic reticulum (ER) localized form, whereas the ~113-kDa protein is endoglycosidase H resistant and represents the Golgi-modified form of ACE2 [19]. The specificity of the antibody was confirmed by displacing the immunoreactive protein bands with excess cold-soluble human recombinant ACE2 (+ rhACE2; Fig. 5B, lane 2). When we analyzed ACE2 forms in the presence of NH_4Cl, a clear stepwise increase in the migration of the ~113-kDa protein was observed with increasing concentrations of NH_4Cl, with a maximal effect observed at 10 mM NH_4Cl, resulting in only the ER form of ACE2 being visible on the gel (Fig. 5B, compare lanes 3–5). This suggested that the trimming and/or terminal modifications of the N-glycosylated chains of ACE2 were affected by NH_4Cl treatment. In addition, at 10 mM NH_4Cl, the ER form of ACE2 migrated with slightly faster mobility, indicating that NH_4Cl at that concentration might also affect core glyco-

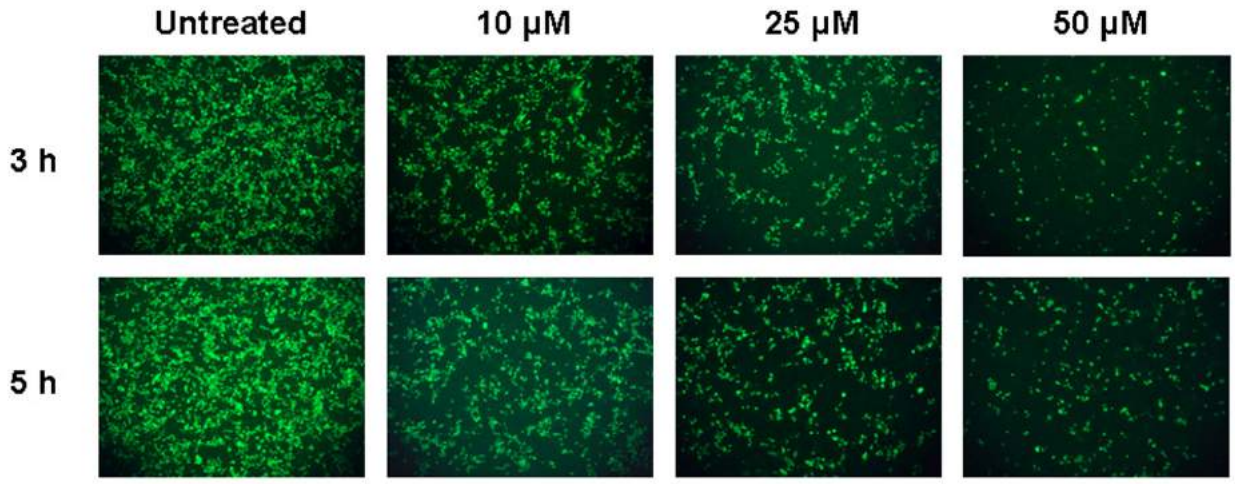

Figure 3
Timed post-infection treatment with chloroquine. This experiment is similar to that depicted in Fig. 2 except that cells were infected at 1 multiplicity of infection, and chloroquine (10, 25, and 50 μM) was added 3 or 5 h after infection.

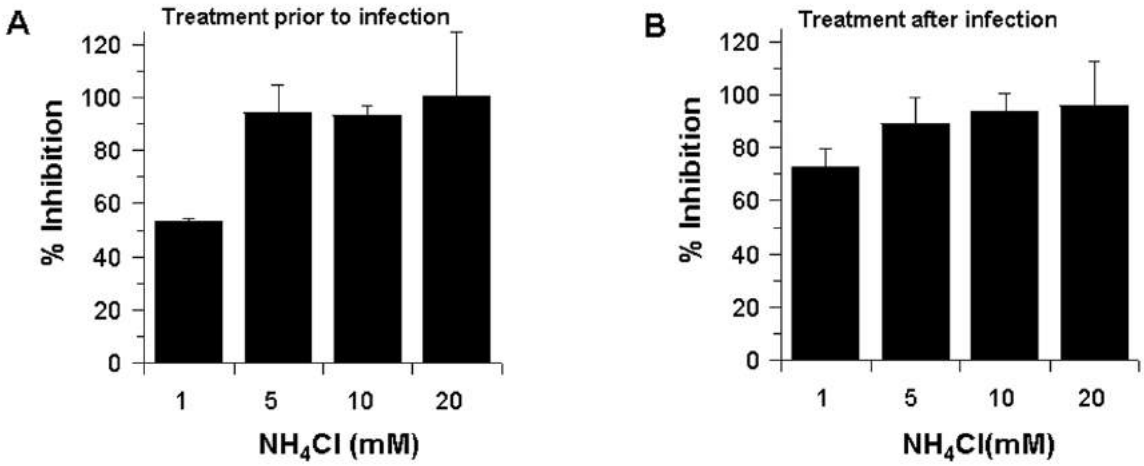

Figure 4
NH_4Cl inhibits SARS-CoV during pre or post infection treatment. NH_4Cl was added to the cells either before (A) or after (B) infection, similar to what was done for chloroquine in Figs 1 and 2. Antigen-positive cells were counted, and the results were presented as in Fig. 1B.

sylation. We also examined the terminal glycosylation status of ACE2 when the cells were treated with chloroquine (Fig. 5C). Similar to NH_4Cl, a stepwise increase in the electrophoretic mobility of ACE2 was observed with increasing concentrations of chloroquine. At 25 μM chloroquine, the faster electrophoretic mobility of the Golgi-modified form of ACE2 was clearly evident. On the basis of the flow cytometry and immunoprecipitation analyses,

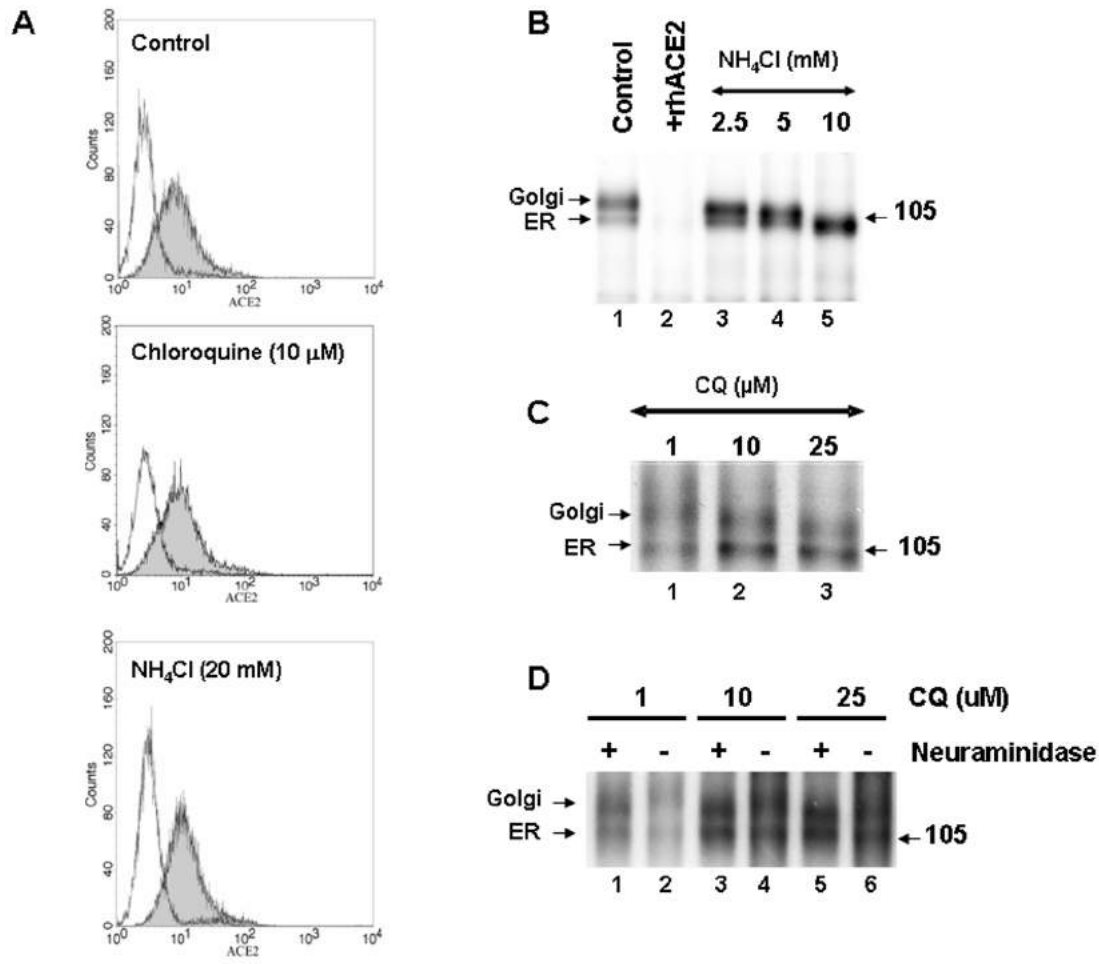

Figure 5

Effect of lysomotropic agents on the cell-surface expression and biosynthesis of ACE2. **(A)** Vero E6 cells were cultured for 20 h in the absence (control) or presence of chloroquine (10 μM) or NH_4Cl (20 mM). Cells were labeled with anti-ACE2 (grey histogram) or with a secondary antibody alone (white histogram). **(B)** Biosynthesis of ACE2 in untreated cells or in cells treated with NH_4Cl. Vero E6 cells were pulse-labeled for 3 h with ^{35}S-Met, and the cell lysates were immunoprecipitated with an ACE2 antibody (lane 1). Preincunbation of the antibody with recombinant human ACE2 (rhACE2) completely abolished the signal (lane 2). The positions of the endoglycosidase H-sensitive ER form and the endoglycosidase H-resistant Golgi form of ACE2 are emphasized. Note that the increasing concentration of NH_4Cl resulting in the decrease of the Golgi form of ACE2. **(C)** A similar experiment was performed in the presence of the indicated concentrations of chloroquine. Note the loss of terminal glycans with increasing concentrations of chloroquine. **(D)** The terminal glycosidic modification of ACE2 was evaluated by neuraminidase treatment of immunoprecipitated ACE2. Here cells were treated with 1–25 μM concentrations of chloroquine during starvation, pulse, and 3-h chase.

it can be inferred that NH_4Cl and chloroquine both impaired the terminal glycosylation of ACE2, while NH_4Cl resulted in a more dramatic effect. Although ACE2 is expressed in similar quantities at the cell surface, the variations in its glycosylation status might render the ACE2-SARS-CoV interaction less efficient and inhibit virus entry when the cells are treated with NH_4Cl and chloroquine.

To confirm that ACE2 undergoes terminal sugar modifications and that the terminal glycosylation is affected by NH_4Cl or chloroquine treatment, we performed immunopreipitation of ^{35}S-labeled ACE2 and subjected the immu-

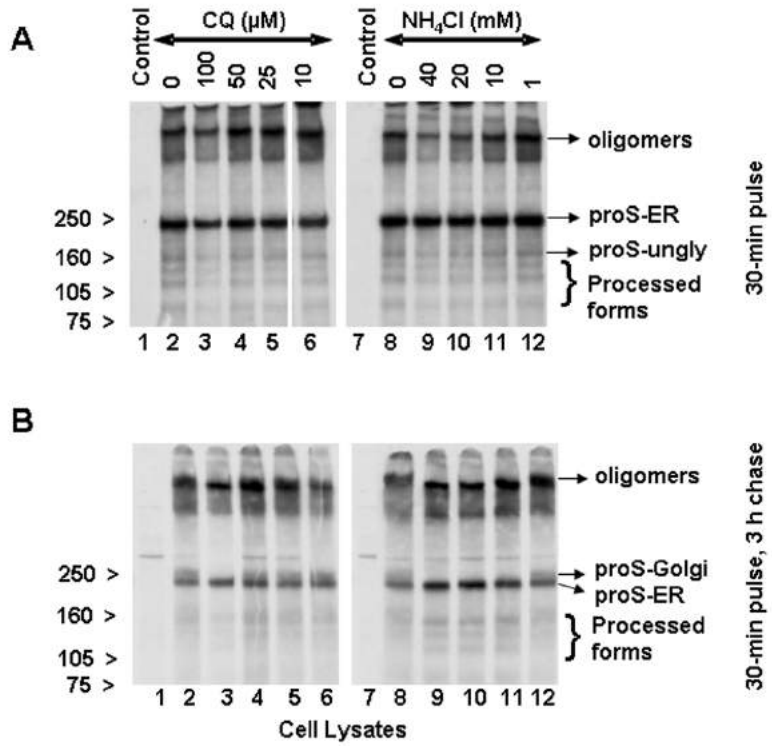

Figure 6

Effects of NH_4Cl and chloroquine (CQ) on the biosynthesis, processing, and glycosylation of SARS-CoV spike protein. Vero E6 cells were infected with SARS-CoV as described in Fig. 2. CQ or NH_4Cl was added during the periods of starvation (1 h) and labeling (30 min) with ^{35}S-Cys and followed by chase for 3 h in the presence of unlabeled medium. Cells were lysed in RIPA buffer and immunoprecipitated with HMAF. Virus proteins were resolved using 3–8% NuPAGE gel (Invitrogen). The cells presented were labeled for 30 min **(A)** and chased for 3 h **(B)**. The migration positions of the various spike molecular forms are indicated at the right side, and those of the molecular standards are shown to the left side. proS-ER and proS-Golgi are the pro-spike of SARS-Co in the ER and Golgi compartments, respectively and proS-ungly is the unglycosylated pro-spike ER.

noprecipitates to neuraminidase digestion. Proteins were resolved using SDS-PAGE (Fig 5D). It is evident from the slightly faster mobility of the Golgi form of ACE2 after neuraminidase treatment (Fig 5D, compare lanes 1 and 2), that ACE2 undergoes terminal glycosylation; however, the ER form of ACE2 was not affected by neuraminidase. Cells treated with 10 μM chloroquine did not result in a significant shift; whereas 25 μM chloroquine caused the Golgi form of ACE2 to resolve similar to the neuraminidase-treated ACE2 (Fig 5D, compare lanes 5 and 6). These data provide evidence that ACE2 undergoes terminal glycosylation and that chloroquine at anti-SARS-CoV concentrations abrogates the process.

Effect of chloroquine and NH_4Cl on the biosynthesis and processing of SARS-CoV spike protein

We next addressed whether the lysosomotropic drugs (NH_4Cl and chloroquine) affect the biosynthesis, glycosylation, and/or trafficking of the SARS-CoV spike glycoprotein. For this purpose, Vero E6 cells were infected with SARS-CoV for 18 h. Chloroquine or ammonium chloride was added to these cells during while they were being starved (1 h), labeled (30 min) or chased (3 h). The cell lysates were analyzed by immunoprecipitation with the SARS-specific polyclonal antibody (HMAF). The 30-min pulse results indicated that pro-spike (proS) was synthesized as a ~190-kDa precursor (proS-ER) and processed into ~125-, ~105-, and ~80-kDa proteins (Fig. 6A, lane 2), a result identical to that in our previous analysis [6]. Except for the 100 μM chloroquine (Fig. 6A, lane 3), there was no significant difference in the biosynthesis or processing of the virus spike protein in untreated or chloroquine-treated cells (Fig. 6A, lanes 4–6). It should be noted that chloroquine at 100 μM resulted in an overall decrease in biosynthesis and in the levels of processed virus glycoprotein. In view of the lack of reduction in the

biosynthesis and processing of the spike glycoprotein in the presence of chloroquine concentrations (10 and 50 μM) that caused large reductions in SARS-CoV replication and spread, we conclude that the antiviral effect is probably not due to alteration of virus glycoprotein biosynthesis and processing. Similar analyses were performed with NH_4Cl, and the data suggested that the biosynthesis and processing of the spike protein were also not negatively affected by NH_4Cl (Fig. 6A, lanes 7–12). Consistent with our previous analysis [6], we observed the presence of a larger protein, which is referred to here as oligomers. Recently, Song et al. [20] provided evidence that these are homotrimers of the SARS-CoV spike protein and were incorporated into the virions. Interestingly, the levels of the homotrimers in cells treated with 100 μM chloroquine and 40 and 20 mM NH_4Cl (Fig. 6A, lanes 3, 9, and 10) were slightly lower than in control cells or cells treated with lower drug concentrations.

The data obtained from a 30-min pulse followed by a 3-h chase (Fig. 6B, lanes 2 and 8) confirmed our earlier observation that the SARS-CoV spike protein precursor (proS-ER) acquires Golgi-specific modifications (proS-Golgi) resulting in a ~210-kDa protein [6]. Chloroquine at 10, 25, and 50 μM had no substantial negative impact on the appearance of the Golgi form (Fig. 6B, compare lane 2 to lanes 4–6). Only at 100 μM chloroquine was a reduction in the level of the Golgi-modified pro-spike observed (lane 3). On the other hand, NH_4Cl abrogated the appearance of Golgi-modified forms at ≥10 mM (compare lane 8 with 9–11) and had a milder effect at 1 mM (lane 12). These data clearly demonstrate that the biosynthesis and proteolytic processing of SARS-CoV spike protein are not affected at chloroquine (25 and 50 μM) and NH_4Cl (1 mM) doses that cause virus inhibitory effects. In addition, with 40, 20, and 10 mM NH_4Cl, there was an increased accumulation of proS-ER with a concomitant decrease in the amount of oligomers (Fig. 6B, lanes 9–11). When we examined the homotrimers, we found that chloroquine at 100 μM and NH_4Cl at 40 and 20 mM resulted in slightly faster mobility of the trimers (Fig. 6B, lanes 3, 9, and 10), but lower drug doses, which did exhibit significant antiviral effects, did not result in appreciable differences. These data suggest that the newly synthesized intracellular spike protein may not be a major target for chloroquine and NH_4Cl antiviral action. The faster mobility of the trimer at certain higher concentration of the drugs might be due the effect of these drugs on the terminal glycosylation of the trimers.

Discussion

We have identified chloroquine as an effective antiviral agent for SARS-CoV in cell culture conditions, as evidenced by its inhibitory effect when the drug was added prior to infection or after the initiation and establishment of infection. The fact that chloroquine exerts an antiviral effect during pre- and post-infection conditions suggest that it is likely to have both prophylactic and therapeutic advantages. Recently, Keyaerts et al. [21] reported the antiviral properties of chloroquine and identified that the drug affects SARS-CoV replication in cell culture, as evidenced by quantitative RT-PCR. Taken together with the findings of Keyaerts et al. [21], our analysis provides further evidence that chloroquine is effective against SARS-CoV Frankfurt and Urbani strains. We have provided evidence that chloroquine is effective in preventing SARS-CoV infection in cell culture if the drug is added to the cells 24 h prior to infection. In addition, chloroquine was significantly effective even when the drug was added 3–5 h after infection, suggesting an antiviral effect even after the establishment of infection. Since similar results were obtained by NH_4Cl treatment of Vero E6 cells, the underlying mechanism(s) of action of these drugs might be similar.

Apart from the probable role of chloroquine on SARS-CoV replication, the mechanisms of action of chloroquine on SARS-CoV are not fully understood. Previous studies have suggested the elevation of pH as a mechanism by which chloroquine reduces the transduction of SARS-CoV pseudotype viruses [17,18]. We examined the effect of chloroquine and NH_4Cl on the SARS-CoV spike proteins and on its receptor, ACE2. Immunoprecipitation results of ACE2 clearly demonstrated that effective anti-SARS-CoV concentrations of chloroquine and NH_4Cl also impaired the terminal glycosylation of ACE2. However, the flow cytometry data demonstrated that there are no significant differences in the cell surface expression of ACE2 in cells treated with chloroquine or NH_4Cl. On the basis of these results, it is reasonable to suggest that the pre-treatment with NH_4Cl or chloroquine has possibly resulted in the surface expression of the under-glycosylated ACE2. In the case of chloroquine treatment prior to infection, the impairment of terminal glycosylation of ACE2 may result in reduced binding affinities between ACE2 and SARS-CoV spike protein and negatively influence the initiation of SARS-CoV infection. Since the biosynthesis, processing, Golgi modification, and oligomerization of the newly synthesized spike protein were not appreciably affected by anti-SARS-CoV concentrations of either chloroquine or NH_4Cl, we conclude that these events occur in the cell independent of the presence of the drugs. The potential contribution of these drugs in the elevation of endosomal pH and its impact on subsequent virus entry or exit could not be ruled out. A decrease in SARS-CoV pseudotype transduction in the presence of NH_4Cl was observed and was attributed to the effect on intracellular pH [17,18]. When chloroquine or NH_4Cl are added after infection, these agents can rapidly raise the pH and subvert on-going

fusion events between virus and endosomes, thus inhibiting the infection.

In addition, the mechanism of action of NH_4Cl and chloroquine might depend on when they were added to the cells. When added after the initiation of infection, these drugs might affect the endosome-mediated fusion, subsequent virus replication, or assembly and release. Previous studies of chloroquine have demonstrated that it has multiple effects on mammalian cells in addition to the elevation of endosomal pH, including the prevention of terminal glycosyaltion of immunoglobulins [22]. When added to virus-infected cells, chloroquine inhibited later stages in vesicular stomatitis virus maturation by inhibiting the glycoprotein expression at the cell surface [23], and it inhibited the production of infectious HIV-1 particles by interfering with terminal glycosylation of the glycoprotein [24,25]. On the basis of these properties, we suggest that the cell surface expression of under-glycosylated ACE2 and its poor affinity to SARS-CoV spike protein may be the primary mechanism by which infection is prevented by drug pretreatment of cells prior to infection. On the other hand, rapid elevation of endosomal pH and abrogation of virus-endosome fusion may be the primary mechanism by which virus infection is prevented under post-treatment conditions. More detailed SARS CoV spike-ACE2 binding assays in the presence or absence of chloroquine will be performed to confirm our findings. Our studies indicate that the impact of NH_4Cl and chloroquine on the ACE2 and spike protein profiles are significantly different. NH_4Cl exhibits a more pronounced effect than does chloroquine on terminal glycosylation, highlighting the novel intricate differences between chloroquine and ammonium chloride in affecting the protein transport or glycosylation of SARS-CoV spike protein and its receptor, ACE2, despite their well-established similar effects of endosomal pH elevation.

The infectivity of coronaviruses other than SARS-CoV are also affected by chloroquine, as exemplified by the human CoV-229E [15]. The inhibitory effects observed on SARS-CoV infectivity and cell spread occurred in the presence of 1–10 μM chloroquine, which are plasma concentrations achievable during the prophylaxis and treatment of malaria (varying from 1.6–12.5 μM) [26] and hence are well tolerated by patients. It recently was speculated that chloroquine might be effective against SARS and the authors suggested that this compound might block the production of TNFα, IL6, or IFNγ [15]. Our data provide evidence for the possibility of using the well-established drug chloroquine in the clinical management of SARS.

Conclusion

Chloroquine, a relatively safe, effective and cheap drug used for treating many human diseases including malaria, amoebiosis and human immunodeficiency virus is effective in inhibiting the infection and spread of SARS CoV in cell culture. The fact that the drug has significant inhibitory antiviral effect when the susceptible cells were treated either prior to or after infection suggests a possible prophylactic and therapeutic use.

Methods

SARS-CoV infection, immunofluorescence, and immunoprecipitation analyses

Vero E6 cells (an African green monkey kidney cell line) were infected with SARS-CoV (Urbani strain) at a multiplicity of infection of 0.5 for 1 h. The cells were washed with PBS and then incubated in OPTI-MEM (Invitrogen) medium with or without various concentrations of either chloroquine or NH_4Cl (both from Sigma). Immunofluorescence staining was performed with SARS-CoV-specific hyperimmune mouse ascitic fluid (HMAF) [8] followed by anti-mouse fluorescein-coupled antibody.

Eighteen hours after infection, the virus-containing supernatants were removed, and the cells were pulsed with ^{35}S-(Cys) for 30 min and chased for 3 h before lysis in RIPA buffer. Clarified cell lysates and media were incubated with HMAF, and immunoprecipitated proteins were separated by 3–8% NuPAGE gel (Invitrogen); proteins were visualized by autoradiography. In some experiments, cells were chased for 3 h with isotope-free medium. Clarified cell supernatants were also immunoprecipitated with SARS-CoV-specific HMAF.

ACE2 flow cytometry analysis and biosynthesis

Vero E6 cells were seeded in Dulbecco's modified Eagle medium (Invitrogen) supplemented with 10% fetal bovine serum. The next day, the cells were incubated in Opti-MEM (Invitrogen) in the presence or absence of 10 μM chloroquine or 20 mM NH_4Cl. To analyze the levels of ACE2 at the cell surface, cells were incubated on ice with 10 μg/mL affinity-purified goat anti-ACE2 antibody (R&D Systems) and then incubated with FITC-labeled swine anti-goat IgG antibody (Caltag Laboratories). Labeled cells were analyzed by flow cytometry with a FACSCalibur flow cytometer (BD Biosciences). For ACE2 biosynthesis studies, Vero E6 cells were pulsed with 250 μCi ^{35}S-(Met) (Perkin Elmer) for 3 h with the indicated concentrations of chloroquine or NH_4Cl and then lysed in RIPA buffer. Clarified lysates were immunoprecipitated with an affinity-purified goat anti-ACE2 antibody (R&D systems), and the immunoprecipitated proteins were separated by SDS-polyacrylamide gel electrophoresis.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

MV did all the experiments pertaining to SARS CoV infection and coordinated the drafting of the manuscript. EB and SB performed experiments on ACE2 biosynthesis and FACS analysis. BE performed data acquisition from the immunofluorescence experiments. PR and TK provided critical reagents and revised the manuscript critically. NS and SN along with MV and EB participated in the planning of the experiments, review and interpretation of data and critical review of the manuscript. All authors read and approved the content of the manuscript.

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Exhibit "O"

ORIGINAL ARTICLE

Waning Immunity after the BNT162b2 Vaccine in Israel

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[redacted]

This is Exhibit A referred t
in the affidavit of Dr. Govt Gan
Sworn before me herein this 9
day of December, 2021

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor

ABSTRACT

BACKGROUND

In December 2020, Israel began a mass vaccination campaign against coronavirus disease 2019 (Covid-19) by administering the BNT162b2 vaccine, which led to a sharp curtailing of the outbreak. After a period with almost no cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a resurgent Covid-19 outbreak began in mid-June 2021. Possible reasons for the resurgence were reduced vaccine effectiveness against the delta (B.1.617.2) variant and waning immunity. The extent of waning immunity of the vaccine against the delta variant in Israel is unclear.

METHODS

We used data on confirmed infection and severe disease collected from an Israeli national database for the period of July 11 to 31, 2021, for all Israeli residents who had been fully vaccinated before June 2021. We used a Poisson regression model to compare rates of confirmed SARS-CoV-2 infection and severe Covid-19 among persons vaccinated during different time periods, with stratification according to age group and with adjustment for possible confounding factors.

RESULTS

Among persons 60 years of age or older, the rate of infection in the July 11–31 period was higher among persons who became fully vaccinated in January 2021 (when they were first eligible) than among those fully vaccinated 2 months later, in March (rate ratio, 1.6; 95% confidence interval [CI], 1.3 to 2.0). Among persons 40 to 59 years of age, the rate ratio for infection among those fully vaccinated in February (when they were first eligible), as compared with 2 months later, in April, was 1.7 (95% CI, 1.4 to 2.1). Among persons 16 to 39 years of age, the rate ratio for infection among those fully vaccinated in March (when they were first eligible), as compared with 2 months later, in May, was 1.6 (95% CI, 1.3 to 2.0). The rate ratio for severe disease among persons fully vaccinated in the month when they were first eligible, as compared with those fully vaccinated in March, was 1.8 (95% CI, 1.1 to 2.9) among persons 60 years of age or older and 2.2 (95% CI, 0.6 to 7.7) among those 40 to 59 years of age; owing to small numbers, the rate ratio could not be calculated among persons 16 to 39 years of age.

CONCLUSIONS

These findings indicate that immunity against the delta variant of SARS-CoV-2 waned in all age groups a few months after receipt of the second dose of vaccine.

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A key to the containment of the coronavirus disease 2019 (Covid-19) pandemic is mass vaccination of the population. However, the success of this policy is challenged by breakthrough infection and disease in fully vaccinated persons. One potential cause of breakthrough infection is the emergence of new variants of concern[1] that escape immunity, thus reducing the effectiveness of the vaccine. Several studies investigating the effectiveness of the BNT162b2 vaccine (Pfizer–BioNTech) against the beta (B.1.351)[2,3] and delta (B.1.617.2)[4-6] variants showed only modest rates of breakthrough infection and disease, whereas other studies showed higher rates.[7,8]

A second potential cause of breakthrough infection is waning of the immunity conferred by the vaccine. Mass vaccination with the BNT162b2 vaccine began in December 2020, and little is known about waning immunity over time. A recent study on longer-term follow-up of the participants in the phase 2–3 randomized trial of the BNT162b2 vaccine[9] showed a reduction in vaccine efficacy from 96% (in the period of 7 days to <2 months after receipt of the second dose) to 84% (in the period of 4 months to approximately 7 months after receipt of the second dose), which indicated a decrease in protection by a factor of four (i.e., [100−84]÷[100−96]). Preliminary reports of waning effectiveness of the same vaccine have come from a health maintenance organization in Israel[10] and from the United States,[11] and a decrease in vaccine-induced neutralization titers during the first 6 months after receipt of the second dose of vaccine has been reported.[12]

Israel conducted a very successful vaccination campaign using the BNT162b2 vaccine.[13-15] Starting in December 2020, more than half the adult population received two doses of vaccine within 3 months. The vaccination campaign, together with social measures, led to a sharp curtailing of the outbreak. By May 2021, infection rates had decreased to a few dozen cases daily, most of which were in unvaccinated persons or in persons returning from abroad. However, the number of polymerase-chain-reaction (PCR) tests that were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started to rise exponentially in June 2021, with a substantial number of infections being reported in vaccinated persons (Fig. 1). This rise in community transmission was followed by a concomitant increase in the numbers of severe cases and deaths, in both the vaccinated and unvaccinated populations. Genetic analysis showed that as of June 2021, more than 98% of the positive cases in Israel were attributed to the delta variant.[16] In this study, we estimated the role of waning immunity in the observed breakthrough against the delta variant.

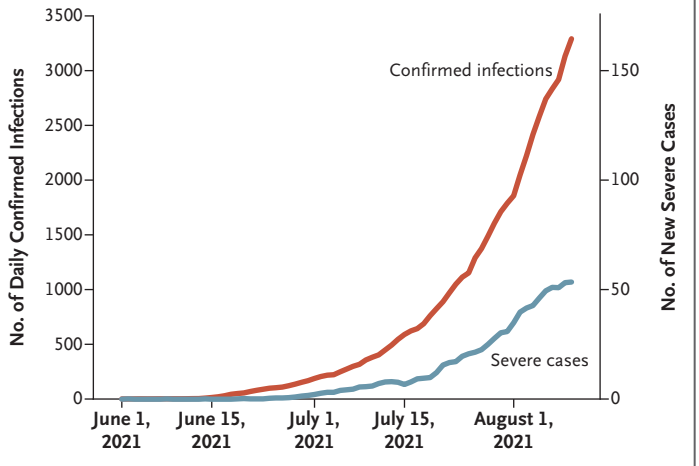

Figure 1. Daily Confirmed SARS-CoV-2 Infections and New Cases of Severe Covid-19 among Fully Vaccinated Persons in Israel, June through Early August 2021.

The graph shows increases in the numbers of daily severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and new cases of severe coronavirus disease 2019 (Covid-19), on different scales, during the delta variant wave among persons who had received two doses of vaccine.

METHODS

DATA SOURCE

Data on all residents of Israel who had been fully vaccinated before June 1, 2021, and who had not been infected before the study period were extracted from the Israeli Ministry of Health database on September 2, 2021. We defined fully vaccinated persons as those for whom 7 days or more had passed since receipt of the second dose of the BNT162b2 vaccine. We used the Ministry of Health official database that contains all information regarding Covid-19 (see Supplementary Methods 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We extracted from the database information on all documented SARS-CoV-2 infections (i.e., positive result on PCR assay) and on the severity of the disease after infection. We focused on infections that had been documented

in the period from July 11 through 31, 2021 (study period), removing from the data all confirmed cases that had been documented before that period. The start date was selected as a time when the virus had already spread throughout the entire country and across population sectors. The end date was just after Israel had initiated a campaign regarding the use of a booster vaccine (third dose). The study period happened to coincide with the school summer vacation.

We omitted from all the analyses children and adolescents younger than 16 years of age (most of whom were unvaccinated or had been recently vaccinated). Only persons 40 years of age or older were included in the analysis of severe disease because severe disease was rare in the younger population. Severe disease was defined as a resting respiratory rate of more than 30 breaths per minute, oxygen saturation of less than 94% while the person was breathing ambient air, or a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 300.[14] Persons who died from Covid-19 during the follow-up period were included in the study and categorized as having had severe disease.

During the study period, approximately 10% of the detected infections were in residents of Israel returning from abroad. Most residents who traveled abroad had been vaccinated and were exposed to different populations, so their risk of infection differed from that in the rest of the study population. We therefore removed from the analysis all residents who had returned from abroad in July.

VACCINATION SCHEDULE

The official vaccination regimen in Israel involved the administration of the second dose 3 weeks after the first dose. All residents 60 years of age or older were eligible for vaccination starting on December 20, 2020, thus becoming fully vaccinated starting in mid-January 2021. At that time, younger persons were eligible for vaccination only if they belonged to designated groups (e.g., health care workers and severely immunocompromised adults). The eligibility age was reduced to 55 years on January 12, 2021, and to 40 years on January 19, 2021. On February 4, 2021, all persons 16 years of age or older became eligible for vaccination. Thus, if they did not belong to a designated group, persons 40 to 59 years of age received the second dose starting in mid-February, and those 16 to 39 years of age received the second dose starting in the beginning of March. On the basis of these dates, we defined our periods of interest in half months starting from January 16; vaccination periods for individual persons were determined according to the time that they had become fully vaccinated (i.e., 1 week after receipt of the second dose). All the analyses were stratified according to vaccination period and to age group (16 to 39 years, 40 to 59 years, and ≥60 years).

STATISTICAL ANALYSIS

The association between the rate of confirmed infections and the period of vaccination provides a measure of waning immunity. Without waning of immunity, one would expect to see no differences in infection rates among persons vaccinated at different times. To examine the effect of waning immunity during the period when the delta variant was predominant, we compared the rate of confirmed infections (per 1000 persons) during the study period (July 11 to 31, 2021) among persons who became fully vaccinated during various periods. The 95% confidence intervals for the rates were calculated by multiplying the standard confidence intervals for proportions by 1000. A similar analysis was performed to compare the association between the rate of severe Covid-19 and the vaccination period, but for this outcome we used periods of entire months because there were fewer cases of severe disease.

To account for possible confounders, we fitted Poisson regressions. The outcome variable was the number of documented SARS-CoV-2 infections or cases of severe Covid-19 during the study period. The period of vaccination, which was defined as 7 days after receipt of the second dose of the Covid-19 vaccine, was the primary exposure of interest. The models compared the rates per 1000 persons between different vaccination periods, in which the reference period for each age group was set according to the time at which all persons in that group first became eligible for vaccination. A differential effect of the vaccination period for each age group was allowed by the inclusion of an interaction term between age and vaccination period. Additional potential confounders were added as covariates, as described below, and the natural logarithm of the number of persons was added as an offset. For each vaccination period and age group, an

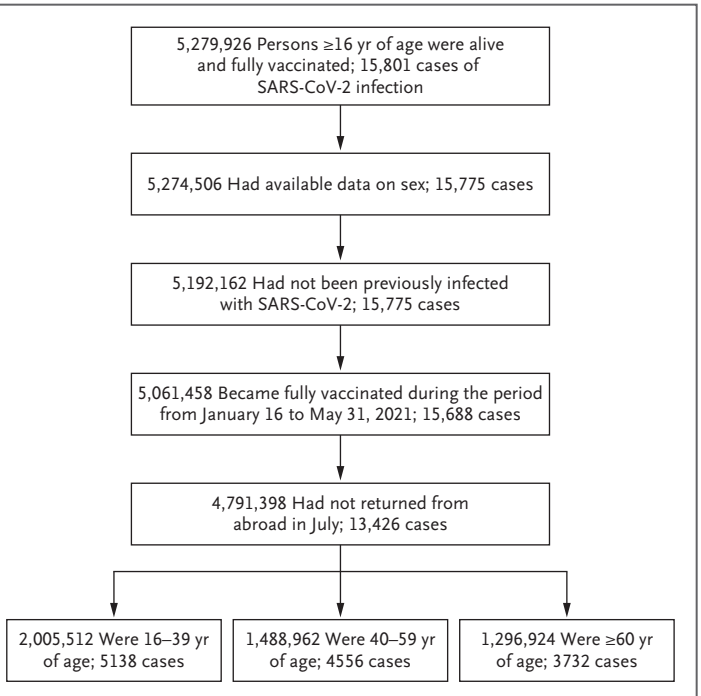

Figure 2. Study Population.

The population included persons who were fully vaccinated before June 1, 2021, were not abroad during July 2021, and had no documented SARS-CoV-2 infection according to polymerase-chain-reaction assay before July 11, 2021.

adjusted rate was calculated as the expected number of weekly events per 100,000 persons if all the persons in that age group had been vaccinated in that period. All the analyses were performed with the use of the glm function in the R statistical software package.[17]

In addition to age and sex, the regression analysis included as covariates the following confounders. First, because the event rates were rising rapidly during the study period (Fig. 1), we included the week in which the event was recorded. Second, although PCR testing is free in Israel for all residents, compliance with PCR-testing recommendations is variable and is a possible source of detection bias. To partially account for this, we stratified persons according to the number of PCR tests that had been performed during the period of March 1 to November 31, 2020, which was before the initiation of the vaccination campaign. We defined three levels of use: zero, one, and two or more PCR tests. Finally, the three major population groups in Israel (general Jewish, Arab, and ultra-Orthodox Jewish) have varying risk factors for infection. The proportion of vaccinated persons, as well as the level of exposure to the virus, differed among these groups.[18] Although we restricted the study to dates when the virus was found throughout the country, we included population sector as a covariate to control for any residual confounding effect.

We conducted several secondary analyses to test the robustness of the results, including calculation of the rate of confirmed infection in a finer, 10-year age grouping and an analysis restricted to the general Jewish population (in which the delta outbreak began), which comprises the majority of persons in Israel. In addition, a model including a measure of socioeconomic status as a covariate was fitted to the data, because this was an important risk factor in a previous study.[18] Since socioeconomic status was unknown for 5% of the persons in our study and the missingness of the data seemed to be informative, and also owing to concern regarding nondifferential misclassification (persons with unknown socioeconomic status may have had different rates of vaccination, infection, and severe disease), we did not include socioeconomic status in the main analysis. Finally, we compared the association between the number of PCR tests that had been conducted before the vaccination campaign (i.e., before December 2020) with the number that were conducted during the study period in order to evaluate the possible magnitude of detection bias in our analysis. A good correlation between past behavior regarding PCR testing and behavior during the study period would provide reassurance that the inclusion of past behavior as a covariate in the model would control, at least in part, for detection bias.

RESULTS

STUDY POPULATION

Among 5,279,926 fully vaccinated adults, we retained data on 4,791,398 persons for the main analysis (Fig. 2). Among these persons, 13,426 had a positive PCR test (confirmed SARS-CoV-2 infection) and 403 had severe Covid-19. Table 1 provides the number of events according to vaccination period, and Table S1 in the Supplementary Appendix provides a more detailed summary according to vaccination period and age group. Table 1 shows the characteristics of the study population according to vaccination period; Ta-

Table 1. Demographic and Clinical Characteristics of the Study Population According to Vaccination Period.*

Variable	Vaccination Period						
	Jan. 16–31 (N=1,076,708)	Feb. 1–15 (N=972,835)	Feb. 16–28 (N=747,788)	March 1–15 (N=819,040)	March 16–31 (N=749,422)	April 1–30 (N=325,201)	May 1–31 (N=100,404)
No. of positive SARS-CoV-2 PCR tests	3779	3182	2259	2146	1459	459	142
No. of cases of severe Covid-19	251	108	16	17	5	5	1
Male sex — no. (%)	518,196 (48)	459,251 (47)	380,135 (51)	410,371 (50)	358,398 (48)	153,619 (47)	46,352 (46)
Age group — no. (%)							
16–39 yr	125,977 (12)	195,961 (20)	352,722 (47)	549,090 (67)	496,779 (66)	217,731 (67)	67,252 (67)
40–59 yr	243,741 (23)	418,282 (43)	328,038 (44)	208,064 (25)	190,326 (25)	78,281 (24)	22,230 (22)
≥60 yr	706,990 (66)	358,592 (37)	67,028 (9)	61,886 (8)	62,317 (8)	29,189 (9)	10,922 (11)
No. of previous SARS-CoV-2 PCR tests — no. (%)†							
0	700,766 (65)	655,201 (67)	502,035 (67)	564,855 (69)	536,943 (72)	240,548 (74)	75,696 (75)
1	204,238 (19)	197,137 (20)	163,752 (22)	172,576 (21)	144,087 (19)	56,873 (17)	16,320 (16)
≥2	171,704 (16)	120,497 (12)	82,001 (11)	81,609 (10)	68,392 (9)	27,780 (9)	8,388 (8)
Population sector — no. (%)‡							
General Jewish	970,782 (90)	826,783 (85)	617,113 (83)	656,786 (80)	506,554 (68)	201,850 (62)	72,292 (72)
Arab	62,003 (6)	107,704 (11)	90,289 (12)	115,399 (14)	198,375 (26)	102,798 (32)	20,740 (21)
Ultra-Orthodox Jewish	43,923 (4)	38,348 (4)	40,386 (5)	46,855 (6)	44,493 (6)	20,553 (6)	7,372 (7)

* The numbers of persons in the column heads represent the numbers of persons who were fully vaccinated during that period. Positivity on the polymerase-chain-reaction (PCR) assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; i.e., confirmed infection) and cases of severe coronavirus disease 2019 (Covid-19) were assessed in the study period of July 11 to 31, 2021. Percentages may not total 100 because of rounding.

† Shown are the numbers of PCR tests that had been performed during the period of March 1 to November 31, 2020, which was before the initiation of the vaccination campaign.

‡ Population sector was determined on the basis of the area of residency, with the use of classifications provided by the Israeli Bureau of Statistics.

bles S2 through S4 show these data for each of the three age groups.

Because of the risk-based vaccination policy in Israel, persons who were vaccinated in January were older than those who were vaccinated later. In addition, the lower risk of Covid-19–related complications among younger persons may have caused a belief that vaccination was not urgent or even necessary, which also affected the age distribution of vaccination over the months.[19] The distribution of the number of previous PCR tests changed slightly between the periods, with 65% of the persons who became fully vaccinated in the second half of January having had no previous tests, as compared with 75% of those fully vaccinated in May. The number of tests seemed to be inversely correlated with age. A considerable difference was noted in the time of vaccination among the main population sectors: Arabs and ultra-Orthodox Jewish persons received vaccines later than did persons in the general Jewish population. Age and cultural differences contribute to these disparities.[18] (These differences in risk factors were adjusted for by their inclusion as covariates in the Poisson regression analysis.)

DESCRIPTIVE ANALYSIS

The rate of confirmed SARS-CoV-2 infection showed a clear increase as a function of time from vaccination. Among persons 60 years of age or older who were fully vaccinated in the second half of January, the rate was 3.3 confirmed infections per 1000 persons during the study period, as compared with 2.2 confirmed infections per 1000 persons who became fully vaccinated in the second half of February and 1.7 confirmed infections per 1000 persons fully vaccinated in the second half of March (Fig. 3A). Similar results were observed in the other age groups and when the analysis was categorized according to age in decades (Figs. 3A and S1). However, primarily health care workers and severely immunocompromised adults became fully vaccinated during the first three vaccination periods (January 16 to February 28) in the 16–39-year-old group and during the first two vaccination periods (January 16 to February 15) in the 40–59-year-old group; thus, the results for those vaccination periods in these age groups may be biased owing to selective samples and should be interpreted with caution.

A similar pattern was observed in the analysis of severe Covid-19 in the group of persons 60 years of age or older (Fig. 3B). In this analysis, vaccination periods were defined as January, February, March, and the combined April–May period because of the small numbers of severe cases in each age group. The rate of severe Covid-19 among persons 60 years of age or older who were fully vaccinated in January was 0.34 cases per 1000 persons over the study period and decreased to 0.26 cases per 1000 persons among those who were fully vaccinated in February, 0.15 cases per 1000 persons fully vaccinated in March, and 0.12 cases per 1000 persons fully vaccinated in the April–May period. The numbers of severe cases in the younger age groups were too small for conclusions to be drawn.

REGRESSION ANALYSIS

Tables 2 and 3 present the results of the regression analyses regarding confirmed SARS-CoV-2 infection and severe Covid-19, respectively; the complete set of estimated coefficients is provided in Tables S5 and S6. For each age group, the numbers in the tables show the ratios between the estimated rates in the first period when the persons in that group were eligible to become fully vaccinated (i.e., the second half of January for persons ≥60 years of age, the second half of February for those 40 to 59 years of age, and the first half of March for those 16 to 39 years of age) and the estimated rates in the other periods. The tables also include the adjusted rates for each vaccination period. In the group of persons 60 years of age or older, the rate of confirmed infection among those vaccinated in the second half of January was 1.1 times as high as the rate among those vaccinated in the first half of February. The rate ratio increased to 1.6 and 2.2 when comparing January vaccinees with those who were vaccinated in March and in April, respectively. The same phenomenon, of an increasing rate of confirmed infection with increased time since vaccination, was observed in all age groups.

Fewer cases of severe Covid-19 were noted in persons younger than 60 years of age, especially in the group of persons 16 to 39 years of age (Table S1), so the model could be fitted only to the groups of persons 40 to 59 years of age and those 60 years of age or older and only for the vaccination months of January through March.

The confidence intervals were wide; however, the results suggest a monotonic increase in the rate of severe disease as time since vaccination increased.

The analysis was repeated with socioeconomic status as an additional covariate, with the use of four categories (0 to 3 [indicating low socioeconomic level], 4 to 6 [indicating medium socioeconomic level], 7 to 10 [indicating high socioeconomic level], and unknown) and yielded similar results with only slightly smaller rate ratios (Table S8). Similar results were obtained when the analysis was restricted to the general Jewish population (Table S9).

DISCUSSION

The centralized health care system in Israel succeeded in vaccinating most of the Israeli population relatively early and in a short time.[13-15] This population is, therefore, useful for studying the effects of the BNT162b2 vaccine on the spread of SARS-CoV-2 infection and severity of Covid-19, as well as for studying the waning of vaccine protection over time. The appearance and rapid predominance of the delta variant in June 2021 resulted in a dramatic increase in the number of new SARS-CoV-2 infections among fully vaccinated persons, which aroused concern regarding

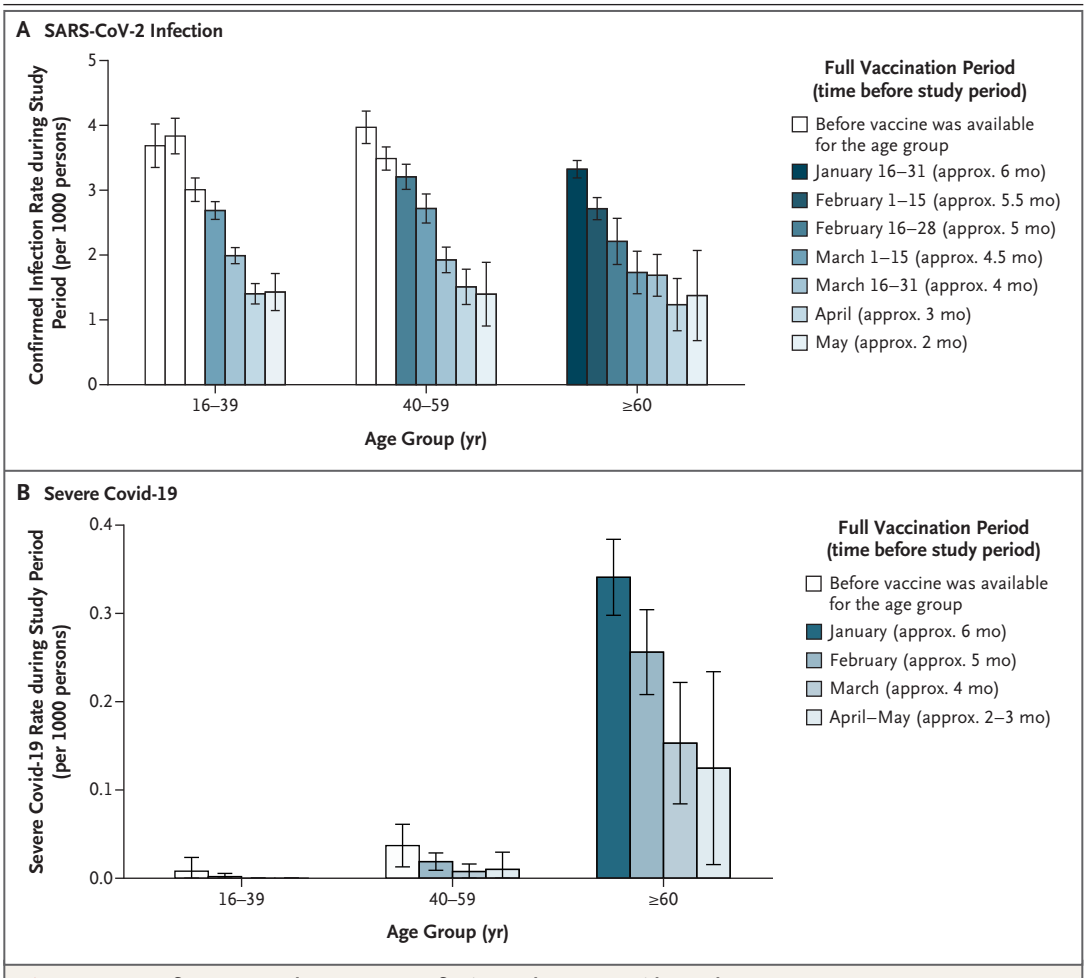

Figure 3. Rates of Documented SARS-CoV-2 Infection and Severe Covid-19, July 11 to 31, 2021.

Shown are the rates of documented infection per 1000 persons (Panel A) and rates of severe Covid-19 per 1000 persons (Panel B), according to period of second dose of Covid-19 vaccine and age group. In the analyses in the age groups younger than 60 years, white bars represent periods during which vaccination was restricted to only designated groups (e.g., health care workers and severely immunocompromised adults). I bars represent 95% confidence intervals, which are not adjusted for multiplicity. In Panel A, white bars represent half a month; in Panel B, white bars represent a month.

Table 2. Rate Ratios of Confirmed SARS-CoV-2 Infection According to Age Group and Vaccination Period.*

Age Group	Vaccination Period						
	Jan. 16–31	Feb. 1–15	Feb. 16–28	March 1–15	March 16–31	April 1–30	May 1–31
16–39 Yr							
Rate ratio of reference vs. period (95% CI)	0.8 (0.7–0.9)	0.7 (0.7–0.8)	0.9 (0.8–1.0)	Reference	1.2 (1.1–1.3)	1.5 (1.4–1.8)	1.6 (1.3–2.0)
Adjusted rate — no. of events/wk/100,000 persons	108.7	117.9	93.4	85.7	72.7	55.4	52.1
40–59 Yr							
Rate ratio of reference vs. period (95% CI)	0.9 (0.8–1.0)	1.0 (0.9–1.0)	Reference	1.1 (1.0–1.2)	1.4 (1.3–1.6)	1.7 (1.4–2.1)	2.1 (1.4–3.0)
Adjusted rate — no. of events/wk/100,000 persons	117.2	110.7	106.0	95.9	75.0	61.3	51.2
≥60 Yr							
Rate ratio of reference vs. period (95% CI)	Reference	1.1 (1.1–1.2)	1.3 (1.1–1.5)	1.6 (1.4–2.0)	1.6 (1.3–2.0)	2.2 (1.6–3.1)	2.2 (1.3–3.6)
Adjusted rate — no. of events/wk/100,000 persons	105.7	92.4	82.3	64.3	65.2	47.9	49.1

* Analyses were adjusted for week of infection, number of previous PCR tests (0, 1, or ≥2), population sector, and sex. Shown are rate ratios for confirmed SARS-CoV-2 infection during the period of July 11 through 31, 2021 (study period), as a function of time since full vaccination. We defined fully vaccinated persons as those for whom 7 days or more had passed since receipt of the second dose of the BNT162b2 vaccine. The comparison was between the estimated rate among persons who became fully vaccinated during the first vaccination period in which their age group was eligible (reference; i.e., January 16 to 31 for persons ≥60 years of age, February 16 to 28 for persons 40 to 59 years of age, and March 1 to 15 for persons 16 to 39 years of age) and the estimated rate among persons who became fully vaccinated in another vaccination period. For example, among persons 60 years of age or older, the rate of confirmed SARS-CoV-2 infection during the July 11–31 period among those vaccinated in January (105.7 events per week per 100,000 persons) was divided by the rate among those vaccinated in the second half of March (65.2 events per week per 100,000), yielding a rate ratio of 1.6. The 95% confidence intervals are not adjusted for multiplicity.

Table 3. Rate Ratios of Severe Covid-19 According to Age Group and Vaccination Period.*

Age Group	Vaccination Period		
	January	February	March
40–59 Yr			
Rate ratio of reference vs. period (95% CI)	0.6 (0.3–1.4)	Reference	2.2 (0.6–7.7)
Adjusted rate — no. of events/wk/100,000 persons	1.0	0.6	0.3
≥60 Yr			
Rate ratio of reference vs. period (95% CI)	Reference	1.2 (1.0–1.5)	1.8 (1.1–2.9)
Adjusted rate — no. of events/wk/100,000 persons	10.7	9.0	5.9

* For severe Covid-19, estimates are provided for the whole months of January, February, and March. Estimates are not provided for the youngest age group (16 to 39 years of age) and for the latest vaccination periods (April and May) because of very low case numbers. Analyses were adjusted for week of infection, number of previous PCR tests (0, 1, or ≥2), population sector, and sex. Shown are rate ratios during the period of July 11 through 31, 2021, as a function of time since full vaccination. The numbers in each age group are the ratios between the estimated rates in the first period when persons in that group were eligible to receive vaccination and the estimated rates in the other periods. The 95% confidence intervals are not adjusted for multiplicity.

decreased efficacy of the vaccine over time (Fig. 1).

A comparison of the rate of confirmed infection among persons vaccinated at different times revealed a clear increase in the rate as the time from vaccination increased in all age groups, with and without correction for measured confounding factors (Fig. 3A and Table 2). The rate of confirmed infection among persons 60 years of age or older who became fully vaccinated in the second half of January was 1.6 times as high as that among persons in the same age group who became fully vaccinated in March. The data show a similar increase in rate with increasing time since vaccination in the other age groups. The rate of severe Covid-19 cases also increased as a function of time from vaccination. Serologic studies in Israel have shown a correlated time-dependent reduction in neutralization titers,[12,20] which might be the biologic mechanism governing the observed waning immunity, and thus support the finding in this population-based research.

In contrast to early findings from the United Kingdom,[5] approximately two thirds of the cases of severe Covid-19 in Israel during the study period occurred in persons who had received two doses of the BNT162b2 vaccine. Two major differences exist between the studies. First, the current analysis used data from July 2021, a time when, for most of the Israeli population, at least 5 months had passed since receipt of their second dose of vaccine. The U.K. data were collected during the period of April through June 2021, with a much shorter time from vaccination to infection. Second, Israel has followed the original Pfizer–BioNTech protocol of administering the second dose 3 weeks (21 days) after the initial injection in most recipients, whereas the time between doses in the United Kingdom has typically been longer.[6]

A comparison of vaccinated persons with unvaccinated persons is of interest in order to predict the future burden on the health system. We therefore obtained data on the entire Israeli population from the Israeli Central Bureau of Statistics and calculated the number of unvaccinated persons indirectly. Moreover, unvaccinated persons might differ from the vaccinated population in important characteristics that could result in biased estimates. Nevertheless, we estimated the effectiveness of the vaccine against confirmed SARS-CoV-2 infection (see Supplementary Analysis 1). Vaccinated persons were found to be protected even after 6 months, as compared with unvaccinated persons. However, vaccine effectiveness was considerably lower than it had been closer to the vaccination date. Our findings are in line with findings from the randomized trial of the BNT162b2 vaccine, which showed a reduction in vaccine efficacy against symptomatic infection from 96% in the first 2 months after vaccination to 84% at 4 to 7 months after vaccination, when averaged over all age groups combined.[9]

Observational studies are subject to confound-

ing bias and detection bias. We examined these biases by using different sensitivity analyses (see Supplementary Analysis 2) and obtained similar results. Nevertheless, some sources of bias might remain; for instance, any effects that were due to differences in coexisting conditions between the vaccination periods could not be controlled for, because coexisting conditions are not recorded in the national database.

We did not separate the contribution of vaccine breakthrough due to waning immunity from the contribution due to the change in the dominant variant from alpha (B.1.1.7) to delta. Our analysis showed only the clear effect of waning vaccine-induced immunity against the delta variant. In addition, we were not able to quantify the extent of waning in the months immediately after vaccination (when the prevalence was extremely low in Israel).

Understanding the extent of waning immunity is critical for policy making, especially regarding vaccination strategies. The results presented here provided an epidemiologic basis for the decision by the Israeli Ministry of Health on July 30, 2021, to approve the administration of a booster (third dose) of Covid-19 vaccine to persons who had been vaccinated at least 5 months previously. The findings also suggest the need to follow the effects of waning immunity closely and to inform policymakers worldwide who are facing decisions regarding the administration of booster vaccinations.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Exhibit "P"

[redacted]

This is Exhibit P referred to
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Read The CDC Disclaimer

VAERS COVID Vaccine Adverse Event Reports

Reports from the Vaccine Adverse Events Reporting System. Our default data reflects all VAERS data including the "nondomestic" reports.

All VAERS COVID Reports | US/Territories/Unknown

894,143 Reports
Through November 12, 2021

18,853
DEATHS

94,537
HOSPITALIZATIONS

99,470
URGENT CARE

139,952

DOCTOR OFFICE VISITS

8,082

ANAPHYLAXIS

11,229

BELL'S PALSY

2,996

Miscarriages

9,332

Heart Attacks

13,237

Myocarditis/Pericarditis

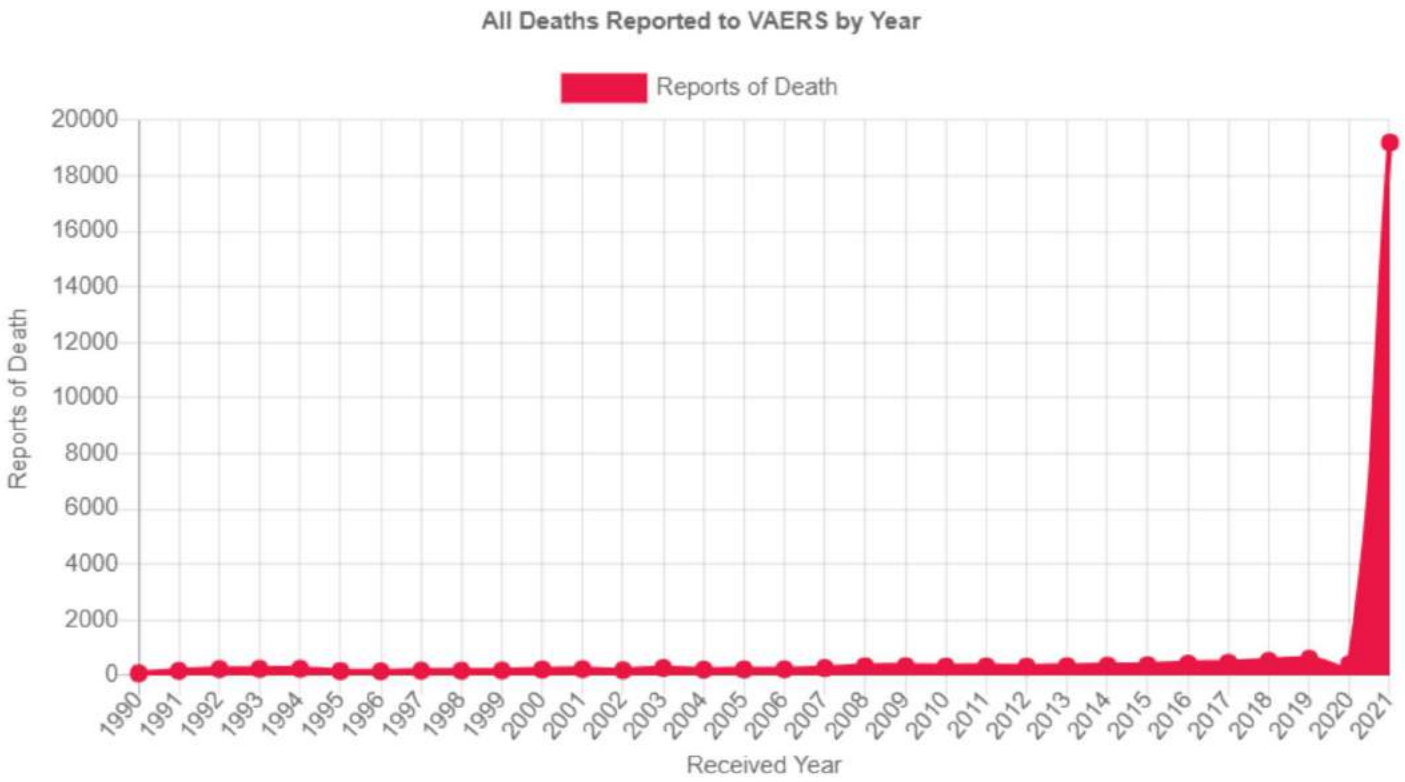
30,010
Permanently Disabled

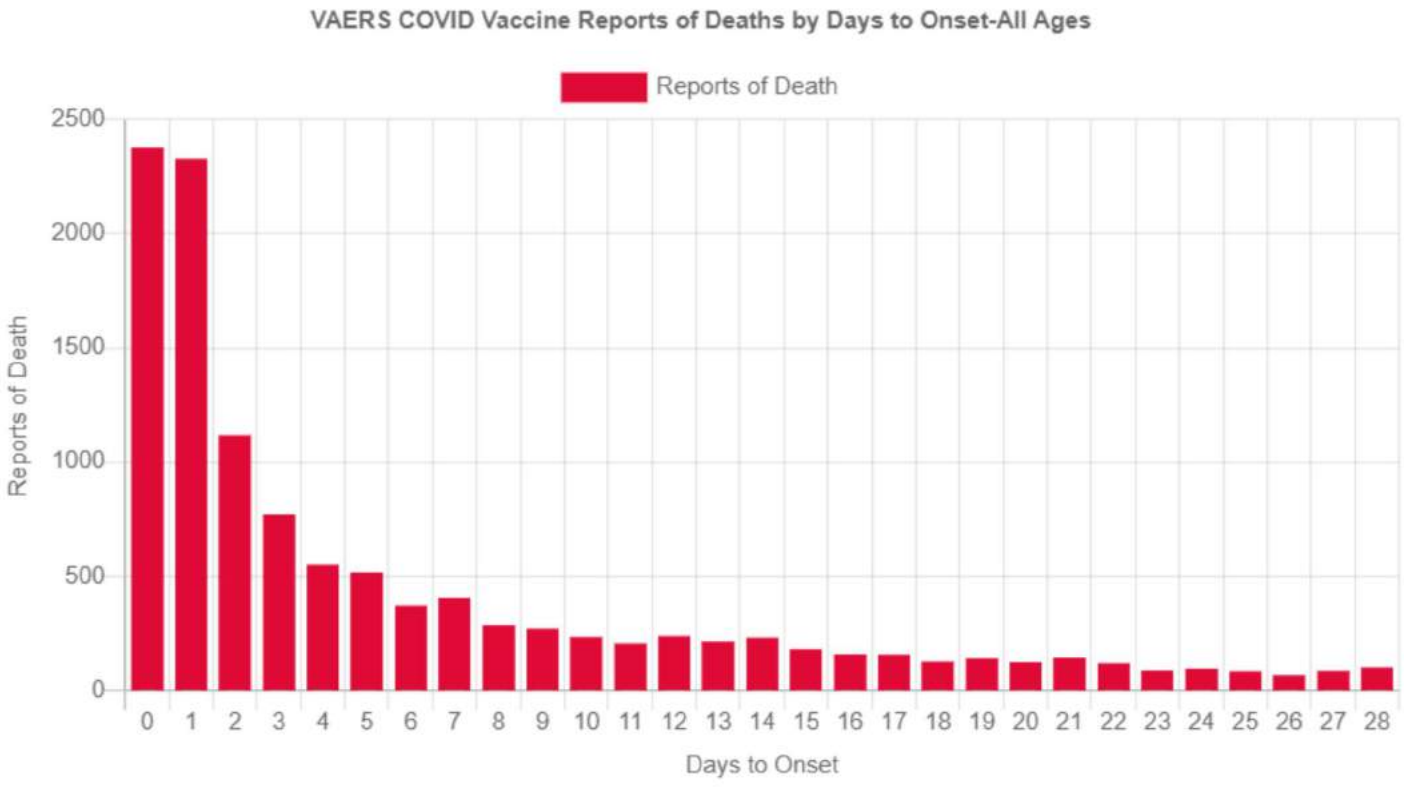
4,387
Thrombocytopenia/
Low Platelet

21,089
Life Threatening

33,660
Severe Allergic Reaction

10,455
Shingles





Questions? Comments? Bugs?

info@openvaers.com

Due to the high volume of inquiries, please be patient with response times.

AND PLEASE read the FAQ first.

OpenVAERS is a private organization that posts publicly available CDC/FDA data of injuries reported post-vaccination.
Reports are not proof of causality.

Exhibit "Q"

World Health Organization

[redacted]

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< Go back to all Coronavirus disease 2019 Q&As

Coronavirus disease (COVID-19): Herd immunity, lockdowns and COVID-19

15 October 2020 | Q&A

What is 'herd immunity'?

'Herd immunity', also known as 'population immunity', is a concept used for vaccination, in which a population can be protected from a certain virus if a threshold of vaccination is reached.

Herd immunity is achieved by protecting people from a virus, not by exposing them to it.

Vaccines train our immune systems to create proteins that fight disease, known as 'antibodies', just as would happen when we are exposed to a disease but – crucially – vaccines work without making us sick. Vaccinated people are protected from getting the disease in question and passing it on, breaking any chains of transmission. *Visit our webpage on COVID-19 and vaccines for more detail.*

World Health Organization

Coronavirus disease (COVID-19): Serology

9 June 2020 | Q&A

The identification of any new pathogen, such as the COVID-19 virus, is accompanied by many unknowns, particularly its ability to spread in the human population and its virulence. Initial surveillance strategies focus primarily on the use of molecular testing (RT-PCR) to measure acute infection in patients with severe disease, as these are the individuals who seek and require health care. This may miss the fraction of mild or asymptomatic infections that do not require medical attention, and as such, the full spectrum of the disease is not known. The answers to the questions below are based on our current understanding of the COVID-19 virus and the disease it causes. WHO will continue to update these answers as new information becomes available.

What are the expected results from serologic studies?

When can we expect results?

What are the limitations of serology for a novel pathogen?

What are the results of seroepidemiology studies?

What do these results mean?

What is herd immunity?

Herd immunity is the indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection. This means that even people who haven't been infected, or in whom an infection hasn't triggered an immune response, they are protected because people around them who are immune can act as buffers between them and an infected person. The threshold for establishing herd immunity for COVID-19 is not yet clear.

What is an immunity passport or a risk-free certificate and what is WHO's view of this?

WHO TEAM Emergencies Preparedness, WHO Headquarters (HQ)

Related

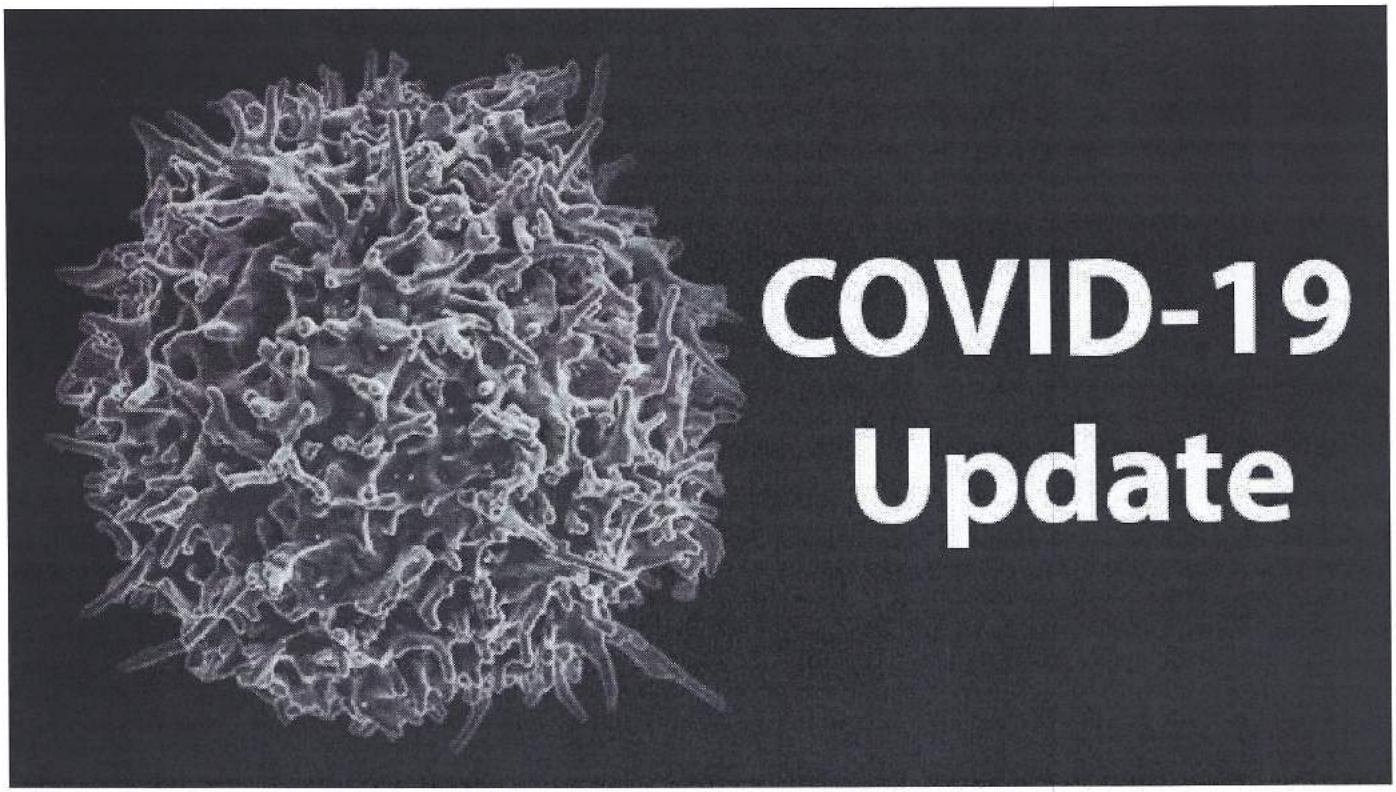
Exhibit "R"

NIH Director's Blog

Immune T Cells May Offer Lasting Protection Against COVID-19

Dr. Francis Collins

1 year ago



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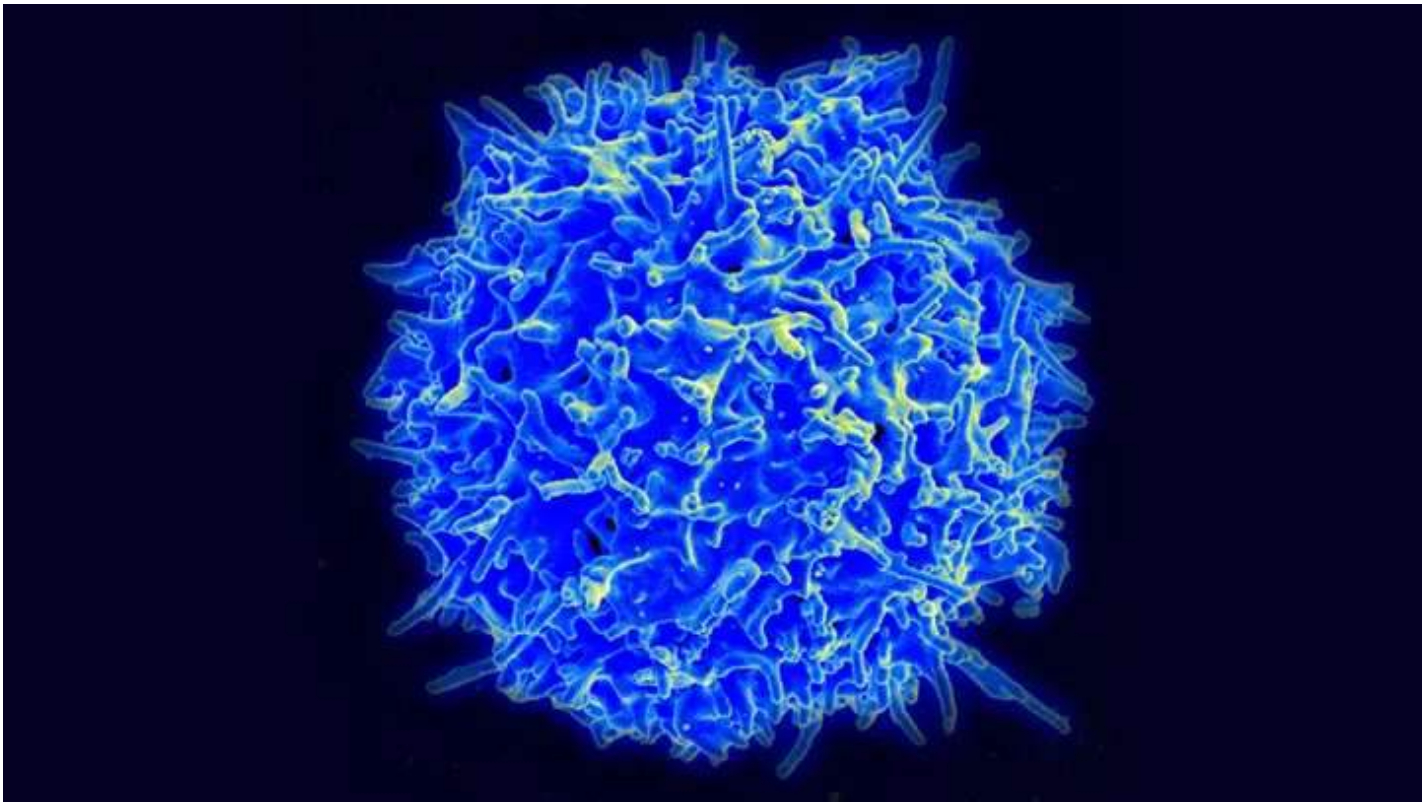

Caption: Scanning electron micrograph of a human T lymphocyte (T cell) from a healthy donor's immune system. Credit: National Institute of Allergy and Infectious Diseases/NIH

Much of the study on the immune response to SARS-CoV-2, the novel coronavirus that causes COVID-19, has focused on the production of antibodies. But, in fact, immune cells known as memory T cells also play an important role in the ability of our immune systems to protect us against many viral infections, including—it now appears—COVID-19.

An intriguing new study of these memory T cells suggests they might protect some people newly infected with SARS-CoV-2 by remembering past encounters with other human coronaviruses. This might potentially explain why some people seem to fend off the virus and may be less susceptible to becoming severely ill with COVID-19.

The findings, reported in the journal *Nature*, come from the lab of Antonio Bertoletti at the Duke-NUS Medical School in Singapore [1]. Bertoletti is an expert in viral infections, particularly hepatitis B. But, like so many researchers around the world, his team has shifted their focus recently to help fight the COVID-19 pandemic.

Bertoletti's team recognized that many factors could help to explain how a single virus can cause respiratory, circulatory, and other symptoms that vary widely in their nature and severity—as we've witnessed in this pandemic. One of those potential factors is prior immunity to other, closely related viruses.

SARS-CoV-2 belongs to a large family of coronaviruses, six of which were previously known to infect humans. Four of them are responsible for the common cold. The other two are more dangerous: SARS-CoV-1, the virus responsible for the outbreak of Severe Acute Respiratory Syndrome (SARS), which ended in 2004; and MERS-CoV, the virus that causes Middle East Respiratory Syndrome (MERS), first identified in Saudi Arabia in 2012.

All six previously known coronaviruses spark production of both antibodies and memory T cells. In addition, studies of immunity to SARS-CoV-1 have shown that T cells stick around for many years longer than acquired antibodies. So, Bertoletti's team set out to gain a better understanding of T cell immunity against the novel coronavirus.

The researchers gathered blood samples from 36 people who'd recently recovered from mild to severe COVID-19. They focused their attention on T cells (including CD4 helper and CD8 cytotoxic, both of which can function as memory T cells). They identified T cells that respond to the SARS-CoV-2 nucleocapsid, which is a structural protein inside the virus. They also detected T cell responses to two non-structural proteins that SARS-CoV-2 needs to make additional copies of its genome and spread. The team found that all those recently recovered from COVID-19 produced T cells that recognize multiple parts of SARS-CoV-2.

Next, they looked at blood samples from 23 people who'd survived SARS. Their studies showed that those individuals still had lasting memory T cells today, 17 years after the outbreak. Those memory T cells, acquired in response to SARS-CoV-1, also recognized parts of SARS-CoV-2.

Finally, Bertoletti's team looked for such T cells in blood samples from 37 healthy individuals with no history of either COVID-19 or SARS. To their surprise, more than half had T cells that recognize one or more of the SARS-CoV-2 proteins under study here. It's still not clear if this acquired immunity stems from previous infection with coronaviruses that cause the common cold or perhaps from exposure to other as-yet unknown coronaviruses.

What's clear from this study is our past experiences with coronavirus infections may have something important to tell us about COVID-19. Bertoletti's team and others are pursuing this intriguing lead to see where it will lead—not only in explaining our varied responses to the virus, but also in designing new treatments and optimized vaccines.

Reference:

[1] SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Le Bert N, Tan AT, Kunasegaran K, et al. Nature. 2020 July 15. [published online ahead of print]

Links:

Coronavirus (COVID-19) (NIH)

Overview of the Immune System (National Institute of Allergy and Infectious Diseases/NIAID)

Bertoletti Lab (Duke-NUS Medical School, Singapore)

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Leave a Comment

Exhibit "S"

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Tri-Council Policy Statement

Ethical Conduct for Research Involving Humans

TCPS2 2018

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Tri-Council Policy Statement

Ethical Conduct for Research Involving Humans

TCPS2 2018

Canadian Institutes of Health Research
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Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, December 2018.

Note: For the most recent information on amendments, please consult the official online version of the TCPS at www.pre.ethics.gc.ca.

CHAPTER 3

THE CONSENT PROCESS

Introduction

This chapter sets out the ethical requirements for consent in research involving humans. Throughout this Policy, the term "consent" means "free, informed and ongoing consent." For the purpose of this Policy, "free" and "voluntary" are used interchangeably.

Respect for Persons implies that individuals who participate in research should do so voluntarily, understanding the purpose of the research, and its risks and potential benefits, as fully as reasonably possible. Where a person has the capacity to understand this information, and the ability to act on it voluntarily, the decision to participate is generally seen as an expression of autonomy. The Policy refers to the process of seeking consent from prospective participants, which may result in either agreement or refusal to participate. This process is meant to emphasize Respect for Persons. Under no circumstances may researchers proceed to conduct research with anyone who has refused to participate. Subject to exceptions set out in this Policy, consent must be obtained from participants prior to the conduct of research.

Equally, Respect for Persons implies that those who lack the capacity to decide for themselves should nevertheless have the opportunity to participate in research that may be of benefit to themselves or others. Authorized third parties acting on behalf of these individuals may decide whether participation would be appropriate. For the purposes of this Policy, the term "authorized third party" (also known as "authorized third party decision makers") refers to any person with the necessary legal authority to make decisions on behalf of an individual who lacks the capacity to decide whether to participate or to continue to participate in a particular research project. These decisions involve considerations of Concern for Welfare and Justice.

Certain types of research require alternate processes for seeking consent. These are also described in this chapter. Researchers may request an alteration to consent requirements if they can meet the criteria of Article 3.7A. These include a requirement to satisfy the research ethics board (REB) that it is impossible, impracticable (see Glossary) or inappropriate to address the research question without the requested alteration. Where elements of the consent process may need to be adapted to the requirements of a particular research project, the REB can play an educational and consultative role in determining the appropriate process for seeking and maintaining consent. REBs must consider whether the requested alterations are justified or whether another approach would make it possible, practicable and appropriate to follow the normal consent requirements.

The head of the research team, also known as the "principal investigator," is responsible for ensuring that the consent process is followed. This person is also responsible for the actions of any member of the research team involved in the consent process.

In addition to this Policy, researchers are responsible for ensuring that all applicable legal and regulatory requirements with respect to consent are met. In some circumstances, researchers may have further legal obligations that may be determined in part by the nature of the research and the jurisdiction in which the research is being conducted.[1]

A. General Principles

Consent Shall Be Given Voluntarily

Article 3.1

a. Consent shall be given voluntarily.

b. Consent can be withdrawn at any time.

c. If a participant withdraws consent, the participant can also request the withdrawal of their data or human biological materials.

Application

(a) The voluntariness of consent is important because it respects human dignity and means that individuals have chosen to participate in research according to their own values, preferences and wishes.

The approach to recruitment is an important element in assuring voluntariness. In particular, how, when and where participants are approached and who recruits them are important elements in assuring (or undermining) voluntariness. In considering the voluntariness of consent, REBs and researchers should be cognizant of situations where undue influence, coercion or the offer of incentives may undermine the voluntariness of a participant's consent to participate in research.

Undue influence

Undue influence and manipulation may arise when prospective participants are recruited by individuals in a position of authority. The influence of power relationships (e.g., employers and employees, teachers and students, commanding officers and members of the military or correctional officers and prisoners) on the voluntariness of consent should be judged from the perspective of prospective participants, since the individuals being recruited may feel constrained to follow the wishes of those who have some form of control over them. This control may be physical, psychological, financial or professional, for example, and may involve offering some form of inducement or threatening some form of deprivation. In such situations, the control exerted in a power relationship may place undue pressure on the prospective participants. At the extreme, there can be no voluntariness if consent is secured by the order of authorities.

REBs and researchers should also pay particular attention to elements of trust and dependency in relationships (e.g., between physician and patient or between professor and student). These relationships can impose undue influence on the individual in the position of dependence to participate in research projects. Any relationship of dependency, even a nurturing one, may give rise to undue influence even if it is not applied overtly. There may be a greater risk of undue influence in situations of ongoing or significant dependency.

Pre-existing entitlements to care, education and other services should not be prejudiced by the decision of whether to participate in or withdraw from a research project. Accordingly, for example, a physician should ensure that continued clinical care is not linked to research participation. Similarly, where students do not wish to participate in research studies for course credits, they should be offered a comparable alternative.

Coercion

Coercion is a more extreme form of undue influence, involving a threat of harm or punishment for failure to participate. Coercion would negate the voluntariness of a decision to participate or remain in a research project.

Incentives

Incentives are anything offered to participants, monetary or otherwise, for participation in research (incentives differ from reimbursements and compensation for injury, which are discussed in Article 3.2[j]). Because incentives are used to encourage participation in a research project, they are an important consideration in assessing voluntariness. Where incentives are offered to participants, they should not be so large or attractive as to encourage reckless disregard of risks. This is a particular consideration in the case of healthy volunteers for the early phases of clinical trials, as discussed in Article 11.2. The offer of incentives in some contexts may be perceived by prospective participants as a way for them to gain favour or improve their situation. This may amount to undue inducement and thus negate the voluntariness of participants' consent.

This Policy neither recommends nor discourages the use of incentives. The onus is on the researcher to justify to the REB the use of a particular model and the level of incentives. In considering the possibility of undue influence in research involving financial or other incentives, researchers and REBs should be sensitive to issues such as the economic circumstances of those in the pool of prospective participants, the age and decision-making capacity of participants, the customs and practices of the community, and the magnitude and probability of harms (Chapter 4, Section B). Guardians and authorized third parties should not receive incentives for arranging the involvement in research of the individual they represent. However, they may accept reasonable incentives or compensation on behalf of that individual, as long as these are suitable to the circumstances.

(b) To maintain the element of voluntariness, participants shall be free to withdraw their consent to participate in the research at any time, without offering any reason for doing so. In some cases, however, the physical practicalities of the project may prevent the actual withdrawal of the participant partway through, for example, if the project involves only a single intervention, or if the termination of a medical research procedure may compromise the safety of the participant.

The participant should not suffer any disadvantage or reprisal for withdrawing, nor should any payment due prior to the point of withdrawal be withheld. If the research project used a lump-sum incentive for participation, the participant is entitled to the entire amount. If a payment schedule is used, participants shall be paid in proportion to their participation.

(c) The consent process should set out any circumstances that do not allow withdrawal of data or human biological materials once collected. In some research projects, the withdrawal of data or human biological materials may not be possible (e.g., when personal information has been anonymized and added to a data pool). Researchers must provide a rationale to the REB for using collection methods that do not permit subsequent withdrawal of data or human biological materials. Where the terms of the research do not allow for withdrawal of their data or human biological materials, the identity of the participants shall be protected at all times during the project and after its completion. Participants shall also be informed that it is impracticable, if not impossible, to withdraw results once they have been published or otherwise disseminated.

Consent Shall Be Informed

Article 3.2 Researchers shall provide to prospective participants, or authorized third parties, full disclosure of all information necessary for making an informed decision to participate in a research project.

Application

At the commencement of any process of consent, researchers (or their qualified representatives) shall provide prospective participants with the information set out in the following list, as appropriate to the particular research project. Not all the listed elements are required for all research. However, additional information may be required in particular types of research or under particular circumstances.

If a researcher does not include some of the listed disclosure requirements, they should explain to the REB why these requirements do not apply to that particular project. It is also up to the REB to consider whether all elements listed, or additional elements, are necessary to the consent process of the research project.

The information generally required for informed consent includes:

a. information that the individual is being invited to participate in a research project;

b. a statement of the research purpose in plain language, the identity of the researcher, the identity of the funder or sponsor, the expected duration and nature of participation, a description of research procedures, and an explanation of the responsibilities of the participant;

c. a plain language description of all reasonably foreseeable risks and potential benefits, both to the participants and in general, that may arise from research participation;

d. an assurance that prospective participants:

- are under no obligation to participate and are free to withdraw at any time without prejudice to pre-existing entitlements;
- will be given, in a timely manner throughout the course of the research project, information that is relevant to their decision to continue or withdraw from participation; and
- will be given information on their right to request the withdrawal of data or human biological materials, including any limitations on the feasibility of that withdrawal;

e. information concerning the possibility of commercialization of research findings, and the presence of any real, potential or perceived conflicts of interest on the part of the researchers, their institutions or the research sponsors;

f. the measures to be undertaken for dissemination of research results and whether participants will be identified directly or indirectly;

g. the identity and contact information of a qualified designated representative who can explain scientific or scholarly aspects of the research to participants;

h. the identity and contact information of the appropriate individual(s) outside the research team whom participants may contact regarding possible ethical issues in the research;

i. an indication of what information will be collected about participants and for what purposes; an indication of who will have access to information collected about the identity of participants; a description of how confidentiality will be protected (Article 5.2); a description of the anticipated uses of data; and information indicating who may have a duty to disclose information collected, and to whom such disclosures could be made;

j. information about any payments, including incentives for participants, reimbursement for participation-related expenses and compensation for injury;

k. a statement to the effect that, by consenting, participants have not waived any rights to legal recourse in the event of research-related harm; and

l. in clinical trials, information on stopping rules and when researchers may remove participants from trial.

For consent to be informed, prospective participants shall be given adequate time and opportunity to assimilate the information provided, pose any questions they may have, and discuss and consider whether they will participate. The time required for this initial phase of the consent process will depend on such factors as the magnitude and probability of harms, the complexity of the information conveyed, and the setting where the information is given.

The key to informed consent is that prospective participants understand the information being conveyed to them by researchers. Researchers and REBs should consider how best to convey that information to facilitate understanding. For example, written documentation may be supplemented with audio and/or visual aids or accompanied by video presentations.

When language barriers necessitate the assistance of an intermediary for communication between the research team and participants, the researcher should select an intermediary who has the necessary language skills to ensure effective communication (Article 4.1). The involvement of such intermediaries may raise confidentiality issues (Article 5.2).

Paragraphs (a) to (c) require researchers to clearly explain the nature and goals of the research, and other essential information, in a manner that best promotes understanding on the part of prospective participants.

Paragraph (b) requires the disclosure of those who support a particular research project, through funding or sponsorship. It is unethical for researchers to engage in clandestine activities for intelligence, police or military purposes under the guise of research.

Paragraph (c) requires researchers to consider all reasonably foreseeable risks that may result from participation. When research is conducted about an organization or a community, researchers should inform prospective participants within that organization or community of the extent to which the organization or community is collaborating with the research, and of any risk this collaboration may pose to the participant.

Paragraph (d) helps to ensure that a prospective participant's choice to participate is voluntary. Paragraph (d) also supports the requirement that the consent process continue throughout the research. The consent process should set out any circumstances that do not allow withdrawal of data or human biological materials once collected (Article 3.1[c]).

Paragraph (e) aims at managing real, potential or perceived conflicts of interests. Researchers should separate, to the greatest extent possible, their role as researcher from their other roles as therapists, caregivers, teachers, advisors, consultants, supervisors, employers or the like. If a researcher is acting in dual roles, this fact must always be disclosed to the participant. Conflict of interest matters are further elaborated in Chapter 7.

Paragraph (f) requires that researchers provide a reasonable explanation of the measures they will undertake to publish and otherwise disseminate the results of the research – to the extent that it is feasible, and in a manner that is appropriate. Beyond the ethical obligation to disseminate results in such areas as clinical trials, this requirement is grounded on the reasonable expectation of participants that results will be published or otherwise disseminated in the public domain to advance societal knowledge (addressed further in Articles 11.10 and 4.8). With respect to research involving Indigenous peoples and disclosure of information, see Chapter 9.

Paragraph (h) acknowledges that some institutions may decide to either name an ombudsman for participants or designate a resource person to handle queries, receive complaints and transmit those complaints to the REB. This is a matter for institutions to determine.

Paragraph (i) touches on issues of privacy and confidentiality, secondary use of data, and the possibility of compelled disclosure by the researcher to third parties for administrative and/or legal purposes. These issues are addressed in further detail in Chapter 5 and, in particular, Article 5.2.

Paragraph (j) ensures that participants are informed of the payments they will receive (if any) for their participation. Reimbursement for participation-related expenses is intended to ensure that participants are not put at a direct or indirect financial disadvantage for the time and inconvenience of participation in research. Direct expenses are costs incurred because of research participation (e.g., paying for transportation to, or parking at, the research site), while indirect expenses refer to losses that arise from participation (e.g., taking unpaid leave from work). Participants should also be informed about any compensation they may be entitled to for research-related injuries.

Paragraph (l) is intended to inform the prospective participant in clinical trials of circumstances under which the researcher may end the participant's involvement in a research project. Clinical trials have stopping rules: statistically significant end points and safety considerations determined in advance that once reached, dictate that the trial must be terminated. As well, researchers may remove participants who are not following the procedures of the clinical trial or for safety reasons (Article 11.6).

Consent Shall Be an Ongoing Process

Article 3.3 Consent shall be maintained throughout the research project. Researchers have an ongoing duty to provide participants with all information relevant to their ongoing consent to participate in the research.

Application

Consent encompasses a process that begins with the initial contact (e.g., recruitment) and carries through to the end of participants' involvement in the project. Throughout the process, researchers have an ongoing duty to provide participants and REBs with all information relevant to participants' ongoing consent to participate in the research. The researcher has an ongoing ethical and legal obligation to bring to participants' attention any changes to the research project that may affect them. These changes may have ethical implications, may be germane to their decision to continue research participation, or may be relevant to the particular circumstances of individual participants. In particular, researchers shall disclose changes to the risks or potential benefits of the research. This gives participants the opportunity to reconsider the basis for their consent in light of the new information.

Rather than an age-based approach to consent, TCPS 2 (2018) advocates an approach based on decision-making capacity as long as it does not conflict with any laws governing research participation. Some children begin participation in a project on the basis of consent from an authorized third party (due to the determination that they lacked capacity to decide on their own behalf) and on the basis of their own assent (Article 3.10). In these cases, if the children mature sufficiently to decide on their own behalf (subject to legal requirements), the researcher must seek the children's autonomous consent in order for their participation to continue. Similarly, in the case of children who are unable to assent to research participation (e.g., infants) at the beginning of a project, the researcher must seek their assent to continue their participation once they are able to understand the purpose of the research as well as its risks and benefits.

Incidental Findings

An "incidental finding" is a discovery about research participants or prospective participants that is made in the course of research, but is outside the objectives of the research study. Incidental findings are considered to be material incidental findings if they are reasonably determined to have significant welfare implications for the participant or prospective participant. Material incidental findings may appear at any stage of the research. For example, material incidental findings can be discovered while screening for eligibility to participate in a study, while collecting baseline information, during study procedure, or during follow-up evaluations.

Article 3.4 Within the limits of consent provided by the participant, researchers shall disclose to the participant any material incidental findings discovered in the course of research.[2]

Application

Determination of materiality

To determine whether an incidental finding is material, expertise relevant to the finding is required. If researchers do not have such expertise, and are unsure of how to interpret the findings or are uncertain whether findings are material, they should seek expertise relevant to the finding and/or refer to professional practices and standards.

Management of foreseeable and non-foreseeable material incidental findings

Incidental findings can arise in any type of research. In some areas of research, such as genetic or genomic research and research that includes imaging, material incidental findings can reasonably be foreseeable in the specific participant population for the study. Where material incidental findings are foreseeable, researchers shall inform participants, as part of the initial consent process, of the likelihood of discovering material incidental findings, and where applicable, should provide information on their strategy to disclose such findings to participants. In addition, researchers should develop a management plan for review by the REB. For genetic research, researchers are required to develop a plan for managing information that may be revealed through their research, and submit the plan for REB review (Article 13.2).

In other areas of research, material incidental findings may not be reasonably foreseeable, but can be discovered unexpectedly in the course of the research. Upon discovery of an incidental finding, the researcher shall determine whether the finding is material, and report the discovery to the REB in accordance with guidance in Article 6.15. The researcher should describe the process used to determine the materiality of the finding(s), and present a plan for disclosing such findings to the participants.

Regardless of whether the material incidental findings were foreseeable, REBs should assess the researcher's plan to disclose material incidental findings to participants. If there is uncertainty as to whether a research project requires such a plan, researchers and REBs can make this determination on a case-by-case basis. The final decision on the need for a plan rests with the REB.

Consent and departures from consent

Upon discovery of a material incidental finding, the principle of Concern for Welfare places an obligation on researchers to share it with the relevant participants. To respect the participants' autonomy, the communication of the findings determined to be material can only be done when participants or their authorized third parties have consented to receiving them initially or as part of the ongoing consent process. See Articles 3.1, 3.2 and 3.3 for the consent process and Article 13.3 for human genetic research).

Where the researchers have undertaken, in the course of the consent process, not to disclose material incidental findings, and researchers discover an unforeseeable material incidental finding that can be addressed with a potentially significantly beneficial intervention, researchers should consult their REBs

to determine whether there is a sufficient ethical basis to disclose the finding to the participant, and if so, how to disclose it.

There may be limitations to the consent to receiving material incidental findings. For example, in the case of children, authorized third parties, who, by law, must always exercise their authority in the best interest of the child, must receive any findings for the child that are actionable immediately or during childhood.

Researchers should exercise care and sensitivity in determining who discloses material incidental findings that may have a negative impact on the welfare of participants, and how that disclosure is made. Researchers should assist participants in understanding the material incidental finding(s). Researchers' assistance may include suggesting that participants consider seeking additional advice from people they trust, such as family members, friends, experts or professionals. When necessary, researchers should direct participants to a qualified professional to discuss the possible implications of material incidental findings for their welfare.

In some cases, incidental findings may trigger legal reporting obligations. Researchers should be aware of these obligations and, as part of the initial consent process, should inform participants of the limits to confidentiality (Article 5.1).

Exceptions to the obligation to disclose

Researchers may also request an exception to their obligation to disclose material incidental findings, based on the impracticability or impossibility of disclosing such findings to the participant. "Impracticable" refers to undue hardship or onerousness that jeopardizes the conduct of the research; it does not mean mere inconvenience. Disclosure may be impossible or impracticable when participants or their authorized party may be deceased or difficult to track due to insufficient identifiers, cost, or time elapsed. The onus is on the researcher to justify to the REB the need for the exception.

Consent Shall Precede Collection of, or Access to, Research Data

Article 3.5 Research shall begin only after the participants, or their authorized third parties, have provided their consent.

Application

In keeping with the principle of Respect for Persons, participants shall provide their consent prior to engaging in research. This is the clearest demonstration that their participation is based on consideration of the risks and potential benefits of the research project, and other principles in this Policy.

There are exceptions to this general ethical requirement, however, set out in Articles 3.7A and 3.8.

This article does not apply to conversations that researchers may have with prospective participants as part of the development of the design of their research. These preliminary conversations – which may include negotiations concerning the terms on which a researcher may engage with a particular community or group – do not in themselves constitute research and therefore do not require consent (Chapter 2, Article 6.11, Articles 9.3 to 9.6 and Article 10.1).

Exhibit "T"

WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the

researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

[redacted]

This is Exhibit 1 referred to
in the affidavit of Dr. Gerald Gruber
Sworn before me herein this 9
day of December, 2021

NICOLE D. JAMES
A Commissioner for Oaths
In And For
The Province Of Alberta
Being A Solicitor