

COVID-19 Scientific Advisory Group Rapid Evidence Brief

COVID-19 Vaccination: Medical Exemptions, and assessment for initial vaccination and subsequent doses after suspected adverse events

Jurisdictional Scan: September 2021

Updated scan and targeted evidence review: March 2022

8 July 2022

The research evidence around COVID-19 is constantly evolving. Since completion of this report, additional potentially relevant papers has come to attention to be reviewed for inclusion in any possible future update of this literature synthesis, with the following a notable example:

Le Vu, S., Bertrand, M., Jabagi, M. J., Botton, J., Drouin, J., Baricault, B., ... & Zureik, M. (2022). Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines. *Nature communications*, 13(1), 1-9.

<https://www.nature.com/articles/s41467-022-31401-5>



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Table of contents

Table of contents.....	2
Lay Summary.....	3
Authorship and Committee Members.....	4
Topic.....	5
Context.....	5
Key Messages.....	5
Practical Guidance.....	11
Research Gaps.....	12
Strength of Evidence.....	13
Limitations of this review.....	13
Summary of Evidence.....	13
1. <i>What medical conditions should be considered as valid exemptions from required COVID-19 vaccination using current vaccine products?</i>	13
<i>Evidence from secondary and grey literature</i>	13
<i>Synthesis of the Information Relating to Question 1</i>	16
2. Is there any additional evidence around specific adverse events (myocarditis/pericarditis) related to the mRNA COVID-19 vaccines that would alter current guidance around vaccine exemptions?	17
Evidence from secondary and grey literature	17
Evidence from the primary literature – Post-Vaccination Myocarditis Data.....	25
Synthesis of the Information Relating to Question 2	29
Evolving Evidence.....	30
Appendix.....	30
Methods.....	30
Literature Search (Update).....	30
Critical Evaluation of the Evidence.....	30
Search Strategy.....	31
References.....	32
Appendix A-Jurisdiction Specific Guidance.....	37
Appendix B: NHS Flowchart for managing individuals with allergic reactions.....	46
Appendix C: Tools that may assist with determining vaccine administration.....	47
Appendix D: Pregnancy, Breastfeeding and Fertility and the COVID-19 Vaccine.....	48

Lay Summary

- It is very important that all Albertans that are able to receive the COVID-19 vaccine to protect themselves from severe COVID-19 outcomes, reduce spread, and to end the pandemic.
- Across all of the guidelines reviewed, there were no medical reasons that would completely prevent someone from taking one of the available COVID-19 vaccines, although some conditions may need specialist review before decisions are made.

The guidance reviewed can be summarized as:

- Those people who had a documented severe allergic (anaphylactic) reaction to a first dose of vaccine or to a known vaccine ingredient should be seen by an Allergy specialist physician to determine how best to get them a COVID-19 vaccine. It may mean they may need extra monitoring or may need to take a different type of COVID-19 vaccine.
- Someone that developed a very rare reaction such as myocarditis to the first dose of the vaccine may need to be seen by a specialist to be assessed before further doses of a COVID-19 vaccine. The risk of any kind of myocarditis (from infections including COVID-19, immune reactions, or vaccines) is higher in younger men, and is different between vaccine doses and vaccine types.
- Almost all Albertans can and should receive COVID-19 vaccines. If individuals have specific questions about their eligibility for one of the available vaccines, then they should speak with their family doctor, specialist, or call HealthLink.

Authorship and Committee Members

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Topic: Medical Exemption for COVID-19 Vaccination

1. What medical conditions should be considered as valid exemptions from required COVID-19 vaccination using current vaccine products?
2. (New) Is there any additional evidence around specific adverse events (myocarditis/pericarditis) related to the mRNA COVID-19 vaccines that would alter current guidance around vaccine exemptions? (literature until February 2022)

Context

- This Rapid Review is primarily a Jurisdictional Scan, now supplemented with an additional targeted literature review related to myocarditis/pericarditis potentially related to COVID-19 vaccination. New additions to the report have been highlighted. The purpose of a jurisdictional scan is to identify policy/approaches used in other jurisdictions (provinces, nations, organizations) including their evidence base, to gain an understanding of how decisions are made.
 - Selected guidelines and a targeted evidence review are used to inform considerations around both initial vaccination and subsequent doses, where risk assessment around suspect prior potential adverse events is required.
 - This review considers medical exemptions and does not address human rights, religious or other possible non-medical reasons for seeking vaccine exemptions
- The information in this review provides examples of policy related to medical exemption for vaccination against COVID-19 from major public health organizations, and provides an evidence update around myocarditis risk around COVID-19 vaccination. As vaccine mandate recommendations are in evolution, there was increased focus on considerations around risk assessment for initial and subsequent doses rather than exemptions in this update.

Key Messages

Vaccine adverse effects and exemptions:

- COVID-19 vaccines have been shown to have an excellent vaccine safety profile in worldwide use since initial human vaccine studies began in March 2020, with over 4.9 billion doses administered worldwide as of February 23, 2022 (<https://OurWorldInData.org>). Medical conditions which affect vaccine planning and medical exemptions from vaccination need to be reviewed periodically as new vaccine products become available and additional data on existing products are analyzed
- In existing guidance there are very few absolute medical grounds for exemption from COVID-19 vaccination; this finding was consistent across jurisdictions.

- The most prominent potential exemption is related to second doses after suspected or documented severe allergy/anaphylaxis to the COVID-19 vaccine itself, which is noted in all documents; however, the guidance on subsequent steps for these individuals varies. Note: severe allergic reactions to the COVID-19 vaccine are rare; even among those deemed as being 'highly allergic' only 0.7% had a severe allergic reaction to the vaccine administered under medical supervision (Shavit et al., 2021). In the United States, the CDC reported 11.1 cases of anaphylaxis for one million doses of vaccine given (CDC, 2021e).
- Assessment by an allergist is warranted in any individual with a suspected allergy to a COVID-19 vaccine or any of its components (Canadian Society for Allergy and Clinical Immunologists, 2021a). Individuals generally are offered monitored vaccination, an alternate vaccine, or deferral after assessment.
- Suspected vaccine adverse event data is collected to monitor vaccine safety. In Alberta, a health care practitioner must report all potential adverse events following immunization (AEFI) that they become aware of, within 3 days:
 - [Adverse Event Following Immunization Reporting | Alberta Health Services https://www.albertahealthservices.ca/info/Page16187.aspx](https://www.albertahealthservices.ca/info/Page16187.aspx)

An AEFI is defined as an unfavourable health occurrence experienced by a patient that:

- Follows immunization
- Cannot be attributed to a pre-existing condition and
- Meets one or more of the following as determined by a health practitioner:
 - A life-threatening health occurrence that requires hospitalization or urgent medical attention.
 - The health occurrence is unusual or unexpected that:
 - Has not previously been identified; or
 - Has been previously identified but has increased frequency
 - The health occurrence cannot be explained by the patient's medical history, recent disease or illness or consumption of medication.
- Patients may call HealthLink at 811 to report an adverse event or contact their provider.

New in this update: Myocarditis data review

In currently recommended vaccination schedules, across all age ranges, the risk of vaccine associated myocarditis appear lower, and the health outcomes less severe, than the risk of COVID-19 infection associated myocarditis

- Myocarditis is inflammation of the heart muscle, which can be caused by viral infections (including COVID-19 infection) and immune conditions. All forms of myocarditis are more frequent in younger males, with most reports showing the highest risk of all-cause myocarditis in males approximately 16-30 years old.

- Common 'viral' myocarditis occurs in 1–10 per 100,000 people per year, with a survival rate of >80%. COVID-19 infection-associated myocarditis is thought to occur in 1- 4% of cases, with a lower survival rate of 30-80%.
- mRNA COVID-19 vaccination is associated with an elevated risk of myocarditis post vaccination, but is estimated to occur much less commonly than myocarditis with COVID-19 infection, at 0.3–5.0 per 100,000 vaccinated people, with a much higher survival rate of greater than 99% (Heymans & Cooper, 2021).
- The risk appears more prominent in males age 12-29, after their second dose of COVID-19 vaccine. Most cases have been mild and resolve quickly ([National Advisory Committee on Immunization, 2022](#)). This small risk appears to be associated more commonly with the Moderna mRNA vaccine than with PfizerBioNTech mRNA vaccine, and is also more significant following the second dose.
- Current data suggests that COVID-19 infection related myocarditis occurs at rates as much as 700X higher than baseline myocarditis rates in the highest risk age group, with 20-70% mortality in these cases.
- Myocarditis after COVID-19 mRNA vaccination is 20-120X less common than myocarditis after COVID-19 infection based on current data, with a survival rate over >99%.and generally good outcomes
- There is insufficient data to comment on myocarditis risk after the Novavax protein subunit vaccine, with monitoring underway.
- Therefore, the risk of COVID-19 mRNA vaccine associated myocarditis, which generally has a favourable outcome, needs to be weighed against the risk of myocarditis from COVID-19 infection, and the risk of any severe outcome from preventable COVID-19 infection. In addition, current data suggests different degrees of possible risk by vaccine dose (apparent higher risk after dose 2) and vaccine type (apparent higher risk in younger males receiving Moderna vaccine). This allows risk reduction through specific recommendations of vaccine product and schedule. Current Canadian data reports a myocarditis rate of 3.0 per 100,000 doses of the Moderna 100 mcg vaccine compared to 1.9 per 100,000 doses of the Pfizer-BioNTech 30 mcg vaccine. Males 18-29 y after the second dose of Moderna 100 mcg vaccine had the highest reported rate at 15.9 per 100, (compared to 2.6 per 100,000 for the Pfizer-BioNTech 30 mcg vaccine.) For males age 12-17 years the rate after the second Pfizer-BioNTech 30 mcg dose was 8.6 per 100,000. (National Advisory Committee on Immunization, 2021c). Preliminary analyses suggest a longer interval between the first and second doses is protective against myocarditis.
- Initial Alberta data from October 8, 2021 showed a reported myocarditis rate after dose 2 of the Pfizer vaccine to be lower, at 0.7 per 100,000 and after second dose of Moderna was 0.8 per 100,000 overall (Alberta Health, 2021). The most recent available data (January 18, 2022) shows a total of 101 reports of myocarditis in Alberta following vaccination over a total of 8,076,666 doses administered (Government of Alberta, 2022).

- In current NACI guidance, it is suggested that people who experienced myocarditis within 6 weeks of COVID-19 vaccination (confirmed by specific testing) can defer further doses of COVID-19 mRNA vaccine but may choose to receive another dose after a risk – benefit assessment with their healthcare provider. These individuals should be offered the Pfizer-BioNTech 30 ug vaccine preferentially due to the lower reported rate of myocarditis. There is not enough data to make a recommendation for use of **Novavax protein subunit vaccine** after suspect or proven myocarditis following a dose of mRNA vaccine. (NACI, 2022a).
- If the diagnosis was pericarditis, or if no abnormalities were found on investigation, vaccination can proceed if at least 90 days have passed since initial vaccination.
- NACI guidance currently supports Novavax use in a heterologous (mixed) primary series or as a booster dose in a heterologous prime-boost series, for individuals for whom mRNA COVID-19 vaccine is contraindicated, inaccessible, or has been refused but it is not yet established as preferred as a second dose is because two teenage males had clinically mild myocarditis after the second dose of Novavax vaccine in trials, and it is unclear if these cases represent a safety signal.
- Data related to the rate of myocarditis related to booster/third, or subsequent doses of mRNA COVID-19 vaccines is evolving, with early reports suggesting increased over baseline risk for 30 days after the third dose of Pfizer vaccine in males <40, with an overall lower risk around the third dose than myocarditis events after COVID-19 infection (Patone et al., 2021b). Given the current vaccination schedule, it is anticipated that data related to this concern will be followed closely.
- **Multiple vaccine safety monitoring systems are an essential part of the benefit and harm assessments that underpin current pandemic management. Ongoing surveillance will inform guidance updates and COVID-19 vaccination protocols, including both assessment of new adverse events of interest and post marketing surveillance of newly approved COVID-19 vaccine products.**
- **Tables 1 and 2 (included on the next two pages) show the updated considerations for vaccine risk assessment, deferral, or modified administration for individuals receiving their initial dose (table 1) and second/subsequent doses (table 2) of COVID-19 vaccine.**

Table 1. **UPDATED** Synthesis of considerations for vaccination risk assessment , deferral, timing or modified administration in specific populations for INITIAL dose of COVID-19 vaccine

Population	Recommendation regarding <u>initial</u> dose planning
<p>People with severe immediate allergic reaction/anaphylaxis to components of mRNA vaccines</p> <p>Allergy specialist assessment recommended</p>	<ul style="list-style-type: none"> • Recommend assessment by an allergist/immunologist regarding COVID-19 vaccine product choice and recommended monitoring. Initial COVID-19 vaccination using Novovax (Nuvaxoid) may be considered without allergist assessment. • Ongoing deferral requires specialist follow-up and reassessment as new safety data and more vaccine products become available
<p>People with current myocarditis or pericarditis who have not had COVID-19 vaccination</p>	<ul style="list-style-type: none"> • mRNA COVID-19 vaccination should be delayed <u>until myocarditis/pericarditis symptoms resolve</u>
<p>People who received antiviral monoclonal antibodies (e.g. Sotrovimab) for COVID-19 treatment</p>	<ul style="list-style-type: none"> • Delay of vaccination for 3 months is suggested (based on antibody half-life, as these treatments may interfere with vaccine response). This remains under evaluation. Expert clinical opinion maybe sought on a case-by-case basis
<p>Unvaccinated people with current active COVID-19 infection*</p>	<ul style="list-style-type: none"> • Receive vaccination 8 weeks after onset of illness (or from positive test associated with acute exposure if they never had symptoms), based on immunological principles. • This delay can be reduced to 4-8 weeks in people who are moderately to severely immunocompromised). • Individuals who have been diagnosed with Multisystem inflammatory syndrome in children (MIS-C) can receive the vaccine dose when clinical recovery has been achieved or ≥3 months since the onset of MIS-C whichever is longer.
<p>Pregnant, breastfeeding, or those of childbearing years</p>	<ul style="list-style-type: none"> • PROCEED: mRNA COVID19 vaccine is recommended for individuals in the authorized age group who are pregnant, breastfeeding, or those planning to become pregnant, Getting the COVID-19 vaccine can help prevent serious illness, hospitalization, and pregnancy complications.
<p>Previous severe allergic reaction to any <u>injectable</u> therapy (e.g., intramuscular, intravenous, or subcutaneous vaccines or therapies)</p>	<ul style="list-style-type: none"> • PROCEED: People with prior reactions to other therapies or vaccines may be routinely vaccinated and do not need referral • An extended period of observation post-vaccination of 30 minutes should be provided
<p>PROCEED: History of any other allergies (allergy not related to a component of authorized COVID-19 vaccines)</p>	<ul style="list-style-type: none"> • Can receive COVID-19 vaccines without any special precautions
<p>Specific to AstraZeneca/COVISHIELD COVID-19 Vaccine Initial dose</p>	
<p>Diagnosis of capillary leak syndrome (CLS) before COVID-19 vaccination</p>	<ul style="list-style-type: none"> • mRNA COVID-19 vaccine should be offered • Rare reports of patients with CLS developing symptoms after AstraZeneca/COVISHIELD COVID-19 vaccine.

*Individuals with active COVID-19 infection may receive their first dose after acute symptoms of COVID-19 have resolved and they are no longer infectious considering biological and social risk factors including likely success of scheduling later vaccination.

Table 2. **UPDATED:** considerations for **SECOND and subsequent doses** of COVID-19 vaccine

Population	Recommendation
People with a potential severe allergic reaction or anaphylaxis following a COVID-19 vaccine	<ul style="list-style-type: none"> • Recommend assessment by an allergist/immunologist regarding subsequent COVID-19 vaccine product choice and recommended monitoring. • COVID-19 series may be continued with Novavax (Nuvaxoid) without allergist assessment. • Ongoing deferral requires specialist follow-up and reassessment as new safety data and more vaccine products become available
People with current active COVID-19 infection after the first dose of COVID-19 vaccine*	<ul style="list-style-type: none"> • Non-immunocompromised, age 5 and up can receive the vaccine 8 weeks after symptom onset or positive test (if asymptomatic and acutely exposed), Moderately or severely immunocompromised can be vaccinated at 4-8 weeks. (Delay intended to maximize the immune response). • This delay interval suggestion is a guide and updated public health recommendations should be consulted
People with current active COVID-19 infection who have had the primary series and are eligible for repeat doses*	<ul style="list-style-type: none"> • Receive vaccination 3 months after onset of illness (or from positive test after acute exposure, if they never had symptoms) provided it is if no least 6 months from completing the primary series.
People with a previous diagnosis of MIS-C	<ul style="list-style-type: none"> • Receive the vaccine dose when clinical recovery has been achieved or ≥3 months since the onset of MIS-C, whichever is longer
People diagnosed with suspect or proven myocarditis or pericarditis following the first dose of an mRNA COVID-19 vaccine	<ul style="list-style-type: none"> • Consider Cardiology or other specialty consultation if the diagnosis is unclear. Current NACI guidance suggests those that had required no cardiac workup or had normal investigations may receive the next dose once asymptomatic and at least 90 days after last vaccination. • Individuals that choose to receive another dose of vaccine after discussing the risks and benefits with their healthcare provider should be offered the Pfizer-BioNTech 30 mcg vaccine. • The risk of recurrence of myocarditis and/or pericarditis following receipt of additional doses of Pfizer-BioNTech COVID-19 vaccine after confirmed myocarditis and/or pericarditis thought related to mRNA vaccine is unknown. The role of Novavax (Nuvaxoid) in this situation is currently unclear (view NACI guidance here)
AstraZeneca/COVISHIELD COVID-19 Vaccine Recipients: Subsequent doses	
Population	Recommendation
People with Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)	<ul style="list-style-type: none"> • Offer an mRNA COVID-19 vaccine - alternate Novavax (Nuvaxoid)

People with thrombosis with thrombocytopenia syndrome (TTS) and coagulation disorders, including thrombotic complications (DVT, cerebral, or MI or CVA) potentially related to vaccination	<ul style="list-style-type: none"> • Offer an mRNA COVID-19 vaccine - alternate Novavax (Nuvaxoid)
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*Individuals with active COVID-19 infection may receive their first dose after acute symptoms of COVID-19 have resolved and they are no longer infectious, considering biological and social risk factors including likely success of scheduling later vaccination.

Younger people (12-29 age group) have a higher myocarditis risk after COVID, after COVID vaccination, and at baseline. Vaccine choice considerations to mitigate myocarditis risk have been issued by NACI (National Advisory Committee on Immunization, 2021c) as follows:

Primary Series	
12-29 years	Pfizer-BioNTech Comirnaty (30 mcg dose), minimum 8 weeks between dose 1 and dose 2 (higher effectiveness and potentially lower myocarditis risk)
Booster Dose Considerations (if eligible)	
12-29 years	Pfizer-BioNTech Comirnaty (30 mcg dose), minimum 6 months after initial series
Primary or booster dose	
30 years or older	Either of the mRNA COVID-19 vaccines should be used

Practical Guidance

1) There are no medical conditions that are universally identified as medical exemptions for initial COVID-19 vaccination. There may be a small number of persons who should have time limited deferrals assigned to allow for an appropriate assessment process. Referral for appropriate specialist assessment of some conditions (in particular anaphylaxis to vaccine components or recent myocarditis) may be considered, or an alternate vaccine product considered. Delay or deferral of initial vaccination should be reassessed with evolving risk of transmission, vaccine safety data and new vaccine product availability.

2) Deferral of vaccination is suggested for individuals experiencing acute COVID-19 illness, in order to optimize the immune response, although there may be circumstances where administration after acute symptoms of COVID-19 have resolved and they are no longer infectious can be considered.

Current NACI guidance suggests (NACI, 2022b), for vaccination after active COVID-19 infection:

- Receive the initial vaccine dose at least 8 weeks after symptom onset (or the first positive test if completely asymptomatic) unless moderately to severely immunocompromised (who may receive at 4-8 weeks if asymptomatic), or have had MIS-C (receive after clinical recovery or >90 days after onset, whichever is longer)

- For subsequent doses, it is recommended to delay for 3 months after symptom onset (or the first positive test if completely asymptomatic), provided the individual is asymptomatic and at it has been at least 6 months since the primary series.

3) A delay of 3 months is currently recommended for individuals that have received COVID antiviral monoclonal antibodies (e.g. sotrovimab) as these therapies may impair the immunologic response to vaccination. This timing remains under evaluation.

4) A time limited deferral of further doses pending designated specialist assessment of potential first dose complications may be warranted. Deferral requires documentation that includes the time frame of the planned assessment/deferral.

5) Suspected myocarditis related to vaccination may be followed by vaccination with Pfizer-BioNTech 30 mcg after a risk benefit discussion and informed consent process (see NACI guidance), or deferral with planned reassessment based on evolving data or new vaccine products.(see table). This decision should be guided by an assessment that includes the risk of COVID-19 exposure, and likelihood of severe outcomes from COVID-19 infection based on age and comorbidity. Specialist referral may be indicated.

6) In general, specialist support and consultation may be considered for assessment of;

- 1) History of severe allergy/anaphylaxis to the first COVID vaccine dose
- 2) History of probable myocarditis after the first COVID vaccine dose
- 3) History of vaccine related thrombosis or thrombocytopenia
- 4) Severe psychiatric or psychologic contraindications such as needle phobia which have been refractory to standard management.

7) The outcome of COVID-19 vaccination assessment referrals may include:

- 1) Deferral of COVID-19 vaccination with planned review. Continued exemption status will require annual review given the evolution of medical knowledge and potential availability of new COVID-19 vaccine products.
- 2) Provision for monitored vaccination.
- 3) Suggestion for use of an alternate vaccine product.

For people with a status of current **COVID-19 vaccine exemption or continued approved deferral**, risk education, and if relevant, discussion of reasonable measures for workplace accommodation is required. When necessary, the Adverse Event Following Immunization (AEFI) protocol should be followed to report any adverse events after vaccination.

Research Gaps

The evidence related to COVID-19 vaccination safety and effectiveness is a rapidly evolving area, with changing estimates of effectiveness of different vaccines in various age groups, different dominant variants over time, and ongoing vaccine safety monitoring program data. Given expanded indication for additional doses of COVID-19 vaccines, there is limited accrued data related to booster doses in various populations. As Novavax is newly approved by Health Canada, the literature on effectiveness

against current VOCs, complications and contraindications is very limited and should be monitored.

Strength of Evidence

The jurisdictional Scan summarizes vaccination guidance but is not a synthesis of primary scientific literature; as such, the evidence and strength of evidence is not assessed. We conducted a search of grey literature, and websites / documentation of jurisdictions in North America and Western Europe for guidance on COVID-19 vaccination, specifically medical contraindications or precautions to vaccination. Where available, the supporting scientific evidence for stated exemptions was reviewed, but a primary search and review of the scientific literature for medical exemptions for COVID-19 vaccination was not conducted. Overall, the first pass jurisdictional scan resulted in identification of consistent exemptions among the three national and four provincial jurisdictions included, and search and inclusion of additional guidelines was not conducted as it was deemed unlikely to additive at this time.

For the March 2022 update, a targeted literature search around myocarditis and pericarditis after vaccination was performed, and new NACI guidance around vaccination after infection, and use of Novavax as an alternate booster in specific situations was incorporated.

Limitations of this review

The Jurisdictional Scan was limited to online resources available reporting medical exemptions for COVID-19 vaccination. Numerous corporations (particularly in the United States) have developed internal policies related to mandatory vaccination and vaccine exemptions that are not readily available. Therefore, this document focuses on available information provided by oversight groups.

Summary of Evidence

1. What medical conditions should be considered as valid exemptions from required COVID-19 vaccination using current vaccine products?

Evidence from secondary and grey literature

Overall guidelines identify similar potential contraindications, however variability in recommended processes exists.

Below is a summary of specific medical exemption categories and considerations (both contraindications and precautions) described by various organizations, however Jurisdiction-specific information is available in Appendix A.

Allergy

Note: mild to moderate immediate allergic reactions are defined as limited in the scope of symptoms and involvement of organ systems or even localized to the site of administration. Severe allergic reaction refers to an anaphylactic reaction.

Canadian guidance: NACI indicates that (Government of Canada, 2021b; National Advisory Committee on Immunization, 2021a):

- COVID-19 vaccine should not be offered **routinely** to individuals with a history of severe allergic reaction (e.g., anaphylaxis) after previous administration of a COVID-19 vaccine using a similar platform (mRNA or viral vector). A COVID-19 vaccine using a different platform may be considered for re-immunization.
- A COVID-19 vaccine should not be routinely offered to individuals who are allergic to any component of the specific COVID-19 vaccine or its components (such as individuals allergic to Polyethylene Glycol (PEG)).
- Individuals with previous severe allergic reaction (e.g., anaphylaxis) to injectable therapy unrelated a component of authorized COVID-19 vaccines may be routinely vaccinated with an extended observation time of 30 minutes.
- Individuals with **suspected but unproven** allergy to a vaccine component (e.g. PEG) may be routinely vaccinated and do not need a specific assessment regarding this suspected allergy with an extended observation time of 30 minutes.
- Individuals with a history of allergy unrelated to a component of COVID-19 vaccines or other injectable therapy (e.g. foods, oral drugs, insect venom or environmental allergens) can receive COVID-19 vaccines without any special precautions.

The Canadian Society of Allergy and Clinical state **(updated November 14, 2021)**:

- “Assessment by an allergist is **WARRANTED** for any individual with **anaphylaxis following the COVID-19 vaccine or to any of its components**. This is strongly preferred over not being vaccinated or withholding vaccination, and includes anyone who has experienced a suspected severe immediate allergic reaction after administration of a COVID-19 vaccine, or someone with a confirmed allergy to a component of the vaccine. There is increasing evidence that these individuals can safely receive a subsequent dose of the same vaccine with low risk of a systemic reaction under the supervision of an allergist. This recommendation is in keeping with the National Advisory Committee on Immunization (NACI) recommendations, which currently recommend that revaccination with the same vaccine or same mRNA platform may be offered in consultation with an allergist. (Canadian Society for Allergy and Clinical Immunologists, 2021b).”
- Assessment by an allergist is **NOT** required for individuals with a history of unrelated allergies or anaphylaxis including to allergies to other vaccines, foods, drugs, insect venom or environmental allergens, or those that have a mild, localized reaction to the COVID-19 vaccine or any of its components.

The National Health Service (NHS), United Kingdom (NHS , 2021b) provides a flowchart to advise on allergic reactions to first dose of vaccine (Appendix B). Additionally, tools that have been developed in the United States and the United Kingdom to assist with determining vaccine safety for specific individuals, provided as potential resources in Appendix C.

Individuals with a history of myocarditis/pericarditis after first dose of mRNA vaccination
NACI in January 2022 revised the guidance on how to proceed with second vaccination for those who experienced myocarditis/pericarditis after their first doses of mRNA vaccine. Their guidance now states:

“Those with a history compatible with pericarditis and who either had no cardiac workup or had normal cardiac investigations, can receive the next dose once they are symptom free and at least 90 days has passed since vaccination.

Some people with confirmed myocarditis (with or without pericarditis) after a dose of an mRNA COVID-19 vaccine may choose to receive another dose of vaccine after discussing the risks and benefits with their healthcare provider. If another dose of vaccine is offered, they should be offered the Pfizer-BioNTech 30 mcg vaccine due to the lower reported rate of myocarditis and/or pericarditis following the Pfizer-BioNTech 30 mcg vaccine compared to the Moderna 100 mcg vaccine. Informed consent should include discussion about the unknown risk of recurrence of myocarditis and/or pericarditis following receipt of additional doses of Pfizer-BioNTech COVID-19 vaccine in individuals with a history of confirmed myocarditis and/or pericarditis after a previous dose of mRNA COVID-19 vaccine, as well as the need to seek immediate medical assessment and care should symptoms develop (National Advisory Committee on Immunization, 2022).”

Individuals with Underlying Medical Conditions who should be advised to receive COVID-19 vaccination:

Individuals may have concerns around vaccination related to medical conditions. Guidance documents from the CDC in the US, Health Canada and the NHS England provide specific reassurance that all concerned groups should be recommended to receive vaccination, as follows:

The CDC states that individuals with underlying medical conditions may be at increased risk of severe outcomes from contracting COVID-19 (CDC, 2021c, 2021d). The current CDC guidance states the following individuals **are advised to be vaccinated**:

- Individuals with weakened immune systems (such as those living with HIV, taking medications that cause immunosuppression, etc.).
- Individuals with autoimmune conditions.
- Individuals with a history of Guillain Barre Syndrome (GBS). If available, the mRNA vaccine may be preferable.
- Individuals with history of Bell’s Palsy.
- Individuals that have received dermal filler. They may experience some swelling near the dermal filler site.
- Individuals with risk factors for venous thromboembolism (VTE), defined as deep vein thrombosis, pulmonary embolism, or both.

Health Canada (Government of Canada, 2021b) also states:

Individuals receiving long-term anticoagulation are not considered to be at higher risk of bleeding complications post-vaccination and may be immunized without discontinuation of their anticoagulation therapy.

Individuals that are Pregnant, Breastfeeding, or of Childbearing Years (fertility related concerns)

- Guidance is consistent across jurisdictions that COVID-19 vaccination should be recommended to individuals that are pregnant, breastfeeding or planning to get pregnant. A brief summary of information specific to this population is provided in Appendix D.

Viral Vector Vaccine Specific Considerations

NACI (National Advisory Committee on Immunization, 2021a) states:

- Patients who have experienced venous or arterial thrombosis with thrombocytopenia following vaccination with a viral vector COVID-19 vaccine should not receive a second dose of a viral vector COVID-19 vaccine.
- Individuals who have experienced a previous cerebral venous sinus thrombosis (CVST) with thrombocytopenia or heparin-induced thrombocytopenia (HIT) should be offered a mRNA vaccine where available. Viral vector vaccine should only be used where the benefit outweighs the potential risk and mRNA is not available.
- Individuals with a history of capillary leak syndrome should not receive the AstraZeneca /COVISHIELD COVID-19 vaccine.

Synthesis of the Information Relating to Question 1

(See Tables 1 & 2) The following summarizes identified potential medical exemptions, risk assessment, delay or deferral of routine administration of the COVID-19 vaccination:

- Anaphylaxis and allergies to a COVID-19 vaccine or any of its components
- Thrombosis and thrombocytopenia following viral vector COVID-19 vaccination (should not receive a subsequent dose of a viral vector vaccine)
- Individuals with a history of capillary leak syndrome should not receive the AstraZeneca /COVISHIELD COVID-19 vaccine.
- COVID-19 vaccines should not be given simultaneously with antiviral monoclonal antibodies or convalescent plasma.

The following summarizes precautions for individuals with the following conditions:

- Individuals with hypersensitivity and allergies may require additional observational periods
- In persons with acute COVID-19 illness, vaccination should be deferred at least until symptoms resolve and the person is noninfectious, with immunologic considerations for a potential 2 month delay of first dose or three month delay of subsequent doses with some specific considerations for MIS-C patients and immunocompromised (see table).
- In individuals with bleeding disorders, their condition should be managed prior to immunization to minimize the risk of bleeding

- Individuals with a history of both thrombosis and thrombocytopenia should only receive a viral vector COVID-19 vaccine if the potential benefits outweigh the potential risks. An alternate COVID-19 vaccine (mRNA) should be offered
- In those with mRNA associated myocarditis and/or pericarditis, the second dose in the mRNA COVID-19 vaccination may be deferred, however some people with confirmed myocarditis (with or without pericarditis) after a dose of an mRNA COVID-19 vaccine may choose to receive another dose of vaccine after discussing the risks and benefits with their healthcare provider.

2. *Is there any additional evidence around specific adverse events (myocarditis/pericarditis) related to the mRNA COVID-19 vaccines that would alter current guidance around vaccine exemptions?*

Individuals who experience myocarditis after mRNA COVID-19 vaccination require assessment, and may defer subsequent doses with reassessment as new vaccine products become available or may be offered vaccination preferentially with Pfizer 30 ug after a risk – benefit assessment.

Evidence from secondary and grey literature

Myocarditis is inflammation of the heart muscle, which can be caused by viral infections (including COVID-19 infection) and immune conditions. All forms of myocarditis are more frequent in younger males. In a population-based study in the pre COVID era, the highest rates of hospitalized myocarditis occurred in those age 16-20y, and 21-30y at 12.8 and 11.1 per 100,000 in 2019, with those under 14 and >50 having lower rates (< 3 and <4 per 100,000) (Ozierański et al., 2021). COVID-19 infection myocarditis has been reported to occur more frequently in younger people (12-29 year old males, 5610-8760 per 100,000; and in 12-19 year old females, 213-708 per 100,000) (Singer, Taub & Kaelber, preprint). Overall COVID-19 infection-associated myocarditis and cardiac injury incidence is reported to occur at a rate of 1,000–4,000 per 100,000 people with SARS-CoV-2 infection (30-80% survival rate), while myocarditis after COVID-19 mRNA vaccination incidence is reported at 0.3–5.0 per 100,000 vaccinated people (>99% survival rate) (Heymans & Cooper, 2021).

Cardiovascular adverse events, specifically myocarditis, have been noted after a variety of infections as well as after other vaccinations following vaccination are not unique to the COVID-19 vaccine. Historically there were cases of myocarditis following vaccinations for smallpox, hepatitis B, and influenza (Hana et al., 2021). In July, 2021 the COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) stated that cases of myocarditis/pericarditis are rare (World Health Organization, 2021). Those that have occurred, are more often in adolescents or young adults) males, more commonly after the second dose and typically within a few days of receiving a mRNA COVID-19 vaccine (European Centre for Disease Prevention and Control, 2021; World Health Organization, 2021).

Table 3. Comparison of viral myocarditis, and COVID-19-associated myocarditis and myocarditis after COVID-19 mRNA vaccination. (Taken from Heymans & Cooper, 2021)

Myocarditis Type	Incidence	Survival (%)	Potential Mechanism
'Common' viral myocarditis	1–10 per 100,000 people per year	>80	Myocardial injury Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Immune crossreactivity Sex-related factors
COVID-19-associated myocarditis and cardiac injury	1,000–4,000 per 100,000 people with SARS-CoV-2 infection	30–80	Endothelial injury and microthrombosis Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Sepsis and shock
Myocarditis after COVID-19 mRNA vaccination	0.3–5.0 per 100,000 vaccinated people	>99	Hypersensitivity reaction Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Immune crossreactivity Sex related factors

Emerging Canadian safety surveillance data suggest that an extended interval (more than the trial based 21-28 day interval) between the first and second dose may reduce the risk of myocarditis/pericarditis associated with the second dose of an mRNA COVID-19 vaccine, with these data currently under preparation for publication. (National Advisory Committee on Immunization, 2021b). Data from the US suggests the risk of myocarditis/pericarditis following mRNA COVID-19 vaccination may be higher in older adolescents aged 16-17 years compared to younger adolescents aged 12-15 years (Oster, 2021).

Recommendations on management of people who experienced myocarditis after a previous mRNA COVID-19 vaccine dose:

In current NACI guidance, it is suggested that people who experienced myocarditis within 6 weeks of COVID-19 vaccination (confirmed by specific testing) can defer further doses of COVID-19 mRNA vaccine, but may choose to receive another dose after a risk – benefit assessment with their healthcare provider. These individuals should be offered the Pfizer-BioNTech 30 ug vaccine preferentially due to the lower reported rate of myocarditis. If the diagnosis was pericarditis, or if no abnormalities were found on investigation, vaccination can proceed if at least 90 days have passed since initial vaccination.

The role of **Novavax protein subunit vaccine**, which was approved in Canada in February 2022, in subsequent immunization after suspect or proven myocarditis following a dose of mRNA vaccine remains uncertain awaiting further data (NACI, 2022a). NACI guidance currently supports Novavax use in a heterologous (mixed) primary series or as a booster dose in a heterologous prime-boost series, for individuals for whom mRNA COVID-19 vaccine is contraindicated, inaccessible, or has been

refused , however two teenage males had clinically mild myocarditis after the second dose of Novavax vaccine in trials, and it is unclear if these cases represent a safety signal.

Data related to the rate of myocarditis related to booster/third, or subsequent doses of mRNA COVID-19 vaccines is evolving, with early reports suggesting increased over baseline risk for 30 days after the third dose of Pfizer vaccine in males <40, with an overall lower risk around the third dose than myocarditis events after COVID-19 infection (Patone et al., 2021b). Given the current vaccination schedule, it is anticipated that data related to this concern will be followed closely.

Canadian and Alberta based data on myocarditis after COVID-19 vaccination:

Canadian data on post vaccination myocarditis up to November 12, 2021 (published December 3, 2021) suggests a reported rate of myocarditis of 3.0 per 100,000 doses administered following any dose of the Moderna 100 mcg vaccine compared to 1.9 per 100,000 doses administered following any dose of the Pfizer-BioNTech 30 mcg vaccine. For males 18-29 years of age, the highest risk group for myocarditis, the rate after the second dose of Moderna 100 ug vaccine was 15.9 per 100,000, and 2.6 per 100,000 for the Pfizer-BioNTech 30 mcg vaccine. For males age 12-17 years second vaccine dose myocarditis rate for the Pfizer-BioNTech 30 mcg was 8.6 per 100,000 , and no rate was calculable for Moderna dose two as one case was documented. (National Advisory Committee on Immunization, 2021c). Preliminary analyses suggest a longer interval between the first and second doses may be associated with lower risk compared to a 3-4 week interval.

In Alberta, as of October 8, 2021, the rate of reported myocarditis after the second dose of the Pfizer vaccine was 6.6 per million, while the rate after second dose of Moderna was 8.3 per million for all ages and sexes combined (Alberta Health, 2021). The most recent available data (January 18, 2022) shows a total of 101 reports of myocarditis in Alberta following vaccination over a total of 8,076,666 doses administered (Government of Alberta, 2022). The Chief Medical Officer of Health indicated that “The risk of cardiac complications, including myocarditis, has been shown to be substantially increased following COVID-19 infection, and it is higher following infection than after vaccination”(Alberta Health, 2021).

NACI Guidance:

Additional data review around myocarditis/pericarditis reveals a probable link between mRNA COVID vaccination and an elevated risk of post vaccination myocarditis which appears more prominent in males age 12-29, after their second dose of COVID-19 vaccine. Most cases have been mild and resolve quickly ([National Advisory Committee on Immunization, 2022](#)). This small risk appears to be associated more commonly with the Moderna mRNA vaccine than with Pfizer-BioNTech mRNA vaccine, and is also more significant following the second dose. There is insufficient data on myocarditis risk after the Novavax protein subunit vaccine. In assessing these data, the risk of vaccine associated myocarditis, which generally has a favourable outcome, needs to be weighed against the numerically greater risk of myocarditis from COVID-19 infection, and the risk of any severe outcome from COVID-19 infection.

In December 2021, the National Advisory Council on Immunizations (NACI) published a rapid response related to risk of myocarditis/pericarditis (henceforth pericarditis will be considered with the term myocarditis) from several countries and updated their recommendation as follows:

- NACI preferentially recommends that a complete series with an mRNA COVID-19 vaccine should be offered to individuals 12 years and older without contraindications to the vaccine. (Strong NACI Recommendation)

For individuals aged 12 to 29 years receiving an mRNA COVID-19 vaccine primary series:

- The use of Pfizer-BioNTech Comirnaty (30 mcg dose) is preferred to Moderna Spikevax (100 mcg dose) to start or continue the mRNA primary vaccine series.
- The second dose of mRNA vaccine should be provided 8 weeks after the first dose. The longer interval between doses is associated with higher vaccine effectiveness and potentially lower risk of myocarditis.

NACI recommends for individuals aged 18 to 29 years who are eligible to receive a booster dose of vaccine:

- The use of Pfizer-BioNTech Comirnaty booster dose (30 mcg dose) may be preferred to Moderna Spikevax booster dose (50 mcg dose).
- The booster dose should be provided at least six months after completing the primary vaccine series (National Advisory Committee on Immunization, 2021c).

It should be noted that with the high transmission of the Omicron Variant of Concern (VOC) across communities timing of second and booster doses will be subject to ongoing risk versus benefit assessment (Alberta Health, 2021).

For individuals age 30 years or older, either Moderna Spikevax or Pfizer BioNTech Comirnaty should be used (this age group does not have evidence of an elevated risk of myocarditis around mRNA vaccination)

For individuals 5-11 years of age, Pfizer-BioNTech 10 mcg is currently recommended. Classic myocarditis is less common in younger children 5-11 years of age. It is unknown whether myocarditis/pericarditis will occur after the lower doses of mRNA present within pediatric COVID-19 vaccines for children 5-11 years of age (Oster, 2021).

Canadian data up to November 12, 2021 (published December 3, 2021) suggests a reported rate of myocarditis of 3.0 per 100,000 doses administered following any dose of the Moderna 100 mcg vaccine compared to 1.9 per 100,000 doses administered following any dose of the Pfizer-BioNTech 30 mcg vaccine. For males 18-29 years of age the rate of myocarditis/pericarditis following administration of the second dose of vaccine were of 15.9 per 100,000 for the Moderna 100 mcg vaccine and 2.6 per 100,000 for the Pfizer-BioNTech 30 mcg vaccine. In the 12-17 years of age males group following the second vaccine dose rate was 8.6 per 100,000 for the Pfizer-BioNTech 30 mcg, with one case reported following Moderna (National Advisory Committee on Immunization, 2021c). In Alberta, as of October 8, 2021, the rate of myocarditis after second dose of the Pfizer vaccine is 6.6 per million, while the rate after second dose of

Moderna is 8.3 per million for all ages and sexes combined (Alberta Health, 2021). Most recent data (January 18, 2022) shows a total of 101 reports of myocarditis in Alberta following vaccination over a total of 8,076,666 doses administered (Government of Alberta, 2022).

Table 4. Jurisdictional Scan of Vaccine Recommendations Specific to Myocarditis Risk By Organization, Inclusive of Age-Specific Guidance (Where Available).

ORGANIZATION	RECOMMENDATIONS
<p>NACI-Rapid Response (National Advisory Committee on Immunization, 2021c)</p>	<p>1. NACI preferentially recommends that a complete series with an mRNA COVID-19 vaccine should be offered to individuals 12 years and older without contraindications to the vaccine. (Strong NACI Recommendation)</p> <p>1a. For individuals aged 12 to 29 years receiving an mRNA COVID-19 vaccine primary series:</p> <ul style="list-style-type: none"> • The use of Pfizer-BioNTech Comirnaty (30 mcg dose) is preferred to Moderna Spikevax (100 mcg dose) to start or continue the mRNA primary vaccine series. • The second dose of mRNA vaccine should be provided 8 weeks after the first dose as a longer interval between doses is associated with higher vaccine effectiveness and potentially lower risk of myocarditis/pericarditis. <p>1b. For individuals aged 18 to 29 years who are eligible to receive a booster dose of vaccine:</p> <ul style="list-style-type: none"> • The use of Pfizer-BioNTech Comirnaty booster dose (30 mcg dose) may be preferred to Moderna Spikevax booster dose (50 mcg dose). • The booster dose should be provided at least 6 months after completing the primary vaccine series. <p>1c. For individuals aged 30 years or older receiving an mRNA COVID-19 vaccine primary series or booster dose:</p> <ul style="list-style-type: none"> • Either of the mRNA COVID-19 vaccines (Moderna Spikevax or Pfizer-BioNTech Comirnaty) should be used. • The second dose of mRNA vaccine should be provided 8 weeks after the first dose as a longer interval between doses is associated with higher vaccine effectiveness and potentially lower risk of myocarditis/pericarditis. • The booster dose should be provided at least 6 months after completing the primary vaccine series.
<p>WHO-subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) (World Health Organization, 2021)</p>	<ul style="list-style-type: none"> • The benefits of mRNA COVID-19 vaccines outweigh the risks in reducing hospitalizations and deaths due to COVID-19 infections. • Very rare cases of myocarditis and pericarditis have been observed following vaccination with the mRNA COVID-19 vaccines. These cases occurred more often in younger men and after the second dose of the vaccine, typically within few days after vaccination. Current evidence suggests a likely causal association between myocarditis and the mRNA vaccines • Available data suggest that the immediate course of myocarditis and pericarditis following vaccination is generally mild and responds to conservative treatment (e.g. rest, treatment with nonsteroidal anti-inflammatory drugs etc). Follow-up is ongoing to determine long term outcomes. • More rigorous studies using alternative data sources and more robust study designs including comparison of vaccinated and unvaccinated populations as well as investigations monitoring for longer term follow up are underway; the GACVS subcommittee will continue to review this signal as more data become available.

	<ul style="list-style-type: none"> • The US Food and Drug Administration (FDA) and the EMA have provided updates to the Product Information for the mRNA vaccines (Comirnaty and Spikevax). These and other agencies have issued advisories and various communication materials, to the public and healthcare professionals, with guidance or actions to take following vaccinations with mRNA vaccines. • Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as new onset and persisting chest pain, shortness of breath, or palpitations following vaccination. • Clinicians should be aware of the risk of myocarditis and pericarditis with mRNA vaccines and those most likely to be affected. They should be alert to presentations such as acute chest pain, shortness of breath and palpitations that may be suggestive of myocarditis after vaccination, especially in adolescent or young males. Coronary events are less likely to be the source of such symptoms among younger people. • Where possible, suspected cases should be evaluated, provided guidance and be followed up with cardiologist consultation. • It is important to rule out other potential causes of myocarditis and pericarditis, including COVID-19 infection and other viral etiologies. An infectious disease specialist and/or rheumatologist may need to be consulted to assist in this evaluation.
<p>CDC (Center for Disease Control and Prevention, 2021)</p>	<ul style="list-style-type: none"> • CDC continues to recommend COVID-19 vaccination for everyone 5 years of age and older given the greater risk of other serious complications related to COVID-19, such as hospitalization, multisystem inflammatory syndrome in children (MIS-C), or death. • Report all cases of myocarditis and pericarditis post COVID-19 vaccination to VAERS. • Consider myocarditis and pericarditis in adolescents or young adults with acute chest pain, shortness of breath, or palpitations. In this younger population, coronary events are less likely to be a source of these symptoms. • Ask about prior COVID-19 vaccination if you identify these symptoms, as well as relevant other medical, travel, and social history. • For initial evaluation, consider an ECG, troponin level, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. In the setting of normal ECG, troponin, and inflammatory markers, myocarditis or pericarditis are unlikely. • For suspected cases, consider consultation with cardiology for assistance with cardiac evaluation and management. Evaluation and management may vary depending on the patient age, clinical presentation, potential causes, or practice preference of the provider. • For follow-up of patients with myocarditis, consult the new guidance from the American Heart Association. • It is important to rule out other potential causes of myocarditis and pericarditis. Consider consultation with infectious disease and/or rheumatology to assist in this evaluation. <ul style="list-style-type: none"> ○ Where available, evaluate for potential etiologies of myocarditis and pericarditis, particularly acute COVID-19 infection (e.g., PCR testing), prior SARS-CoV-2 infection (e.g., detection of SARS-CoV-2 nucleocapsid antibodies), and other viral etiologies (e.g., enterovirus PCR and comprehensive respiratory viral pathogen testing).
<p>Australian Government (Australian)</p>	<ul style="list-style-type: none"> • A small increased risk of pericarditis and/or myocarditis has been observed in people who have received an mRNA COVID-19 vaccine (including

<p>Government Department of Health, 2021)</p>	<p>Comirnaty (Pfizer) and Spikevax (Moderna), compared to unvaccinated people.</p> <ul style="list-style-type: none"> • COVID-19 itself is associated with a substantially higher risk of myocarditis and other cardiac complications compared to vaccination. • Emphasise that the overwhelming benefits of vaccination in protecting against COVID-19 greatly outweigh the rare risk of myocarditis and/or pericarditis. Comirnaty and Spikevax continue to be recommended for all people aged 12 years and above. • Pericarditis and myocarditis after mRNA COVID-19 vaccines have been reported most commonly in males under 30 years of age, and most commonly after the second vaccine dose. Most myocarditis and pericarditis linked to mRNA vaccination has been mild and patients have recovered quickly. Longer-term follow-up is ongoing. • Vaxzevria (AstraZeneca) is not associated with an increased risk of myocarditis and/or pericarditis. While cases have been reported after this vaccine, they have not been reported more frequently than what is expected in the absence of vaccination (the 'background rate'). • Pre-existing cardiac conditions are not regarded as a contraindication to vaccination. • People with a history of any of the following conditions can receive an mRNA vaccine (e.g. Comirnaty or Spikevax) but should consult a GP, immunisation specialist service or cardiologist about the best timing of vaccination and whether any additional precautions are recommended: Recent (i.e., within the last 3 months) myocarditis or pericarditis, Acute rheumatic fever or acute rheumatic heart disease (i.e., with evidence of active inflammation), Acute decompensated heart failure • Symptoms of myocarditis or pericarditis typically appear within 1-5 days of an mRNA vaccine dose and may include chest pain, palpitations (irregular heartbeat), syncope (fainting) or shortness of breath. People who experience any of these symptoms after having an mRNA COVID-19 vaccine should seek prompt medical attention.
<p>Alberta Government (Office of the Chief Medical Officer, 2021)</p>	<ul style="list-style-type: none"> • As of November 23, 2021, Alberta is recommending that Pfizer-BioNTech (Comirnaty) COVID-19 vaccine be offered as the preferred choice of mRNA COVID-19 vaccine for Albertans 12 to 29 years of age to start and/or complete their primary series (including immunocompromised individuals who are eligible for a third dose as their primary series). • The preferential recommendation is based on a higher rate of myocarditis and/or pericarditis following immunization with Moderna (Spikevax) COVID-19 vaccine relative to Pfizer-BioNTech (Comirnaty) COVID-19 vaccine in those aged 12 to 29 years, particularly among males. It should be noted that the risk is still considered rare. • This recommendation is supported by the Alberta Advisory Committee on Immunization (AACI), based on their review of all currently available evidence including the most up-to-date Alberta data. • People 12 to 29 years old can still take the Moderna (Spikevax) COVID-19 vaccine, if they so choose, with informed consent. • In Alberta, as of November 15, 2021, there have been 72 confirmed cases of myocarditis after COVID-19 vaccination out of over 6 million vaccine doses administered. Of these 72 cases, there were 8 females and 64 males, with the majority of cases affecting ages 12-29. The majority of cases had mild illness, responded well to symptomatic treatment (antiinflammatory medication) and rest, and their symptoms improved quickly within days. • The benefits of COVID-19 vaccination still outweigh the risks, including in adolescents and young adults. The risk of cardiac complications, like

	<p>myocarditis, substantially increases following COVID-19 infection, and it is higher following infection than after vaccination.</p>
<p>Public Health Ontario (Public Health Ontario, 2021)</p>	<ul style="list-style-type: none"> • NACI continues to strongly recommend that a complete series with an mRNA vaccine should be offered to all eligible individuals without contraindications, including those 12 years of age and older. • The benefits of COVID-19 mRNA vaccines continue to outweigh the risks of COVID-19 illness in the authorized populations as mRNA vaccines are effective in reducing COVID-19 infections, hospitalizations, and deaths. • The Ontario Ministry of Health preferentially recommends the use of Pfizer-BioNTech COVID-19 vaccine for individuals 18-24 years and the continued use of Pfizer-BioNTech for individuals 12- 17 years of age. • As a precautionary measure, NACI recommends that all individuals who have experienced myocarditis/pericarditis following vaccination with a first dose of an mRNA COVID-19 vaccine should defer the second dose in the vaccination series until more information is available. • Clinicians and vaccine-recipients need to maintain ongoing vigilance for this clinical syndrome. All patients presenting symptoms concerning myocarditis/pericarditis in the following days after COVID19 mRNA vaccination should be rapidly assessed in-person by a physician. • Public Health Ontario will continue to monitor for reported events of myocarditis/pericarditis following COVID-19 vaccination in partnership with the Ontario Ministry of Health and federal/provincial/territorial vaccine safety networks, and will provide timely updates as more information becomes available
<p>Manitoba Government (Manitoba Government, 2021)</p>	<ul style="list-style-type: none"> • Manitoba recommends that a complete series with a Pfizer COVID-19 vaccine be offered to eligible individuals 12 to 29 years of age, who do not have contraindications to the vaccine, where feasible. • In the context of sufficient vaccine supply and in order to maximize the benefits while minimizing the risks associated with the vaccine among individuals aged 12 to 29 years, Pfizer is preferred to Moderna because of a lower reported rate of myocarditis/pericarditis following Pfizer (30 mcg) compared to Moderna (100 mcg). • Analyses of Canadian data suggests that with the primary series, the incidence of myocarditis is rare with either mRNA vaccine, but higher following Moderna (100 mcg) compared to Pfizer (30 mcg). The reported rates of myocarditis/pericarditis among males aged 18 to 29 years after the second dose were 15.9 per 100,000 for Moderna (100 mcg) and 2.6 per 100,000 for Pfizer (30 mcg) • Vaccination is recommended as the benefits of vaccination to prevent COVID-19 including variants of concern, outweigh very rare cases of myocarditis or pericarditis. NACI advises that anyone receiving an authorized mRNA COVID-19 vaccine should be informed of the risk of myocarditis and pericarditis and advised to seek medical attention if they develop symptoms including chest pain, shortness of breath or the feeling of a fast, pounding or fluttering heartbeat.

Evidence from the primary literature – Post-Vaccination Myocarditis Data

Many of the publications in this area are based on passive surveillance without verification of adverse events and assessment of potential causality. Given the heightened public scrutiny of potential cardiac issues following vaccination there is a possibility of very low threshold reporting and resultant poor data quality.

Passive surveillance system –raw data: Between December 29, 2020, and September 10, 2021, a total of 1,670 cases of myocarditis (median age 24 years for both males and females) (1,108 with Pfizer, 519 with Moderna, 39 with Janssen, 4 unknown) and 1,115 cases of pericarditis (median age 24 years for males and 54 years for females) (662 with Pfizer, 388 with Moderna, 60 with Janssen, 5 unknown) were reported to the VAERS system as adverse events in the United States, with approximately $\frac{3}{4}$ being diagnosed following the second dose of the vaccine (Hana et al., 2021). **These data are from a passive reporting system which does not determine if the vaccine caused the reported adverse event.** And as such VAERS data are used to inform the need for further assessment of any identified patterns of potential adverse events. In this data set there was a sex association with 1,177 reports of myocarditis in males and 330 reports in females; and 651 reports of pericarditis in males and 340 reports in females (Hana et al., 2021). A second study of the data from Vaccine Adverse Events Reporting System in the United States assessed data from December 2020 to August 2021 to assess myocarditis as an adverse event (Li et al., 2021). They found an incidence rate of 5.98 (95% CI = 5.73–6.24) cases per million doses administered. The incidence rate was higher in adolescents and after the second dose of mRNA vaccines. While still rare, two mRNA vaccines were significantly associated with increased risks for myocarditis/pericarditis (mRNA-1273 (Moderna): ROR = 2.91, 95% CI = 2.21–3.83; BNT162b2 (Pfizer–BioNTech): ROR = 5.37, 95% CI = 4.10–7.04) compared to all other vaccines. In children (<18 years), the VAERS reporting rate per million for myocarditis was 12.4 for boys and 1.4 for girls after the first dose, and 49.6 for boys and 6.1 for girls after the second dose (Cruz et al., 2021). Interestingly, there was a trend for reporting to be highest soon after beginning vaccine schedule, which may indicate a reporting bias (Cruz et al., 2021).

In the United Kingdom, the overall reporting rates for all ages after both the first and second doses of Pfizer/BioNTech are 11 myocarditis cases per million doses and 8 pericarditis cases per million doses (Government of the United Kingdom, 2022). For Moderna the rate is 39 myocarditis cases per million doses and 22 pericarditis cases per million doses. It was consistently highest in the 18 to 29 age group (Government of the United Kingdom, 2022). Recent reports of pediatric data (ages 5 to 11 years) from the United States of 7,141,428 doses administered (as of Dec 9, 2021), with eight confirmed cases of myocarditis (Su, 2021). Two of the cases were after the first dose and the remaining six after the second dose, four were in males and four were in females.

In a pre-print study of the Moderna global safety database (data up to September 30, 2021) 1,439 cases of myocarditis/myopericarditis were identified from approximately 151.1 million mRNA-1273 vaccine recipients (Straus et al., 2021). The overall reporting

rate was 0.95 cases per 100,000 from total vaccine recipients, and was lower than the expected rate (2.12 cases per 100,000 vaccine recipients; RR [95% CI]: 0.45 [0.42–0.48]). Similar to other reports, rates were highest for males aged ≤39 years, particularly those aged 18–24 years (7.40 cases per 100,000 vaccine recipients), which was higher than anticipated (RR [95% CI]: 3.49 [2.88–4.22]). For individuals under the age of 18 years, the rate ratio for myocarditis was 1.05 for males (95% CI, 0.52–2.13) and 0.21 for females (95% CI, 0.04–0.94), respectively. The rate within 7 days of vaccination was highest for males aged 18–24 years after dose 2 (4.9 cases per 100,000 doses administered)(Straus et al., 2021).

An observational retrospective study using a case–non-case design of inflammatory heart reactions reported with mRNA COVID-19 vaccines within the World Health Organization (WHO) global safety database (VigiBase), up to June 30, 2021, found 716,576 reports of adverse events (specific to mRNA vaccines), 2,277 were cases of inflammatory heart reactions, including 1241 (55%) myocarditis and 851 (37%) pericarditis (Chouchana et al., 2021). Myocarditis was impacted by age with higher risk in adolescents (ROR, 22.3, 95% CI 19.2–25.9) and in 18–29 years old (ROR, 6.6, 95% CI 5.9–7.5) compared with older patients, as well as in male patients (ROR, 9.4, 95% CI 8.3–10.6). A pharmacovigilance analysis of mRNA COVID-19 vaccines adverse events reported in VigiBase®, the World Health Organization global database of individual case safety reports from January 1, 2021 to September 14, 2021 of adolescents (12 to 17 years of age)(Foltran et al., 2021). They analyzed 4,942 reports of adverse events with mRNA COVID-19 vaccines in adolescents aged 12 to 17 years old (Pfizer-BioNTech BNT162b2 = 4,659; Moderna mRNA-1273 = 283). A total of 242 pericarditis and/or myocarditis cases were found;233 were reported with Pfizer-BioNTech and 9 with Moderna. Cases reported were primarily male (205, 85%) and had a mean age of 15.8±1.4 years. The second dose was associated with an increased risk of reporting pericarditis and/or myocarditis (ROR 4.95; 95%CI 3.14, 7.89). The risk of reporting pericarditis and/or myocarditis was 10 times higher in boys than in girls at both the first dose (ROR 10.1; 95%CI 4.26, 29.6) and second dose (ROR 10.2; 95%CI 4.88, 25.0).

Patone and colleagues (Patone et al., 2021a) conducted a self-controlled case series study of people aged 16 or older vaccinated for COVID-19 in England between 1 December 2020 and 24 August 2021 to study hospital admission or death from myocarditis, pericarditis and cardiac arrhythmias in one month following adenovirus (ChAdOx1, n= 20,615,911) or messenger RNA-based (BNT162b2, n= 16,993,389; mRNA-1273, n= 1,006,191) vaccines or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test (n= 3,028,867). They estimated an extra two (95% confidence interval (CI) 0, 3), one (95% CI 0, 2) and six (95% CI 2, 8) myocarditis events per 1 million people vaccinated with ChAdOx1 (AstraZeneca) , BNT162b2 (Pfizer) and mRNA-1273 (Moderna), respectively, in the month after a first dose and an extra ten (95% CI 7, 11) myocarditis events per 1 million vaccinated in the 28 days after a second dose of mRNA-1273 (Patone et al., 2021a). Comparatively, they found an extra 40 (95% CI 38, 41) myocarditis events per 1 million patients in the month after a SARS-CoV-2 positive test (Patone et al., 2021a). They observed in individuals under the age of 40 years, an increased risks of myocarditis in days 1–28 after a first dose of

BNT162b2 (IRR 1.83, 95% CI 1.20, 2.79) and of mRNA-1273 (IRR 3.89, 95% CI 1.60, 9.44), following a second dose of BNT162b2 (IRR 3.40, 95% CI 1.91, 6.04) and of mRNA-1273 (IRR 20.71, 95% CI 4.02, 106.68) and after a SARS-CoV-2 positive test (IRR 4.06, 95% CI 2.21, 7.45) (Patone et al., 2021a). There was not an association with the ChAdOx1 vaccine. For individuals over the age of 40 years, the risk of myocarditis was increased in the 1–28 days after an initial dose of ChAdOx1 (IRR 1.33, 95% CI 1.06, 1.67) and a SARS-CoV-2 positive test (IRR 12.18, 95% CI 9.01, 16.46). Of note, the increased risk of myocarditis associated with the two mRNA vaccines was present in those under the age of 40 years only (Patone et al., 2021a). An update of this self-controlled case series analysis was issued, including 10,978,507 people receiving a third dose (Patone et al., 2021b). An association was seen in males under 40 receiving a third dose with mRNA-1273 (Moderna) only, where there was 13 additional events per million following a third dose (compared with 101 additional events after a second dose and 7 additional event after COVID infection).

Population cohorts: In Hong Kong, a population cohort study of adolescents aged between 12 and 17 years following Pfizer-BioNTech vaccination was conducted (June 2021 and September 2021). A total of 33 adolescents developed acute myocarditis/pericarditis (Chua et al., 2021). The incidence after the first and second doses were 3.37 (95% CI 1.12-9.51) and 21.22 (95% CI 13.78-32.28 per 100,000 persons vaccinated. Among male adolescents, the incidence after the first and second doses were 5.57 (95% CI 2.38-12.53) and 37.32 (95% CI 26.98-51.25) per 100,000 persons vaccinated.

In Israel 54 cases of myocarditis were identified in over 2.5 million individuals over 16 years of age that were vaccinated, with an estimated incidence 2.13 cases per 100,000 persons (95% confidence interval [CI], 1.56 to 2.70) (Witberg et al., 2021). The highest incidence of myocarditis (10.69 cases per 100,000 persons; 95% CI, 6.93 to 14.46) was found in young males, between 16 and 29 years of age. A total of 76% of cases of myocarditis were considered mild, 22% as intermediate; 1 case was severe. A second study of the Israeli population found overall risk difference between the first and second doses of MRNA vaccine was 1.76 per 100,000 persons (95% confidence interval [CI], 1.33 to 2.19), and the largest difference was among adolescent males (16 to 19 years) (difference, 13.73 per 100,000 persons; 95% CI, 8.11 to 19.46) (Mevorach et al., 2021).

A Canadian study (pre-print) explored the provincial COVID-19 vaccine registry and provincial adverse events following immunization database to assess the rate of myocarditis in Ontario following administration of mRNA vaccines (Buchan et al., 2021). They found of 297 reports of myocarditis, 69.7% occurred after the second dose of mRNA vaccine and were most prominent in males (76.8%). Males aged 18-24 years following mRNA-1273 second dose had the highest rate of myocarditis, and it was 5.1 (95% CI 1.9-15.5) times higher than the rate after BNT162b2 as the second dose (299.5 vs. 59.2 per million doses, respectively) (Buchan et al., 2021).

In the large health management organization, Kaiser Permanente Southern California plan members aged 18 years or older who received at least 1 dose of the BNT162b2

(Pfizer) or mRNA-1273 (Moderna) mRNA vaccine between December 14, 2020, and July 20, 2021 were included in study to assess incidence of myocarditis (Simone et al., 2021). Potential cases of myocarditis were based upon clinician reports to the local practice committee, and through hospital records, identifying a discharge diagnosis of myocarditis within 10 days of vaccine administration. Of over 2.3 million individuals that were immunized, 50.2% received mRNA-1273 and 50.0% BNT162b2. There were 15 cases of myocarditis (all male) in the vaccinated group (2 following the first dose and 13 following the second), 0.8 cases per 1 million first doses and 5.8 cases per 1 million second doses within ten days of vaccination. In all cases, symptoms resolved with conservative management. A second large HMO (Providence health care system) of over 40 hospitals in Northwestern USA reported events of myocarditis and pericarditis in over 2 million individuals that were vaccinated (Diaz et al., 2021). Twenty individuals had vaccine-related myocarditis (1.0 [95% CI, 0.61-1.54] per 100000) and 37 had pericarditis (1.8 [95% CI, 1.30-2.55] per 100000). Similar to other studies, males predominated (n=15; 75%; 95% CI, 53%-89%); median age was 36 years (IQR, 26-48 years). Also consistent with other reports, adverse events were more common after the second dose (4 after first dose (20%; 95% CI, 8%-42%) and 16 after the second (80%; 95% CI, 58%-92%)). Interestingly, two individuals were given a second vaccination after onset of myocarditis; and there were no reports of worsening symptoms (Diaz et al., 2021). A third study of a group of 48 health care organizations in the United States reported myocarditis rates over a one-year period (April 1, 2020- March 31, 2021) (Singer MPH et al., 2021). They found males aged 12-17 reported 6/6,846 (0.09%) developed myocarditis, for an adjusted rate per million of 876 cases (Wilson score interval 402 - 1,911). In contrast, females of the same age reported 3 (0.04%) cases of myocarditis of 7,361 patients. The adjusted rate was 213 (73 - 627) per million cases (Singer MPH et al., 2021).

A study of 26 pediatric medical centers across the United States and Canada evaluated suspected myocarditis in those under 21 years of age (prior to July 4, 2021) within one month of the COVID-19 vaccination (Truong et al., 2021). They identified 139 adolescents and young adults with 140 episodes of suspected myocarditis (49 confirmed, 91 probable), as commonly found, most were male (N=126, 90.6%) with a median age of 15.8 years (range 12.1-20.3, IQR 14.5-17.0). Suspected myocarditis was determined by clinical assessment/reports including elevated troponin levels and abnormal electrocardiograms (ECGs), cardiac function on non-invasive imaging, or findings consistent with myocarditis on cardiac magnetic resonance imaging (cMRI), including myocardial edema or late gadolinium enhancement (Truong et al., 2021). Authors used the CDC case definitions of probably or confirmed vaccine associated myocarditis to categorize suspected cases. Suspected myocarditis occurred in 136 patients (97.8%) following mRNA vaccine, with 131 (94.2%) following the Pfizer-BioNTech vaccine; 128 (91.4%) occurred after the 2nd dose (Truong et al., 2021).

In Israel, the overall risk difference for myocarditis following the second dose compared to the first dose was 1.76 per 100,000 individuals) (95% CI 1.33 – 2.19). The incidence ratio of myocarditis following the second dose of vaccine and compared to the baseline rate prior to the COVID-19 pandemic was 5.34 (95% CI 4.48 to 6.40), and highest for

males aged 16 to 19 years at 13.6 (95% CI 19.3 – 19.2). The risk was most pronounced in the first week after the second dose (Mevorach et al., 2021).

Systematic Reviews: A systematic review synthesized 24 case reports and case series associated with COVID-19 mRNA vaccine-related myocarditis, and evaluated the risk factors related to clinical outcomes (Woo et al., 2021). In the 24 published studies, they identified 74 patients with myocarditis aged 14–70 years old (median age, 17.6), 49.5% were younger than 20 years and 70 (94.6%) were male. All patients recovered without complications and one-third recovered with only conservative care, while patients with gastrointestinal complications required more intensive care (odds ratio: 20.3, 95% confidence interval 1.90–217, $p = 0.013$) (Woo et al., 2021). Another review of 42 studies reported cardiac side effects post-COVID-19 vaccination (including adverse event reporting systems) reported on the mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), four articles studied the AZD1222 (Oxford-AstraZeneca), and two studied JNJ-78436735 (Johnson & Johnson) (Ho et al., 2021). They identified 314 cases of myocarditis, 59 cases of myo/pericarditis and 8 cases of pericarditis following COVID-19 vaccination. Myocarditis following COVID-19 vaccination outcomes were good, 103 patients recovered and were discharged, eight were admitted to intensive care unit, with one patient dying (Ho et al., 2021).

A pre-print systematic review of 7 RCTs and 22 large observational studies determined the incidence of myocarditis following mRNA vaccines (based on moderate evidence) is low, likely highest in males 12-17 years (55 [7-day risk] to 134 [30-day risk] cases per million; specific to Pfizer) and 18-29 years (40 [7-day risk] to 99 [21-30 day risk]) cases per million) (Pillay et al., 2021). They found that incidence is lower (<20 per million) or little-to-none in older ages and for all females. Among men under the age of 40 years, Moderna compared with Pfizer vaccine may be associated with a small increase (<20 per million) in risk for myocarditis (low evidence). It is important to note that the evidence for youth under 18 years remains unclear (Pillay et al., 2021).

Data related to the rate of myocarditis related to booster/third, or subsequent doses of mRNA COVID-19 vaccines is evolving, with early reports suggesting increased over baseline risk for 30 days after the third dose of Pfizer vaccine in males <40, with an overall lower risk after the third dose than myocarditis events after COVID-19 infection (Patone et al., 2021b).

Synthesis of the Information Relating to Question 2

Rare cases of myocarditis have been reported following vaccination with COVID-19 mRNA vaccines, with potentially higher risk related to Moderna vaccine, most commonly after the second dose, usually within a week of vaccination, more often in males, and more often in those 12-29 years of age. However, current risk benefit analysis evaluating the risk of severe COVID-19 infection and its complications, including myocarditis from infection, supports the use of Pfizer BioNTech with a longer dose 1-2 interval (optimally 8 weeks) in younger males. Most cases recover quickly. Formal assessment regarding deferral of subsequent doses is recommended in cases of suspect myocarditis.

Evolving Evidence

Research on SARS-CoV-2 is continually evolving and as such the evidence will continue to be assessed as new information is provided. Highlight expected upcoming guidelines, or expected studies.

Appendix Methods

Literature Search (Update)

A literature search was conducted by Rachel Zhao from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published from 1946 to December 21, 2021, and included: OVID/Medline and Google. Briefly, the search strategy involved combinations of keywords and subject headings including:

- COVID-19 vaccines
- Vaccination/mass vaccination
- -adverse event
- -myocarditis

Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Table 1 below. 1398 articles were identified by KRS with references and abstracts provided for further review. 1358 were excluded from the review in accordance with the inclusion/exclusion criteria stated below.

Table 1. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none">- Myocarditis/pericarditis related to COVID-19 vaccination All settings and populations- Literature search was until December 21, 2021, grey literature inclusive to January 2022 ever, since 1920, since 1990, Why?- Research methods all methods, only empirical, only certain designs? Why?- English only- Both full text and grey literature- All geographic regions were included	<ul style="list-style-type: none">- Article is not from a credible source- Article does not have a clear research question or issue- Presented data/evidence is not sufficient to address the research questions- Case studies- -pre-print studies (however some hand search pre-prints were included)

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Search Strategy

Search strategy

Ovid MEDLINE(R) ALL 1946 to December 21, 2021

Searches Results

1 COVID-19 Vaccines/ 7417

2 vaccination/ or mass vaccination/ 94213

3 vaccin*.kf,tw. 360200

4 2 or 3 376774

5 exp Coronavirus/ or Coronavirus Infections/ or COVID-19/ or (covid or coronaviru* or corona viru* or ncov* or n-cov* or novel cov* or COVID-19 or COVID19 or COVID-2019 or COVID2019 or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARSCoV19 or SARS-Cov-19 or SARSCov-19 or SARSCoV2019 or SARS-Cov-2019 or SARSCov-2019 or severe acute respiratory syndrome coronaviru* or severe acute respiratory syndrome cov 2 or 2019 ncov or 2019ncov).kf,tw.

228367

6 4 and 5 25283

7 1 or 6 26017

8 exempt*.kf,tw. 7835

9 7 and 8 40

10 (adverse event* or adverse reaction* or myocarditis).kf,tw. 241222

11 Myocarditis/ 15657

12 10 or 11 246221

13 7 and 12 1046

14 COVID-19 Vaccines/ae [Adverse Effects] 902

15 9 or 13 or 14 1778

16 limit 15 to (english language and yr="2019 -Current") 1719

17 remove duplicates from 16 1695

18 limit 17 to (address or autobiography or bibliography or biography or clinical conference or clinical trial, veterinary or clinical trials, veterinary as topic or clinical trial protocol or clinical trial protocols as topic or comment or congress or consensus development conference or consensus development
305

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Appendix A-Jurisdiction Specific Guidance

NACI (Government of Canada, 2021b)

Contraindications

- Thrombosis with thrombocytopenia syndrome (TTS) following vaccination- should not receive a subsequent dose of a viral vector COVID-19 vaccine.
- Capillary leak syndrome (CLS)- should not receive the AstraZeneca Vaxzevria or the Janssen COVID-19 vaccines.

Precautions

- Severe immediate allergic reaction (e.g., anaphylaxis) to a COVID-19 vaccine or a vaccine excipient (mRNA vaccines)-individuals with a history of a severe, immediate (≤ 4 h following vaccination) allergic reaction (e.g., anaphylaxis) after administration of an mRNA COVID-19 vaccine, re-vaccination may be offered with the same vaccine/same mRNA platform following risk/benefit assessment and consent, and with consultation from an allergist or other appropriate physician. If re-vaccinated, vaccine administration should be done in a controlled setting with expertise and equipment to manage anaphylaxis. Individuals should be observed for at least 30 minutes after re-vaccination.
- Viral vector vaccines-In individuals with a history of a severe, immediate (≤ 4 h following vaccination) allergic reaction (e.g., anaphylaxis) after administration of a viral vector COVID-19 vaccine, re-vaccination may be offered with an mRNA platform if a risk assessment deems that the benefits outweigh the potential risks for the individual and if informed consent is provided. If re-vaccinated, individuals should be observed for an extended period of at least 30 minutes after re-vaccination.
- Confirmed allergies to a component of a COVID-19 vaccine-Ingredients of authorized COVID-19 vaccines that have been associated with allergic reactions in other products are: polyethylene glycol [PEG] (included in the Pfizer-BioNTech Comirnaty and Moderna Spikevax COVID-19 vaccines), tromethamine [trometamol or Tris] (included in the Moderna Spikevax COVID-19 vaccine) and polysorbate 80 (included in the AstraZeneca Vaxzevria and Janssen COVID-19 vaccines). In individuals with a confirmed severe, immediate (≤ 4 h following exposure) allergy (e.g., anaphylaxis) to a component of a specific COVID-19 vaccine or its container (e.g., PEG), consultation with an allergist is recommended before receiving the specific COVID-19 vaccine. Individuals who are allergic to tromethamine (found in the Moderna Spikevax product) should be offered the Pfizer-BioNTech Comirnaty vaccine which does not contain this excipient. Individuals who are allergic to polysorbates (found in viral vector vaccines), should be offered an mRNA vaccine.
- Mild to moderate immediate allergic reactions to a COVID-19 vaccine or a vaccine excipient- Re-vaccination may be offered with the same vaccine or the same platform (i.e., mRNA). Offering an mRNA vaccine is preferred over a viral vector vaccine. Assessment by a physician or nurse with expertise in immunization may be warranted and period of observation post-vaccination of at least 30 minutes is preferred.

Other allergies

- The following individuals may be routinely vaccinated with COVID-19 vaccines 30 minute post-vaccination observation period:
 - Those with a proven severe allergic reaction (e.g., anaphylaxis) to injectable therapy not related to a component of the COVID-19 vaccines (e.g., other intramuscular, intravenous, or subcutaneous vaccines or therapies)
 - Those with a suspected but unproven allergy to a vaccine component (e.g., PEG)
- 15 minute post-vaccination observation period:
 - Those with a history of allergy not related to a component of the COVID-19 vaccines or other injectable therapy (e.g., foods, oral drugs, insect venom or environmental allergens)

Acute illness

- Vaccination of individuals who may be currently infected with SARS-CoV-2 is not known to have a detrimental effect on the illness. However, vaccination should be deferred in symptomatic individuals with confirmed or suspected SARS-CoV-2 infection, or those with respiratory symptoms, to minimize the risk of COVID-19 transmission at an immunization clinic/venue.

Hematologic

- In individuals with bleeding disorders, the condition should be managed prior to immunization to minimize the risk of bleeding. Individuals receiving long-term anticoagulation are not considered to be at higher risk of bleeding complications following immunization and may be safely immunized without discontinuation of their anticoagulation therapy.

Thrombosis with thrombocytopenia syndrome (TTS)

- There is no evidence that individuals with previous cerebral venous sinus thrombosis (CVST) with thrombocytopenia not related to a viral vector or people with previous heparin-induced thrombocytopenia (HIT) not related to a viral vector vaccine are at increased risk of VITT compared to other individuals after receiving a viral vector vaccine. However, similar to other individuals, they should only receive a viral vector COVID-19 vaccine if an mRNA vaccine is contraindicated or inaccessible and with an appropriate risk assessment. An mRNA vaccine is preferred.

Myocarditis and/or pericarditis

- As a precautionary measure, additional doses of mRNA COVID-19 vaccine should be deferred in individuals who experience myocarditis or pericarditis following a previous dose of an mRNA COVID-19 vaccine until more information is available.
- Individuals who have a history of myocarditis unrelated to mRNA COVID-19 vaccination should consult their clinical team for individual considerations and recommendations. If the diagnosis is remote and they are no longer followed clinically for cardiac issues, they should receive the vaccine.

Guillain-Barré syndrome

- Individuals with past history of GBS unrelated to COVID-19 vaccination should receive an mRNA COVID-19 vaccine. When mRNA COVID-19 vaccines are contraindicated or inaccessible, individuals may receive a viral vector COVID-19 vaccine after weighing the risks and benefits in consultation with their health care provider.
- Individuals who developed GBS after a previous dose of a COVID-19 vaccine may receive another dose of an mRNA COVID-19 vaccine, after consultation with their health care provider (i.e., if the benefits outweigh the risk and informed consent is provided).

CDC

The United States Centre for Disease Control (CDC, 2021b, 2021d) suggests:

- Individuals that had a severe allergic reaction or an immediate allergic reaction to any ingredient in an mRNA COVID-19 vaccine should not get the mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna). Consideration may be given to vaccination with Janssen (viral vector) COVID-19 vaccine.
- Individuals that had a severe allergic reaction or an immediate allergic reaction to any ingredient in Johnson & Johnson's Janssen (J&J/Janssen) viral vector COVID-19 vaccine, should not get the J&J/Janssen vaccine.
- Individuals that are unable to receive one type of COVID-19 vaccine due to allergy may be able to receive another vaccine. Those receiving a viral vector after receiving an mRNA vaccine (with a possible reaction) should wait 28 days before receiving the viral vector dose.
- Individuals that are allergic to Polyethylene Glycol (PEG) should not receive the mRNA vaccine. Individuals that are allergic to Polysorbate should not receive the J&J/Janssen viral vector COVID-19 vaccine. Polysorbate allergy is now considered a precaution to vaccination, not a contraindication.
- Individuals that have a history of severe allergic reactions not related to vaccines or injectable medications and those with a history of allergies to oral medications or a family history of severe allergic reactions may receive the vaccine.
- Individuals that have had an immediate allergic reaction to another vaccine or injectable should discuss with their health care provider to most appropriate approach to COVID-19 vaccination.
- Of note, allergy to latex, egg or gelatin are NOT contraindications to receiving the COVID-19 vaccine.
- A delayed-onset local reaction (e.g., erythema, induration, pruritus) at the injection site following first administration of the vaccine is not a contraindication to the second dose. It may be advisable to give the second dose in the opposite arm.
- The CDC suggests the following for individuals with a previous history of myocarditis or pericarditis (CDC, 2021c):
 - Individuals that experienced myocarditis/pericarditis from the first dose of the COVID-19 vaccine should defer the second dose, awaiting further safety data. For those that choose to proceed, the myocarditis/pericarditis and underlying inflammation/symptoms should be completely resolved prior to administration.

- Individuals that have a personal history of myocarditis/pericarditis (unrelated to first dose administration of COVID-19 vaccination) may receive the COVID-19 vaccine once the current episode of myocarditis/pericarditis and underlying inflammation/symptoms have completely resolved.
- The CDC suggests the following related to viral vector vaccines (note: in the United States they refer specifically to the Janssen/Johnson & Johnson vaccines and do not reference the AstraZeneca/COVIDShield)(CDC, 2021c):
 - Individuals with a history of an episode of an immune-mediated syndrome characterized by thrombosis and thrombocytopenia, such as heparin-induced thrombocytopenia (HIT), should be offered the mRNA vaccine if it has been >90 days since the thrombosis & thrombocytopenia syndrome (TTS) has resolved.
 - Women under the age of 50 years of age may be at increased risk for the rare TTS related to viral vector vaccines. While they may receive any vaccine available (assuming no other contraindications), they should be made aware of the rare risk and advised regarding the availability of mRNA vaccine options.

NHS

The National Health Service (NHS) England suggests that there are very few individuals who cannot receive one of the COVID-19 vaccines (National Health Service, 2021a). Where there may be concern of contraindication, referral/advice should be sought from the appropriate specialist rather than withholding the vaccine (National Health Service, 2021a).

The NHS (National Health Service, 2021b) also suggests:

- Individuals with Polyethylene glycol/PEG allergy should defer mRNA vaccine until they are referred to an allergist/immunologist for vaccine consultation.
- If available, a viral vector vaccine (such as AZ) may be used instead, however those with a PEG allergy may also be allergic to polysorbate 80. Polysorbate 80 is used widely in foods and medications, and those who have tolerated it previously (such as in flu shots) can receive the viral vector vaccine under the following conditions:
 - Following a discussion with an allergist/immunologist;
 - in a setting with full resuscitation facilities (e.g. a hospital);
 - with a 30 minute observation period
 - with pre-treatment with antihistamine where necessary (although note that this may mask initial symptoms of a reaction).
 - A history of myocarditis or pericarditis unrelated to COVID-19 vaccination is not a contraindication to receiving a COVID-19 vaccine (National Health Service, 2021c). The mechanism of action and risk of recurrence of mRNA associated myocarditis and pericarditis with a subsequent dose of vaccine are being investigated; current advice is that the second dose should be deferred

- until further information becomes available, including the results of serological testing (National Health Service, 2021c).
- Individuals that are currently taking immunosuppressive medications (such as chemotherapy, those that received organ transplant, long-term immunosuppressive medicines, long-term systemic corticosteroids, etc.) should be prioritized for receiving the COVID-19 vaccine. Patients about to begin immunosuppressive therapy should be prioritized to receive the vaccine prior to initiating therapy (National Health Service, 2021d).

Australia

Valid reasons for a temporary exemption include:

- For an mRNA COVID-19 vaccine, inflammatory cardiac illness within the past 3 months, e.g., myocarditis or pericarditis; acute rheumatic fever or acute rheumatic heart disease (i.e., with active myocardial inflammation); or acute decompensated heart failure

For all COVID-19 vaccines:

- Acute major medical condition (e.g. undergoing major surgery or hospital admission for a serious illness) (time-limited conditions (or the medical treatment for them is time limited).
- PCR-confirmed SARS-CoV-2 infection, (defer 6 months after the infection). Deferred for 90 days in people who have received anti-SARS-CoV-2 monoclonal antibody or convalescent plasma therapy.
- Any serious adverse event attributed to a previous dose of a COVID-19 vaccine, without another cause identified, and with no acceptable alternative vaccine available (*ATAGI Expanded Guidance on Temporary Medical Exemptions for COVID-19 Vaccines* | Australian Government Department of Health, 2021).

Quebec

Quebec guidance states individuals with a previous allergic reaction to a vaccine containing polysorbate can be given the vaccine and observed for 30 minutes afterwards, while those with a PEG allergy should be referred to an allergist (Quebec Ministère de la Santé et des Services Sociaux, 2021).

Ontario

Myocarditis prior to initiating an mRNA COVID19 vaccine series (individuals aged 12-17 years old)

- As per NACI, individuals aged 12-17 years old with a history of myocarditis unrelated to mRNA COVID-19 vaccination should consult their clinical team for individual considerations and recommendations.
- Qualifies for medical exemption if:
 - Discussion with appropriate physician or nurse practitioner has occurred on potential options for immunization with an mRNA COVID-19 vaccine or

alternative; AND o Physician or nurse practitioner has determined that the individual is unable to receive any COVID-19 vaccine.

- Severe allergic reaction (including anaphylaxis) to a component of a COVID-19 vaccine
- Qualifies for medical exemption only if:
 - Allergy was documented by an appropriate physician or nurse practitioner; AND
 - Discussion with an appropriate physician or nurse practitioner has occurred on potential options for immunization; AND
 - Physician or nurse practitioner has determined that the individual cannot receive any COVID-19 vaccine with currently available mitigation strategies.

Note: True medical exemptions are expected to be infrequent. In most instances, safe administration of subsequent doses of the COVID-19 vaccine is possible under the management of an appropriate physician or nurse practitioner (Ontario Ministry of Health, 2021)

Manitoba

- Individuals that experienced Thrombosis and Thrombocytopenia Syndrome with the first dose of the AZ viral vector vaccine should not receive a second dose, as well as those that have experienced previously experienced episodes of capillary leak syndrome(Manitoba Government, 2021). They indicate the following individuals should speak to their health care provider prior to receiving a viral vector vaccine (and may be better suited for a mRNA vaccine):
 - have had a history of venous sinus thrombosis in the brain or a history of heparin-induced thrombocytopenia (HIT)
 - are pregnant and/or breastfeeding
 - are allergic to an active substance, or any ingredient of the vaccine, or if you have had a severe allergic reaction after the first dose

British Columbia

Conditions that could warrant an exemption include:

1. Anaphylaxis to components of both mRNA and adenovirus vector vaccine (i.e., polyethylene glycol and polysorbate 80) that has been confirmed by a qualified allergist who offers testing and graded dose administration procedures.
2. Receipt of anti SARS-CoV-2 monoclonal antibodies or convalescent plasma for treatment or prevention of COVID-19 (except tocilizumab or sarilumab).
3. Diagnosis of Multisystem Inflammatory Syndrome.
4. Medical practitioner-diagnosed myocarditis or pericarditis following the first dose of COVID-19 vaccine with no other cause identified.
5. Serious adverse event following first dose of COVID-19 vaccine awaiting recommendation for further vaccination by the medical health officer. Serious adverse

events are those that required urgent medical care, resulted in hospitalization, or permanent disability.

6. Serious adverse event following first dose of vaccine not yet reported to the medical health officer.

7. Serious adverse event following a dose of vaccine and recommendation by the medical health officer to not receive further doses.(British Columbia Center for Disease Control, 2021)

Table 3. Jurisdictional Scan of Vaccine Recommendations for Individuals that Experienced Myocarditis/Pericarditis Following First Dose, January 2022

ORGANIZATION	RECOMMENDATIONS
<p>NACI-Rapid Response (National Advisory Committee on Immunization, 2022)</p>	<ul style="list-style-type: none"> • Those with a history compatible with pericarditis and who either had no cardiac workup or had normal cardiac investigations can receive the next dose once they are symptom free and at least 90 days has passed since vaccination. • Some people with confirmed myocarditis (with or without pericarditis) after a dose of an mRNA COVID-19 vaccine may choose to receive another dose of vaccine after discussing the risks and benefits with their healthcare provider. If another dose of vaccine is offered, they should be offered the Pfizer-BioNTech 30 mcg vaccine due to the lower reported rate of myocarditis and/or pericarditis following the Pfizer-BioNTech 30 mcg vaccine compared to the Moderna 100 mcg vaccine. • Informed consent should include discussion about the unknown risk of recurrence of myocarditis and/or pericarditis following receipt of additional doses of Pfizer-BioNTech COVID-19 vaccine in individuals with a history of confirmed myocarditis and/or pericarditis after a previous dose of mRNA COVID-19 vaccine, as well as the need to seek immediate medical assessment and care should symptoms develop
<p>CDC (Center for Disease Control and Prevention, 2022)</p>	<ul style="list-style-type: none"> • There are no data on the safety of administering a subsequent dose of any COVID-19 vaccine to people who had myocarditis or pericarditis after a dose of an mRNA COVID-19 vaccine. It is unclear if people who developed myocarditis or pericarditis after a dose of an mRNA COVID-19 vaccine may be at increased risk of further adverse cardiac effects following a subsequent dose of the vaccine. Until additional safety data are available, experts advise that people who develop myocarditis or pericarditis after a dose of an mRNA COVID-19 vaccine not receive a subsequent dose of any COVID-19 vaccine. • Administration of a subsequent dose of COVID-19 vaccine before additional safety data are available can be considered in certain circumstances for people who develop myocarditis or pericarditis after receiving a dose of an mRNA COVID-19 vaccine. Considerations for vaccination may include: personal risk of severe acute COVID-19 (e.g., age, underlying conditions), level of COVID-19 community transmission and personal risk of infection, timing of any immunomodulatory therapies; ACIP’s general best practice guidelines for immunization can be consulted for more information • People who choose to receive a subsequent dose of a COVID-19 vaccine should wait at least until their episode of myocarditis or pericarditis has completely resolved. This includes resolution of symptoms attributed to myocarditis or pericarditis, as well as no evidence of ongoing heart inflammation or sequelae as determined by the person’s clinical team,

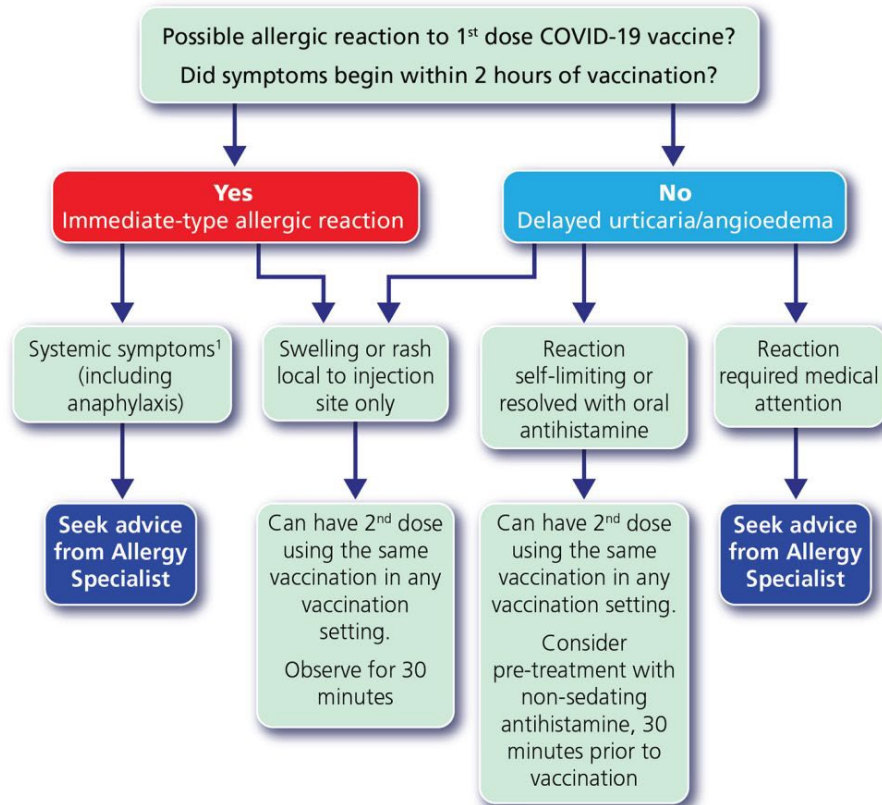
	<p>which may include a cardiologist, and special testing to assess cardiac recovery. For men ages 18 years and older who developed myocarditis or pericarditis after a dose of an mRNA COVID-19 vaccine and who choose to receive a subsequent dose of a COVID-19 vaccine before additional safety data are available, several experts advise that Janssen COVID-19 Vaccine be considered instead of an mRNA COVID-19 vaccine. However, these people should be made aware that there is also a risk of TTS after Janssen COVID-19 Vaccine in men in this age group.</p>
<p>Australian Government (Australian Government Department of Health, 2021)</p>	<ul style="list-style-type: none"> • Future vaccine dose recommendations vary depending on investigation results. • Further doses of an mRNA COVID-9 vaccine can be given to people who have been investigated for pericarditis but who had normal ECG, troponin and inflammatory markers, and who have been symptom-free for at least 6 weeks. This includes people with a clinical diagnosis of pericarditis despite normal investigations. • For people with suspected or proven pericarditis and abnormal investigation results, the need and choice of further doses is informed by age and sex. • People who have had confirmed myocarditis attributed to a dose of Comirnaty or Spikevax should defer further doses of an mRNA COVID-19 vaccine and if they are > 18 years can consider Vaxzevria on a case-by-case basis, after they have recovered from their symptoms. • As the more serious adverse event following immunisation (AEFI), myocarditis should be discussed with a specialist immunisation service (SIS) and/or cardiologist prior to administering a subsequent COVID-19 vaccine dose.
<p>Alberta Government (Alberta Health, 2021)</p>	<ul style="list-style-type: none"> • It is unclear if people who developed myocarditis and/or pericarditis after a first dose of an mRNA COVID-19 vaccine may be at increased risk of further adverse cardiac effects following a second dose of the vaccine. There is currently insufficient evidence around any change to the risk of myocarditis and/or pericarditis after the second dose related to the interval length between first and second doses of vaccines. • Alberta Health recommends that individuals who experienced myocarditis and/or pericarditis after a first dose of an mRNA vaccine should discuss decisions around the second dose, including timing, with their clinician. In general, they are advised to defer receiving a second dose until more data is available. However, a second dose can be considered in specific circumstances.
<p>Ontario Ministry of Health (Ontario Ministry of Health, 2022)</p>	<ul style="list-style-type: none"> • Qualifies for medical exemption if: o Myocarditis/pericarditis was diagnosed within 6 weeks of receiving a previous dose of an mRNA COVID-19 vaccine after medical evaluation (e.g., ER physician, relevant specialist). This includes any person who had an abnormal cardiac investigation including electrocardiogram (ECG), elevated troponins, echocardiogram or cardiac MRI after a dose of an mRNA vaccine. • In situations where there is uncertainty regarding myocarditis diagnosis, discussion should occur with appropriate physician or nurse practitioner on potential options for (re)immunization with the same or alternative COVID-19 vaccine. The individual qualifies for a medical exemption if the physician or nurse practitioner has determined that the individual is unable to receive any COVID-19 vaccine. • Those with a history compatible with pericarditis and who either had no cardiac workup or had normal cardiac investigations, can be (re)immunized once they are symptom free and at least 90 days has passed since vaccination.

**Manitoba
Government**
(Manitoba
Government,
2021)

- People who have experienced myocarditis or pericarditis following vaccination with a first dose of an mRNA COVID-19 vaccine should defer the second dose, and third dose where recommended, in the vaccination series until more information is available.

Appendix B: NHS Flowchart for managing individuals with allergic reactions

Flowchart for managing patients who have allergic reactions to the first dose of COVID-19 vaccine



Appendix C: Tools that may assist with determining vaccine administration

- 1) Resource: Determination of what product to use after a reaction to a first dose, from the Specialist Pharmacy Service of the National Health Service in the UK (<https://www.sps.nhs.uk/articles/prior-allergy-or-dietary-requirements-and-suitability-for-covid-19-vaccination/>)
- 2) Model: The United States offers the Clinical Immunization Safety Assessment (CISA) Project, COVIDVax can provide clinicians with consultations on individual cases to assess feasibility for vaccine administration (<https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html>)

Appendix D: Pregnancy, Breastfeeding and Fertility and the COVID-19 Vaccine

- In Canada, NACI recommends that pregnant/breastfeeding women receive the mRNA complete vaccine series (Government of Canada, 2021a). Given pregnant women are at increased risk of severe outcomes from COVID-19 infection, the vaccine is an important component of prenatal care.
- A new CDC analysis (pre-print) of current data from the v-safe pregnancy registry assessed vaccination early in pregnancy and did not find an increased risk of miscarriage among nearly 2,500 pregnant women who received an mRNA COVID-19 vaccine before 20 weeks of pregnancy (Zauche et al., 2021). Miscarriage rates after receiving a COVID-19 vaccine were 13%, similar to the expected rate of miscarriage in the general population (11-16%) (Zauche et al., 2021).
- According to the CDC, the increased circulation of the highly contagious Delta variant, the low vaccine uptake among pregnant people, and the increased risk of severe illness and pregnancy complications related to COVID-19 infection has created an urgent need for vaccination in pregnant women (CDC, 2021a).
- There is currently no evidence that antibodies made following COVID-19 vaccination or that vaccine ingredients would cause any problems with becoming pregnant now or in the future (CDC, 2021a).
- Additionally, there is no evidence shows that any vaccines, including COVID-19 vaccines, cause male fertility problems (CDC, 2021a).
- Maternal IgG humoral response to mRNA COVID-19 vaccines transfers across the placenta to the fetus, leading to a significant and potentially protective, antibody titre in the neonatal bloodstream one week after the second dose (Government of Canada, 2021b).
- A recent study (pre-print) of the pregnancy outcomes of over 3000 women in the UK during the COVID-19 pandemic found that during Alpha and Delta dominant periods there were more severe infection and worse pregnancy outcomes compared to during the Wildtype infection (Vousden et al., 2021). This demonstrates the increased risk of the Delta variant and the need for vaccination education and uptake for pregnant women.