Recommendations on the use of COVID-19 vaccine(s)

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Preamble

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed

tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Summary

The following highlights key, current information for immunization providers on COVID-19 vaccine. The evidence on COVID-19 disease and vaccines is evolving. Evidence from clinical trial data is limited due to limitations in the size and duration of follow-up of trial populations; however, studies are ongoing. NACI will continue to monitor the data and update its recommendations as needed. Please refer to the remainder of the Statement for details.

What

Disease

- Novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Anyone can be infected with SARS-CoV-2. However, some populations are at increased risk of exposure to the virus (e.g., due to living or work settings), and some populations are at increased risk of severe disease and death due to biological (e.g., advanced age, pre-existing medical conditions) and social (e.g., low socioeconomic status, belonging to a racialized population) factors that may intersect. Risk factors for exposure and severe disease may overlap, further increasing risk. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate consequences for specific populations.

Currently authorized vaccine: Pfizer BioNTech COVID-19

- This vaccine is authorized for use in Canada for individuals 16 years of age and older.
- In clinical trials, the vaccine is efficacious in the short-term against symptomatic, confirmed COVID-19 disease; trials are ongoing.
- Protection offered by the first dose is lower than the efficacy achieved after the second dose. Peak humoral and specific cellular immune responses occur after the second dose.
- There is currently insufficient evidence on the duration of protection and on the efficacy of this vaccine in preventing death, hospitalization, infection and reducing transmission of SARS-CoV-2, although studies are ongoing.
- No serious safety concerns have been identified to date in clinical trials; however, studies are ongoing. Some adverse events are very common and were reported to affect more than 10% of people who receive the vaccine. However, they are mild or moderate and transient, resolving within a few days. These include: pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever. Some adverse events, including fever, are more frequent after the second dose.
- There is currently minimal evidence to inform on differences in vaccine efficacy or safety between those with and those without prior evidence of SARS-CoV-2 infection at the time of vaccination.

Who

NACI makes the following recommendations:

A complete vaccine series of currently authorized COVID-19 vaccine **should be** offered to:

- Individuals in the authorized age group without contraindications to the vaccine. In the context of limited vaccine supply, initial doses of COVID-19 vaccine(s) should be prioritized for the key populations outlined in NACI's Guidance on the Prioritization of Initial Doses of COVID-19 Vaccine(s).

A complete vaccine series of COVID-19 vaccine **may be** offered to:

- Individuals in the authorized age group without contraindications to the vaccine who have had previously PCR-confirmed SARS-CoV-2 infection. In the context of limited vaccine supply, initial doses may be prioritized for those who have not had previously PCR-confirmed SARS-CoV-2 infection. Testing for previous SARS-CoV-2 infection is not needed prior to COVID-19 vaccination.

COVID-19 vaccine **should not** be offered to the following populations excluded from clinical trials until further evidence is available. However, if a risk assessment deems that the benefits of vaccine outweigh the potential risks for the individual (e.g. where the risk of severe outcomes of COVID-19 and risk of exposure to SARS-CoV-2 is high) or for the fetus/infant (in the case of pregnancy/breastfeeding) and if informed consent includes discussion about the insufficient evidence in this population, then a complete series of authorized COVID-19 vaccine **may be** offered to individuals in the following populations:

- Immunosuppressed due to disease or treatment or suffering from autoimmune disorder
- Pregnant or breastfeeding
- Adolescents 12 to 15 years of age

NACI also recommends that:

- All individuals should continue to practice recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission regardless of vaccination with COVID-19 vaccine, at this time, due to insufficient evidence on the duration of protection and effectiveness of COVID-19 vaccines in preventing asymptomatic infection and reducing transmission of SARS-CoV-2.
- Routine immunization programs and immunization with other vaccines recommended by NACI should continue during the COVID-19 pandemic with mitigation of risks of COVID-19 transmission during the immunization process as outlined in the Interim guidance on continuity of immunization programs during the COVID-19 pandemic.
- Clinical trials assessing COVID-19 vaccines should continue to be encouraged to include individuals with potential vulnerabilities to disease related to biological (e.g., pre-existing medical conditions, frailty, pregnancy and breastfeeding, immunocompromised), and social (e.g., residence in long term care facilities or crowded/remote locations, belonging to a racialized population, occupation) factors to ensure that vaccine options are informed by robust safety, immunogenicity, and efficacy data as outlined in NACI's guidance on Research Priorities for COVID-19 Vaccines to Support Public Health Decisions.
- In addition to ongoing vaccine pharmacovigilance activities in Canada with Phase 4 clinical trials and post-marketing studies, additional research and surveillance of COVID-19 vaccination, particularly in populations not currently included in clinical trials (e.g., pregnant, breastfeeding, immunocompromised, seniors living in congregate care settings, children and adolescents) is recommended. Furthermore, NACI recommends the continuation of clinical trials and ongoing follow-up of participants for as long as it is ethically feasible to determine the level of immunity needed to prevent

disease, duration of protection, efficacy in different sub-populations, and medium- and long-term safety.

NACI continues to recommend the following elements to guide ethical decision-making, as outlined in NACI's guidance on Key Populations for Early COVID-19 Immunization:

- Efforts should be made to increase access to immunization services to reduce health inequities without further stigmatization or discrimination, and to engage systemically marginalized populations and racialized populations in immunization program planning.
- Jurisdictions should ensure close and rapid monitoring of safety, coverage and effectiveness of the vaccine(s) in different key populations, as well as effective and efficient immunization of populations in remote and isolated communities.
- Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccine(s) specifically once available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

How

- Currently authorized COVID-19 vaccine is administered intramuscularly in a two-dose schedule with the second dose administered according to the schedule in Table 2.
- Attempts should be made to complete the vaccine series with the same vaccine product.
- Serologic testing is not needed before or after receipt of a COVID-19 vaccine to assess susceptibility to SARS-CoV-2 or immune response to the vaccine.
- COVID-19 vaccines should not be given simultaneously with other live or inactivated vaccines at this time, unless other vaccines are required for post-exposure prophylaxis.
- COVID-19 vaccines should not be given simultaneously with monoclonal antibodies or convalescent plasma.

Why

- The COVID-19 pandemic has caused significant morbidity and mortality, as well as social and economic disruption in Canada and worldwide.
- The authorized COVID-19 vaccine that is recommended for use by NACI in this Statement has demonstrated safety and efficacy against symptomatic laboratory-confirmed COVID-19 disease.

Introduction

The goal of Canada's pandemic response is to minimize serious illness and death while minimizing societal disruption as a result of the COVID-19 pandemic. Safe and effective COVID-19 vaccines could help achieve this goal. Clinical trials of numerous candidate COVID-19 vaccines are currently underway.

This guidance document will provide recommendations on the use of authorized COVID-19 vaccine(s) as they are approved for use in Canada.

COVID-19 vaccines currently authorized for use in Canada:

- The Pfizer-BioNTech COVID-19 vaccine (Pfizer-BioNTech) was authorized for use in Canada on December 9, 2020.

The evidence on COVID-19 and COVID-19 vaccines has been rapidly evolving. To date, NACI has published the following evidence-informed guidance:

1. Research priorities for COVID-19 vaccines to support public health decisions to inform clinical trials of candidate COVID-19 vaccines to protect against infection, serious illness, and deaths caused by SARS-CoV-2.
2. Preliminary guidance on key populations for early COVID-19 immunization to plan for the efficient, effective, and equitable allocation of an eventual COVID-19 vaccine when limited initial vaccine supply will necessitate the immunization of some populations earlier than others.
3. Guidance on the prioritization of initial doses of COVID-19 vaccine(s)for the efficient and equitable prioritization of initial doses of COVID-19 vaccines to assist with the planning for allocation of the first COVID-19 immunization programs.

Guidance objective

The objective of this advisory committee statement is to provide guidance on the effective and equitable use of COVID-19 vaccines authorized for use in Canada in the context of staggered authorization of these vaccines. This evergreen document will be updated as COVID-19 vaccines are authorized for use in Canada, and as evidence on these vaccines evolves. In this guidance document, the evidence and rationale for recommendations as well as current knowledge gaps (e.g. due to the size and short-term follow up in ongoing clinical trials) will be summarized. Clinical trial details on vaccine characteristics for specific COVID-19 vaccines will be included in appendices.

Methods

Details of NACI's recommendation development process can be found elsewhere. [1] [2]

In brief, the broad stages in the preparation of this NACI advisory committee statement included:

1. Knowledge synthesis
2. Synthesis of the body of evidence of benefits and harms, considering the quality of the synthesized evidence and magnitude and certainty of effects observed across the studies
3. Translation of evidence into recommendations

In order to develop comprehensive, appropriate immunization program recommendations, NACI considers a number of factors. In addition to critically appraising evidence on burden of disease and vaccine characteristics such as safety, efficacy, immunogenicity and effectiveness, NACI uses a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into its guidance [2]. The NACI Secretariat applied this framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, Acceptability Matrix) to systematically consider these programmatic factors for the development of clear, comprehensive, appropriate recommendations for timely, transparent decision-making. For details on the development and application of NACI's EEFA Framework and evidence-informed tools (including the Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix), please see A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations.

For this advisory committee statement, NACI used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to develop population-focused recommendations. Further information on this framework can be found in the GRADE handbook.

NACI reviewed and approved the key policy questions used to guide recommendation development on November 25, 2020 and rated the outcomes for their importance for decision-making. The Canadian Immunization Committee (CIC) provided feedback on the key policy questions to ensure alignment with program needs. Important ethical considerations relating to the key policy questions were presented on November 26, 2020 to the PHAC Public Health Ethics Consultative Group, who provided an assessment of ethical considerations that are relevant to the development of recommendations. Knowledge synthesis and quality appraisal were performed by the NACI Secretariat for unpublished clinical trial evidence and were informed by NACI's rating of the outcomes. Unpublished data from Phase 1 and 2/3 clinical trials were presented to the High Consequence Infectious Disease Working Group and NACI on December 4, 2020

for discussion. Proposed recommendations were then presented and approved on December 7, 2020 at an emergency NACI meeting. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

Epidemiology

Information on COVID-19 is continually evolving. The following section will describe the current basis of knowledge, with an emphasis on the best available Canadian data where possible. To access the most recent updates to specific elements, please refer to the links below.

Disease description

Infectious agent

COVID-19 is caused by the SARS-CoV-2, which was first recognized in Wuhan, China in December 2019.

Transmission

Current evidence suggests that COVID-19 is spread through respiratory droplets and aerosols created when an infected person coughs, sneezes, sings, shouts, or talks. A person may be infectious for up to three days before showing symptoms. More information on the transmission of COVID-19 can be found on the PHAC webpages for COVID-19: Main modes of transmission and COVID-19 signs, symptoms and severity of disease: A clinician guide.

Risk factors

Anyone can be infected with SARS-CoV-2. However, some populations are at increased risk of exposure to the virus (e.g., due to living or work settings), and some populations are at increased risk of severe disease and outcomes (e.g., hospitalization and death) due to various biological (e.g. advanced age, pre-existing medical conditions) and social (e.g., socioeconomic status, belonging to a racialized population) factors that may intersect. Exposure and risk of severe disease factors may overlap, further increasing risk. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate consequences for specific populations characterized by increased rates of infection and disease, severe illness, hospitalizations, and/or deaths.

Please see NACI's Advisory Committee Statement on Key Populations for Early COVID-19 Immunization and the Equity Matrix [3] for a summary of inequities associated with COVID-19, potential reasons for and intersections between these inequities, and suggested interventions to reduce inequities and improve access to vaccine(s).

More information on the risk factors associated with COVID-19 can be found on PHAC webpages for People who are at high risk for severe illness from COVID-19 and Vulnerable populations and COVID-19.

Spectrum of clinical illness

The median incubation period for COVID-19 has been estimated to be 5 to 6 days from exposure to symptom onset, with most individuals (97.5%) developing symptoms within 11.5 days of exposure.

Clinical presentation and symptoms of COVID-19 vary in frequency and severity. To date, there is no list of symptoms that has been validated to have high specificity or sensitivity for COVID-19.

More information on the spectrum of clinical illness is available on the PHAC webpage for COVID-19 signs, symptoms and severity of disease: A clinician guide.

Disease incidence

Global

Updated international data on COVID-19 cases and deaths is available at: Interactive data visualizations of COVID-19.

Weekly epidemiological updates highlighting key global, regional and country-level data on COVID-19 cases and deaths are available from the World Health Organization (WHO) at: Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update.

National

Updated national, provincial and territorial-level data on COVID-19 cases and deaths in Canada over time is available from the PHAC webpage on Coronavirus disease (COVID-19): Outbreak update.

Vaccine(s)

The following section summarizes information about COVID-19 vaccines authorized for use in Canada. More detailed vaccine-specific information is included in the appendices. The current landscape of all candidate COVID-19 vaccines in clinical evaluation can be found on the WHO webpage Draft landscape of COVID-19 candidate vaccines. Under the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19, Health Canada can make regulatory decisions for COVID-19 vaccines that have completed Phase 3 clinical trials for authorized use in Canada.

Most vaccine candidates in development that may become authorized for use in Canada use various technologies to deliver SARS-CoV-2 spike protein to vaccine recipients. This protein is expressed on the surface of the SARS-CoV-2 virus and is a major target for binding and neutralizing antibodies as well as cell-mediated immune responses.

mRNA vaccines

COVID-19 vaccines that use messenger RNA (mRNA) platforms contain modified nucleotides that code for the SARS-CoV-2 spike protein. A lipid nanoparticle formulation delivers the mRNA into the recipient's cells. Once inside a cell, the mRNA provides the instructions that allows the cell to manufacture the spike protein. Once manufactured, the spike protein exits the cell, and becomes anchored onto the cell's surface. The immune system is activated to recognize the spike protein as foreign and initiates an immune response. The mRNA and spike protein are then cleared by the immune system.

mRNA vaccines are not live vaccines and cannot cause infection in the host. mRNA vaccines also cannot alter a person's DNA.

Preparation(s) of COVID-19 vaccines authorized for use in Canada

Table 1: COVID-19 vaccine(s) authorized for use in Canada

Product brand name (Manufacturer)	**Pfizer-BioNTech COVID-19 vaccine (Pfizer-BioNTech)**
Type of vaccine	COVID-19 mRNA

Abbreviations:

- IM: intramuscular
- mRNA: messenger ribonucleic acid

Product brand name (Manufacturer)	**Pfizer-BioNTech COVID-19 vaccine (Pfizer-BioNTech)**
Date of authorization in Canada	December 9, 2020
Authorized ages for use	16 years of age and older
Dose	30 mcg of mRNA per 0.3 mL (after dilution - see product monograph for choice of diluent and dilution instructions)
Schedule	2 Doses, a minimum of 19 days apart (recommended interval 21-28 days apart)
Route of administration	IM
Nature of the antigen	Prefusion spike protein
Adjuvant (if present)	None
Primary storage requirements	-80°C to -60°C and protected from light
Formats available	Multi-dose vial (5 doses), preservative-free
Usage limit post-dilution	6 Hours from the time of dilution at 2°C to 25°C.

Abbreviations:

- IM: intramuscular
- mRNA: messenger ribonucleic acid

Efficacy and effectiveness

Due to the availability of only short-term clinical trial data, the duration of COVID-19 vaccine efficacy, and vaccine effectiveness, are currently unknown. However, studies are ongoing.

The following section highlights key efficacy data for the authorized COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine) only. For additional details regarding trial design, including study population, length of follow-up, and efficacy for the Pfizer-BioNTech COVID-19 vaccine, refer to the evidence summary in Appendix A.

Efficacy against symptomatic COVID-19 disease

The currently authorized COVID-19 vaccine has been shown to be highly efficacious in the short term against confirmed symptomatic COVID-19 disease (presence of one or more symptoms plus laboratory confirmation of SARS-CoV-2 infection) from one week after receiving the full two-dose series. This authorized vaccine is similarly efficacious in adults with one or more comorbidities**,** as well as in younger adults and older adults. However, evidence in adults of a much more advanced age (e.g., 85 years and older) and in long-term care facilities is limited.

The clinical trial data demonstrates that the authorized vaccine is efficacious over the short term in individuals with or without evidence of prior SARS-CoV-2 infection. However, participants with laboratory-confirmed SARS-CoV-2 infection prior to trial start were excluded from the trial and the number of trial participants with evidence of previous infection (as defined by trial protocol) who had confirmed symptomatic COVID-19 disease during the trial was small; therefore, the efficacy in this population and how it compares to those without evidence of previous infection is unknown at this time.

The first dose of the authorized vaccine has been shown to offer at least short-term protection against confirmed COVID-19 disease. The highest efficacy is seen after the second dose is administered. There is currently no available evidence on medium- and long-term efficacy of the authorized COVID-19 vaccine, however trials are ongoing and this Statement will be updated as evidence emerges.

Efficacy against severe disease

There are no data yet to be able to assess the efficacy of the authorized COVID-19 vaccine against hospitalizations or deaths specifically.

The authorized COVID-19 vaccine may be efficacious against severe COVID-19 outcomes (refer to Appendix A for definition of outcomes used in clinical trials), but the number of severe cases that have been observed in clinical trials to date are insufficient to draw firm conclusions at this time.

Efficacy against asymptomatic infection and transmission

There is currently no reported evidence on the efficacy of the authorized COVID-19 vaccine to prevent asymptomatic infection, to reduce viral shedding, or to prevent transmission. However, studies are ongoing.

Immunogenicity

No immunological correlate of protection has been determined for SARS-COV-2; therefore, all immunological evidence in support of vaccine efficacy is indirect and cannot directly be used to estimate efficacy.

There are several key knowledge gaps that affect the understanding of immune responses to COVID-19 vaccine:

- Which type of immune responses are important for protection from infection, severe disease, or transmission
- The durability of immune responses and how they may change over time
- How immune responses to natural infection compare to responses elicited from a vaccine
- How immune responses differ across populations (e.g., in immunocompromised, children) or by SARS-CoV-2 serostatus (i.e., past COVID-19 infection)
- How immune responses differ based on previous infection with non-SARS-CoV-2 coronaviruses

Due to limitations in the number of participants and duration of follow up from COVID-19 clinical trial data, medium and long-term evidence on immunogenicity is unknown. However, studies are ongoing.

The following section highlights key immunogenicity data for the authorized COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine) only. For additional details regarding trial design, including study population and length of follow-up, and immunogenicity for the Pfizer-BioNTech COVID-19 vaccine, refer to the evidence summary in Appendix A.

Humoral immune responses

The peak humoral immune response to the Pfizer-BioNTech COVID-19 vaccine occurred one week after administration of the second dose, based on a small number of participants. After four weeks, the antibody response persisted, but evidence beyond four weeks after the second dose with this vaccine is not available at this time. The immune response (neutralizing antibodies) elicited by one dose accounted for up to 20% of the maximum response seen after the second dose, with evidence of boosting after the second dose. In general, immune responses in older adults were lower than immune responses in younger adults; however, age-related differences reduced over time

Cellular immune responses

The Pfizer-BioNTech COVID-19 vaccine produces a cellular immune response by one week after administration of the second dose. Increases in this response were seen in both younger and older adults.

Vaccine administration

For additional vaccine product-specific information, consult the product leaflet or information contained within the product monograph available through Health Canada's Drug Product Database. Refer to Vaccine Administration Practices in the Canadian Immunization Guide (CIG), Part 1 - Key Immunization Information for additional general information.

Dose, route of administration, and schedule

Dose

Pfizer-BioNTech COVID-19 vaccine

Each dose is 0.3 mL after dilution, containing 30 mcg of SARS-CoV-2 spike protein mRNA.

The dose for the Pfizer-BioNTech COVID-19 vaccine (0.3 mL) is unique compared to that of most routine vaccinations. Special precaution should be taken to ensure the correct dose is taken from the multi-dose vial.

Route of administration

COVID-19 vaccine is given as an intramuscular (IM) injection into the deltoid muscle. Please refer to the product monograph for details on a specific COVID-19 vaccine prior to administration.

Refer to Vaccine Administration Practices in Part 1 of the CIG for more information on general vaccine administration practices.

Schedule

Refer to Table 2 for a summary of immunization schedules for authorized COVID-19 vaccines.

Table 2: Recommended immunization schedule, by COVID-19 vaccine

Vaccine product (manufacturer)	Immunization schedule	Minimum interval	Authorized interval	Alternate interval
Pfizer-BioNTech COVID-19 (Pfizer-BioNTech)	2-dose schedule	19 days	21 days	28 days

The Pfizer-BioNTech COVID-19 vaccine is efficacious against symptomatic laboratory-confirmed COVID-19 disease when provided as a two-dose schedule 21 days apart. The majority of participants in the clinical trial received the second dose 21 to 27 days apart; however, some received vaccine with a shortened interval. The per-protocol design was 19 to 23 days. An alternate interval of 28 days may be more feasible to implement. This interval is consistent with the minimum interval required for other routine immunizations (e.g., measles-mumps-rubella vaccine) and other COVID-19 vaccines under review by Health Canada. A harmonized approach to the scheduling of COVID-19 vaccines could prevent erroneous administration of other vaccines at less than the recommended minimal interval, should they be authorized.

If administration of the second dose of a COVID-19 vaccine is delayed, the second dose should be provided as soon as possible. Currently, no data on a maximum interval between doses or on medium- or long-term efficacy of COVID-19 vaccines are available. Therefore, every effort should be made to vaccinate with the second dose according to the recommended schedule.

In general, regardless of the time between doses, interruption of a vaccine series does not require restarting the series as delays between doses do not result in a reduction in final antibody concentrations for most multi-dose products. However, the follow-up time in COVID-19 vaccine clinical trials is short and maximum protection may not be attained until the complete vaccine series has been administered.

Refer to Timing of Vaccine Administration in the CIG, Part 1 - Key Immunization Information for more information on general principles for timing of vaccine administration.

Booster doses and re-immunization

There is currently no evidence on the need for booster doses of COVID-19 vaccine after the vaccine series is complete.

Interchangeability

NACI recommends that the vaccine series be completed with the same COVID-19 vaccine product.

Currently, no data exist on the interchangeability of COVID-19 vaccines.

Refer to Principles of Vaccine Interchangeability in the CIG, Part 1 - Key Immunization Information for information on the interchangeability of vaccines in general.

Post-vaccination counseling

NACI recommends that prophylactic oral analgesics or antipyretics (e.g., acetaminophen or ibuprofen) should not be routinely used before or at the time of vaccination, but their use is not a contraindication to vaccination. Oral analgesics or antipyretics may be considered for the management of adverse events (e.g., pain or fever, respectively), if they occur after vaccination.

Analgesics and antipyretics were used in clinical trials of COVID-19 vaccine for the management of pain and/or fever after vaccination. There is currently no evidence on the benefit from administration of oral analgesics for the prevention of immunization injection pain or systemic reactions.

Refer to Vaccine Administration Practices in the CIG, Part 1 - Key Immunization Information for more information on pre- and post-vaccination counseling.

Serological testing

Serologic testing is not needed before or after immunization with COVID-19 vaccine.

Storage requirements

Pfizer-BioNTech COVID-19 vaccine

Frozen vials prior to use

The Pfizer-BioNTech COVID-19 vaccine must be stored at ultra-low temperatures of -80°C to -60°C and protected from light, in the original packaging, until ready to use.

Refer to the re-icing guidelines packaged with the vaccine for instructions regarding the use of the manufacturer's original thermal container for temporary storage.

Vials prior to dilution

The Pfizer-BioNTech COVID-19 vaccine may be thawed and stored at +2°C to +8°C for up to 120 hours (5 days) or at room temperature (up to +25°C) for no more than 2 hours. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Thawed vials can be handled in room light conditions.

Do not refreeze thawed vials.

Vials after dilution

The Pfizer-BioNTech COVID-19 vaccine must be stored between +2°C to +25°C and used within 6 hours from the time of dilution. During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. After dilution, the vaccine vials can be handled in room light conditions.

For more information, consult the product leaflet or information contained within the product monograph available through Health Canada's Drug Product Database. Refer to Storage and Handling of Immunizing Agents in the CIG, Part 1 - Key Immunization Information for additional general information.

Simultaneous administration with other vaccines

NACI recommends that COVID-19 vaccines should not be given simultaneously with other live or inactivated vaccines.

Currently, no data exist on the simultaneous administration of COVID-19 vaccine with other vaccines. In the absence of evidence, attempts should be made to avoid simultaneous administration to maximize benefits of COVID-19 vaccination while minimizing any risks of harm, including the potential for immune interference or the erroneous attribution of an adverse event following immunization (AEFI) to a particular vaccine. However, if a COVID-19 vaccine is inadvertently administered at the same time as another vaccine, neither dose should be repeated.

In the absence of evidence, it would be prudent to wait for a period of at least 28 days after the administration of the complete two-dose vaccine series of an mRNA COVID-19 vaccine before the administration of another vaccine (except in the case where another vaccine is required for post-exposure prophylaxis) due to the elicitation of an inflammatory cytokine response. It would be prudent to wait for a period of at least 14 days after the administration of another vaccine before administrating a COVID-19 vaccine.

Refer to Timing of Vaccine Administration in the CIG, Part 1 - Key Immunization Information for more information on simultaneous administration of other vaccines in general.

Vaccine safety and adverse events following immunization (AEFI)

Due to limitations in the number of participants and duration of follow-up from COVID-19 clinical trials, medium- and long-term evidence on vaccine safety is limited. However, studies are ongoing.

The following section highlights key safety and AEFI data for the authorized COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine) only. For additional details regarding trial design, including study population and length of follow-up, and safety for the Pfizer-BioNTech COVID-19 vaccine, refer to the evidence summary in Appendix A.

Refer to Part 2 - Vaccine Safety in the CIG for definitions of AEFIs and additional general information on vaccine safety.

Very common and common adverse events

Common adverse events are defined as those that occur in 1% to less than 10% of vaccinees; very common adverse events occur in 10% or more of vaccinees.

Pfizer-BioNTech COVID-19 vaccine

Local

Pain at the injection site is very common after administration of the currently authorized COVID-19 vaccine. More than 80% of recipients experienced injection site pain. Redness and swelling are common after administration. Local adverse events are usually mild or moderate and resolve within a few days of vaccination. Pain at the injection site was slightly more frequent in adults less than 56 years of age.

Systemic

Fatigue, headache, muscle pain, chills, joint pain and fever are all very common after the administration of the currently authorized COVID-19 vaccine. More than half of vaccine recipients experienced headache and/or fatigue. Systemic adverse events are usually mild or moderate intensity and resolve within a few days of vaccination. Systemic reactions are more frequent after the second vaccine dose and among individuals less than 56 years of age.

Uncommon, rare, and very rare adverse events

Uncommon adverse events occur in 0.1% to less than 1% of vaccinees. Rare and very rare adverse events occur in 0.01% to less than 0.1% and less than 0.01% of vaccines, respectively. The probability of detection of very rare adverse events in clinical trials is low given clinical trial population sizes and the duration of follow-up, therefore ongoing pharmacovigilance is essential.

Pfizer-BioNTech COVID-19 vaccine

To date, the available data does not indicate that vaccination of SARS-CoV-2 naïve individuals with authorized COVID-19 vaccines will elicit enhanced or altered disease upon subsequent infection by SARS-CoV-2 (e.g., vaccine-enhanced disease); however, further study is needed.

Lymphadenopathy is an uncommon adverse event that can occur after administration of the currently authorized COVID-19 vaccine.

No other uncommon, rare, or very rare adverse events were reported among vaccinated participants in the clinical trials at this time.

Guidance on reporting adverse events following immunization (AEFI)

Vaccine providers are asked to report AEFIs through local public health departments and to follow AEFI reporting requirements that are specific to their province or territory. In general, any serious (defined as resulting in hospitalization, permanent disability or death) or unexpected adverse event that is temporally related to vaccination should be reported.

In addition to provincial or territorial reporting requirements, the Brighton Collaboration has developed a list of Adverse Events of Special Interest (AESI) that are of particular interest and should be reported, refer to Brighton Collaboration: COVID-19 for the list with definitions.

There may be additional very rare AEFIs that have not been detected through clinical trials to date.

Refer to Adverse Events Following Immunization (AEFI) in the CIG for more information on definitions, reporting, investigating and managing, and causality assessments for AEFIs.

Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada for more information on the completion and submission of AEFI reports.

Contraindications and precautions

Contraindications

The authorized COVID-19 vaccine is contraindicated in individuals with a history of anaphylaxis after previous administration of the vaccine. Vaccine is also contraindicated in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. Clinical trials of the authorized COVID-19 vaccines excluded individuals with a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to

any component of the vaccine. Individuals with a history of severe allergic reaction to a component of the COVID-19 vaccine should not receive the COVID-19 vaccine.

For a comprehensive list of components in the vaccine and its container, please consult the product leaflet or information contained within the product monograph available through Health Canada's Drug Product Database.

Potential non-medicinal ingredients in the vaccines known to cause type 1 hypersensitivity reactions ranging from mild cutaneous reactions to anaphylaxis are summarized in Table 3.

Table 3: Potential allergens known to cause type 1 hypersensitivity reactions

Vaccine product (manufacturer)	Potential allergen included in the vaccine or its container [1]	Other products where the allergen may be found [1]
Pfizer-BioNTech COVID-19(Pfizer-BioNTech)	polyethylene glycol (PEG)	Bowel preparation products for colonoscopy, laxatives, cough syrup, cosmetics, skin care products, and some food and drinks

1 N.B. This may not be a complete list.

Refer to Anaphylaxis and other Acute Reactions Following Vaccination in the CIG for information on the management of anaphylaxis post-vaccination in a community setting.

In situations of suspected hypersensitivity or non-anaphylactic allergy to COVID-19 vaccine components, investigation is indicated which may lead to immunization in a controlled setting. Consultation with an allergist is advised. Most instances of anaphylaxis to a vaccine begin within 30 minutes after administration of vaccine. Therefore, if there is a specific concern about a possible allergy to a component of the COVID-19 vaccine being administered, an extended period of observation post-vaccination of 30 minutes may be warranted. Recommendations for the post-vaccination observation period for other vaccines during the pandemic, such as for influenza vaccine, should continue to be followed.

Refer to Anaphylaxis and other Acute Reactions Following Vaccination in the CIG for definition of AEFIs and additional general information.

Precautions

In individuals with bleeding disorders, the condition should be optimally 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.

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, in order to avoid attributing any complications resulting from infection with SARS-CoV-2 to vaccine-related AEFI and to minimize the risk of COVID-19 transmission at an immunization clinic/venue. If any persons are identified with symptoms on arrival at the venue, they should be instructed to follow current local public health measures.

As a precautionary measure and in light of the need to be able to monitor for COVID-19 vaccine adverse events without potential confounding from symptoms of COVID-19 or other co-existing illnesses, it would be prudent to wait until all symptoms of an acute illness are completely resolved before vaccinating with an authorized COVID-19 vaccine.

Refer to Contraindications and Precautions in the CIG, Part 2 - Vaccine Safety for additional general information.

Drug interactions

There have been no drug interactions studies performed to date.

For more information about potential interactions with products containing anti-SARS-CoV-2 antibodies, refer to section Blood products, human immunoglobulin and timing of immunization, in this Statement.

Blood products, human immunoglobulin and timing of immunization

To date, there is insufficient evidence on the receipt of both a COVID-19 vaccine and anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma for treatment or prevention. Therefore, timing of administration and potential interference between these two products are currently unknown. Administration of these products close together may result in decreased effectiveness of a COVID-

19 vaccine and/or anti-SARS-CoV-2 monoclonal antibodies because the monoclonal antibodies have high affinity for the spike protein expressed by the vaccines.

In the post-exposure setting, expert clinical opinion should be sought on a case-by-case basis when deciding whether anti-SARS-CoV-2 monoclonal antibodies would be appropriate to administer after receipt of COVID-19 vaccine, taking into consideration the risk of exposure and the risk of severe COVID-19 disease in the individual.

To date, there is also insufficient evidence on the receipt of both a COVID-19 vaccine and any monoclonal antibodies or convalescent plasma for treatment or prevention of non-COVID-19 disease. Therefore, timing of administration and potential interference between these two products are currently unknown and expert clinical opinion should be sought on a case-by-case basis.

Recommendations

Following the thorough review of available evidence summarized above, as well as the systematic assessment of ethics, equity, feasibility and acceptability considerations with the EEFA Framework [2] as summarized in NACI's Guidance on Key Populations for Early COVID-19 Immunization, NACI makes the following recommendations for public health program level decision-making for the effective and equitable use of COVID-19 vaccines authorized for use in Canada.

NACI will continue to carefully monitor the scientific developments related to COVID-19 and COVID-19 vaccines, as well as ongoing vaccine pharmacovigilance, and will update recommendations as evidence evolves.

Please note:

- A **strong recommendation** applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.
- A **discretionary recommendation** may be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Please see Table 4 for a more detailed explanation of the strength of NACI recommendations.

Recommendations on authorized COVID-19 vaccine(s) for public health program level decision-making

(i.e., Provinces/Territories making decisions for publicly funded immunization programs)

These recommendations apply only to COVID-19 vaccine(s) currently authorized in Canada (Pfizer-BioNTech). In considering these recommendations and for the purposes of publicly funded program implementation, provinces and territories may consider local programmatic factors (e.g., logistical and operational contexts, resources).

1. NACI recommends that a complete vaccine series of COVID-19 vaccine should be offered to individuals in the authorized age group without contraindications to the vaccine. In the context of limited vaccine supply, initial doses of COVID-19 vaccine should be prioritized for the key populations outlined in NACI's Guidance on the Prioritization of Initial Doses of COVID-19 Vaccine(s). (Strong NACI Recommendation)

Summary of evidence and rationale:

- The COVID-19 pandemic has caused significant morbidity and mortality, as well as social and economic disruption.
- The authorized age range for the Pfizer-BioNTech COVID-19 vaccine is those 16 years of age and older. A complete series is two doses.
- Clinical trial data available to date has shown the Pfizer-BioNTech COVID-19 vaccine to be well-tolerated with no serious safety concerns over a follow-up period of <14 weeks after the second dose, and efficacious in preventing symptomatic laboratory-confirmed cases of COVID-19 in individuals 16 years of age and older. Highest efficacy and maximum immune response were observed after the second dose. There is currently very limited data available on protection provided by an incomplete series. Efficacy of a two-dose series was consistent across age groups, and adverse events were generally milder and less frequent in those 56 years of age and older. The vaccine was similarly efficacious and safe in those with one or more comorbidities (e.g., asthma, body mass index ≥30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).
- Key populations in whom initial doses are prioritized are at increased risk of exposure to SARS-CoV-2 (e.g., due to living or work settings), and/or increased risk of severe disease and outcomes due to various biological (e.g., advanced age, pre-existing medical conditions) and social (e.g., low socioeconomic status, belonging to a racialized population) factors that may overlap. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate outcomes. [3]
- Expert stakeholders [4] and the general Canadian public [5] ranked the relative importance of COVID-19 immunization strategies in the context of limited

vaccine supply as follows: 1) protect those most vulnerable, 2) protect healthcare capacity, 3) minimize spread, 4) protect critical infrastructure.
- Congregate living settings that provide care for seniors (e.g., long-term care facilities) have experienced a large number of outbreaks associated with a high number of fatalities in Canada. Residents in these settings are at an increased risk of exposure to SARS-CoV-2 and residents are more likely to experience a combination of risk factors for severe COVID-19, including advanced age and pre-existing medical conditions. Therefore, if vaccine supplies are limited such that not all populations in Stage 1 can be offered vaccine, jurisdictions may consider prioritizing this population first for initial doses if it is logistically feasible to do so. Distinguishing between vaccine adverse events and symptoms of COVID-19 or complications of co-morbidities will be especially important in this population, and testing may be appropriate. Receipt of a vaccine will not interfere with the results of molecular testing for SARS-CoV-2. SARS-CoV-2 PCR can distinguish between SARS-CoV-2 infection and AEFIs.
- Immunization strategies aimed at protecting healthcare capacity and other services essential for the functioning of society help minimize risks for those who take on a disproportionate burden to protect and serve the public. The public also benefits from the ongoing work of those who provide these services.
- Given the ultra-low temperature storage and handling requirements for the Pfizer-BioNTech COVID-19 vaccine, vaccinating in centralized clinics such as in health care settings and to an entire community may be more feasible.
- Please refer to NACI's previous guidance on key populations for early COVID-19 immunization and prioritization of initial doses of COVID-19 immunization for additional details on sequencing of key populations, including a comprehensive analysis of ethical, equity, feasibility and acceptability considerations.

2. NACI recommends that all individuals should continue to practice recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission regardless of vaccination with COVID-19 vaccine, at this time. (Strong NACI Recommendation)

Summary of evidence and rationale:

- Currently, there is insufficient evidence on the duration of protection of COVID-19 vaccines and the effectiveness of COVID-19 vaccines in preventing asymptomatic infection and reducing transmission of SARS-CoV-2. This recommendation may change as more evidence becomes available.
- There is evidence to support the effectiveness of other recommended public health measures in pre-exposure and post-exposure scenarios, including

physical distancing, masking, hand hygiene, as well as isolation and quarantine.
- Currently, there is no evidence on the use of COVID-19 vaccine for post-exposure prophylaxis.
- Federal and local public health measures for the prevention and control of SARS-CoV-2 should continue to be followed.

NACI also makes the following recommendations for COVID-19 immunization in specific populations excluded from clinical trials. Vaccine may be offered to some individuals in these populations in some circumstances on a case-by-case basis with a risk-benefit analysis, and with transparency about the insufficiency of evidence. These recommendations may change as more evidence becomes available.

3. NACI recommends that a complete series of COVID-19 vaccine may be offered to individuals in the authorized age group without contraindications to the vaccine who have had previously PCR-confirmed SARS-CoV-2 infection. In the context of limited vaccine supply, initial doses may be prioritized for those who have not had a previously PCR-confirmed SARS-CoV-2 infection. (Discretionary NACI Recommendation)

Summary of evidence and rationale:

- Testing for previous SARS-CoV-2 infection is not needed prior to COVID-19 vaccination.
- Currently, there is a lack of evidence on potential differences in vaccine efficacy or safety between those with and without prior evidence of SARS-CoV-2 infection. In the Pfizer-BioNTech clinical trial, individuals with PCR-confirmed SARS-CoV-2 were excluded and there were only a small number of trial participants with serologic evidence of previous infection (IgG+) who had confirmed symptomatic COVID-19, therefore efficacy in this population is uncertain.
- The immune response to SARS-CoV-2, including duration of immunity, is not yet well-understood. Reinfections with SARS-CoV-2 have been reported and research to establish the severity, frequency, and risk factors of reinfection with SARS-CoV-2 is ongoing.
- In the context of limited supply, to allow for the protection of a larger number of at-risk individuals, vaccination with a COVID-19 vaccine may be delayed for 3 months following a PCR-confirmed infection, as reinfections reported to date have been rare within the first three months following infection.
- However, if challenging from a feasibility perspective, jurisdictions may elect to disregard prior PCR-confirmed SARS-CoV-2 infection status and vaccinate everyone in a given target group.

- As a precautionary measure and in light of the need to be able to monitor for COVID-19 vaccine adverse events without potential confounding from symptoms of COVID-19 or other co-existing illnesses, and to minimize the risk of transmission of COVID-19 at an immunization venue, NACI recommends that it is prudent to wait until all symptoms of an acute illness are completely resolved before vaccinating with COVID-19 vaccine, as well as ensuring that the individual is no longer considered infectious based on current criteria.

Immunosuppressed persons

4. NACI recommends that COVID-19 vaccine should not be offered to populations who are immunosuppressed due to disease or treatment or those with an autoimmune disorder until further evidence is available (Strong NACI Recommendation). However, a complete series of COVID-19 vaccine may be offered to individuals in the authorized age group in this population if a risk assessment deems that the benefits outweigh the potential risks for the individual, and if informed consent includes discussion about the absence of evidence on the use of COVID-19 vaccine in this population. (Discretionary NACI Recommendation)

Summary of evidence and rationale:

- Currently, there is limited evidence that immunosuppression is an independent risk factor for severe COVID-19, though evidence is evolving.
- Currently, there are very limited data on COVID-19 vaccination in individuals who are immunosuppressed or suffering from an autoimmune disorder. Participants in the Pfizer-BioNTech COVID-19 vaccine clinical trial only included individuals who were not immunosuppressed, such as those with stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV), and those not receiving immunosuppressive therapy during the trial.
- People living with HIV that are considered immunocompetent may be vaccinated.
- The Pfizer-BioNTech COVID-19 vaccine product monograph notes that: "Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine."
- In general, non-replicating vaccines may be administered to immunocompromised people because the antigens in the vaccine cannot replicate. However, the magnitude and duration of vaccine-induced immunity are often reduced. It is currently unknown whether immunocompromised individuals will be able to mount an immune response to mRNA vaccines.

- Individuals who are immunocompromised, either due to underlying conditions or immunosuppressive agents, are generally more susceptible to infections and severe disease after infection. The relative degree of immunodeficiency is variable depending on the underlying condition, the progression of disease and use of medications that suppress immune function. Therefore, the balance of benefits and risks must be made on a case-by-case basis.
- Active surveillance of any potential adverse outcomes in these vaccine recipients is strongly encouraged.

Refer to the related section in the CIG for definitions of immunocompromised persons and general information on immunization in immunocompromised persons.

Pregnancy and breastfeeding

5. NACI recommends that COVID-19 vaccine should not be offered to individuals who are pregnant until after completion of pregnancy, until further evidence is available (Strong NACI Recommendation). However, a complete series of COVID-19 vaccine may be offered to pregnant individuals in the authorized age group if a risk assessment deems that the benefits outweigh the potential risks for the individual and the fetus, and if informed consent includes discussion about the absence of evidence on the use of COVID-19 vaccine in this population. (Discretionary NACI Recommendation)

6. NACI recommends that COVID-19 vaccine should not be offered to individuals who are breastfeeding, until further evidence is available (Strong NACI Recommendation). However, a complete series of COVID-19 vaccine may be offered to individuals in the authorized age group who are breastfeeding if a risk assessment deems that the benefits outweigh the potential risks for the individual and the infant, and if informed consent includes discussion about the absence of evidence on the use of COVID-19 vaccine in this population. (Discretionary NACI Recommendation)

Summary of evidence and rationale:

- Currently, there is limited evidence of pregnancy as an independent risk factor for severe COVID-19, though evidence is evolving.
- Currently, there are no data on COVID-19 vaccination in pregnancy or during breastfeeding. Pregnant or breastfeeding individuals were excluded from the BioNTech clinical trial. During the trial, twenty-three participants reported pregnancies in the safety database and will be followed for pregnancy outcomes. Currently, there are no data on adverse outcomes of COVID-19

vaccine to the pregnant or breastfeeding individual or their developing fetus or breastfed infant.

- The Pfizer-BioNTech product monograph notes that: "The safety and efficacy of Pfizer-BioNTech COVID-19 Vaccine in pregnant women have not yet been established. It is unknown whether the Pfizer-BioNTech COVID-19 Vaccine is excreted in human milk. A risk to newborns/infants cannot be excluded."
- Individuals who are pregnant, breastfeeding, or of reproductive age may be at increased risk of exposure to SARS-CoV-2 (e.g., healthcare workers) and/or increased risk of severe COVID-19 disease (e.g., due to pre-existing medical condition, body mass index of 40 or more) and may wish to be vaccinated despite the lack of evidence of COVID-19 vaccination in pregnancy or during breastfeeding in order to protect themselves. Therefore, the balance of benefits and risks must be made on a case-by-case basis.
- If pregnancy is determined after inadvertently initiating the vaccination series, completion of the series should be delayed until after pregnancy, unless risk factors for increased exposure or severe COVID-19 are present and informed consent for vaccination is obtained as above. NACI also encourages additional research and surveillance of COVID-19 vaccination in pregnancy, including unintended COVID-19 vaccination during pregnancy.
- Vaccine recipients and health care providers are encouraged to report any exposure to COVID-19 vaccine during pregnancy or breastfeeding to the local public health authority as well as to the vaccine manufacturer (1-866-723-7111). Active surveillance of any potential adverse outcomes is encouraged.

Refer to the related section in the CIG for general information on immunization in pregnancy or during breastfeeding.

Children and adolescents

7. NACI recommends that COVID-19 vaccine(s) should not be offered to individuals who are not in the authorized age group. (Strong NACI Recommendation).

7a. However, a complete series of Pfizer-BioNTech may be offered to individuals 12-15 years of age who are at very high risk of severe outcomes of COVID-19 (e.g., due to a pre-existing medical condition known to be associated with increased risk of hospitalization or mortality) and are at increased risk of exposure (e.g., due to living in a congregate care facility) if informed consent with the individual and the parent or guardian includes discussion about the insufficient evidence on the use of COVID-19 vaccines in this population. (Discretionary NACI Recommendation)

Summary of evidence and rationale:

- Evidence to date suggests that in general, children infected with SARS-CoV-2 are not at increased risk of severe disease.
- Evidence on COVID-19 vaccination in those less than 12 years of age is absent, and only limited clinical data on the safety and efficacy of the Pfizer-BioNTech COVID-19 vaccine in those aged 12 to 15 years is available.
- Evidence on the increased risk of severe COVID-19 disease in individuals with certain medical conditions (e.g., heart failure, diabetes, liver disease, chronic kidney disease) exists [6] and the list of these medical conditions is evolving. For adolescents with certain pre-existing medical conditions compounded by an increased risk of exposure to SARS-CoV-2 (e.g., due to living in a congregate setting such as a group home), the balance of risks and benefits of vaccination with a COVID-19 vaccine must be made on a case-by-case basis.

NACI continues to recommend the following:

- Routine immunization programs and immunization with other vaccines recommended by NACI should continue during the COVID-19 pandemic with mitigation of risks of COVID-19 transmission during the immunization process as outlined in the Interim guidance on continuity of immunization programs during the COVID-19 pandemic.
- Clinical trials assessing COVID-19 vaccines should continue to be encouraged to include individuals with potential vulnerabilities to disease related to biological (e.g., pre-existing medical conditions, frailty, pregnancy and breastfeeding, immunocompromised), and social (e.g., residence in long term care facilities or crowded/remote locations, belonging to a racialized population, occupation) factors to ensure that vaccine options are informed by robust safety, immunogenicity, and efficacy data as outlined in NACI's guidance on Research Priorities for COVID-19 Vaccines to Support Public Health Decisions.
- In addition to ongoing vaccine pharmacovigilance activities in Canada with Phase 4 clinical trials and post-marketing studies, additional research and surveillance of COVID-19 vaccination, particularly in populations not currently included in clinical trials (e.g., pregnant, breastfeeding, immunocompromised, seniors living in congregate care settings, children and adolescents) is recommended. Furthermore, NACI recommends the continuation of clinical trials and ongoing follow-up of participants for as long as it is ethically feasible to determine the level of immunity needed to prevent disease, duration of protection, efficacy in different sub-populations, and medium- and long-term safety.

Refer to the related section in the CIG for more information on vaccine safety and pharmacovigilance in Canada.

NACI continues to recommend the following elements to guide ethical decision-making, as outlined in NACI's guidance on Key Populations for Early COVID-19 Immunization:

- Efforts should be made to increase access to immunization services to reduce health inequities without further stigmatization or discrimination, and to engage systemically marginalized populations and racialized populations in immunization program planning.
- Jurisdictions should ensure close and rapid monitoring of safety, effectiveness, and coverage of the vaccine(s) in different key populations, as well as effective and efficient immunization of populations in remote and isolated communities.
- Efforts should be made to improve knowledge about the benefits of vaccines in general and of COVID-19 vaccine(s) specifically once available, address misinformation, and communicate transparently about COVID-19 vaccine allocation decisions.

Research priorities

COVID-19 disease and vaccine are novel; therefore, there are many areas in which research is warranted. Research to address the following outstanding questions (not ordered in terms of importance) is encouraged, drawing from both short-term and long-term data, where available:

New and emerging research priorities

Efficacy, effectiveness, immunogenicity and safety

1. What is the population effectiveness and medium and long-term duration of protection of a complete series of COVID-19 vaccine?
2. What is the efficacy, effectiveness, immunogenicity, and safety of COVID-19 vaccines across diverse population groups (e.g., adults of advanced age, those with high-risk medical conditions including autoimmune conditions, individuals with social or occupational vulnerabilities, individuals who are pregnant or breastfeeding, children, frailty)?
3. What is the efficacy, effectiveness, immunogenicity and safety of COVID-19 vaccines in individuals who have had a previous laboratory evidence of SARS-CoV-2 infection?
    a. Are there any emerging safety signals with COVID-19 immunization that are not predicted by the current understanding of the safety profile of similar vaccines?

    b. Does vaccination following prior SARS-CoV-2 infection or vaccination of SARS-CoV-2 naïve individuals elicit enhanced or altered disease upon subsequent infection by SARS-CoV-2 or other endemic coronaviruses?
4. Is SARS-CoV-2 natural infection (symptomatic or asymptomatic) associated with protection against re-infection or severe disease? How are immune responses induced by natural infection similar or different from those induced by vaccines against COVID-19?
5. Further immunological evidence is needed in the following areas to inform efficacy predictions:
    a. How do immune responses change over time; what is the durability of immune responses against SARS-COV-2 over the long-term?
    b. Which immune responses are most important for protection from infection (adaptive or innate immunity), severe disease or transmissibility?
    c. Are immunoglobulin (Ig)A/IgG/IgM antibodies protective against SARS-CoV-2 and what is the correlate of protection?
    d. Is there a cell-mediated immunity correlate of protection against SARS-CoV-2?
6. What level of COVID-19 vaccination coverage is required to achieve herd immunity and is herd immunity achievable given the available vaccine(s)' characteristics?
7. What is the efficacy, effectiveness, and immunogenicity of a single dose of COVID-19 vaccine(s) authorized as a two-dose series? How long is the duration of protection for an incomplete series?
8. What is the background level of Canadian vaccine-vector-specific responses? Are these responses higher in some groups? Will these responses interfere with vaccine efficacy of these highly seropositive groups?
9. Are any components of the COVID-19 vaccine at high risk of inducing an anaphylactic reaction?
10. What is the incidence of rare, serious adverse events following immunization with COVID-19 vaccines?
11. Does endemic coronavirus infection history impact the course of SARS-CoV-2 disease? Is there cross-protection or interference from antibodies/exposure to human seasonal coronaviruses when exposed to SARS-CoV-2 or vaccinated against SARS-CoV-2?
12. Are there any negative interactions between COVID-19 vaccination and other medications? What is the recommended timing between COVID-19 vaccines and anti-SARS-CoV-2 prophylactic or therapeutic antibodies or convalescent plasma?

Vaccine administration

13. Are COVID-19 vaccines of similar or different platforms interchangeable?
14. What are the minimum and maximum intervals between doses of a two-dose COVID-19 vaccine schedule that continue to provide protection against disease?
15. Are any other vaccines (e.g., Bacillus Calmette-Guérin) protective against COVID-19 through off-target effects?
16. Can COVID-19 vaccine be simultaneously administered with other, non-COVID-19 vaccines (either live or inactivated vaccines)? If not, what is the minimum interval between administration?
17. Can COVID-19 vaccines be given in individuals who have received convalescent plasma or anti-SARS-CoV-2 spike protein monoclonal antibodies? If so, what is the minimum interval required for vaccine administration following receipt of convalescent plasma or monoclonal antibodies?

Standing research priorities

COVID-19 infection and disease

1. What is the epidemiological profile of COVID-19 (e.g., communicable period, all risk groups)?
    a. What is the disease distribution and spectrum of clinical illness for COVID-19, including burden of illness and risk by age, sex and other demographic variables associated with higher risk?
    b. What are the transmission dynamics of COVID-19, including degree of asymptomatic transmission, role of children in transmission, vertical transmissibility, onset and duration of viral shedding and communicable period, impact of changing weather conditions, and trends over time?
    c. What are the rates of COVID-19 co-infections with other respiratory pathogens and what is the impact on pathogenesis and clinical outcomes?
2. Can COVID-19 vaccine be used to protect household contacts of a case from infection? Does COVID-19 vaccination decrease infectiousness and clinical illness in individuals that have already acquired infection? Is COVID-19 vaccination effective in interrupting transmission?

Ethics, equity, feasibility and acceptability

3. What is the acceptability of (a) publicly funded COVID-19 vaccine(s) and other vaccines over time and over different epidemiological contexts among key populations, marginalized populations, providers and policy-makers in different epidemiological contexts across the country?

    a. What factors affect acceptability of immunization with a COVID-19 vaccine in these groups?
    b. What factors affect acceptability of immunization in general?
    c. How will acceptability of prioritized key populations for early immunization with COVID-19 vaccine(s) evolve in different epidemiological contexts across the country?
    d. What strategies can improve acceptability of a COVID-19 vaccine in these groups?
4. How can vaccine allocation decisions be communicated to individuals and communities in order to maintain trust in public health authorities?
5. What COVID-19 vaccination strategies or implementation strategies can reduce health inequities in populations directly targeted by vaccination and in populations not directly targeted by immunization?
6. Can a different COVID-19 vaccine be used to complete a primary series or as a booster dose? How are returning travellers managed if they have initiated but did not complete a COVID-19 vaccine series abroad?

Health-related quality of life and well-being

7. What is the health-related quality of life or well-being of COVID-19 patients and caregivers over time (e.g., health utilities, patient-reported outcomes, patient-reported experiences measures)?
8. What is the impact of COVID-19 vaccination on health-related quality of life or well-being on individuals?

Surveillance issues

Ongoing and systematic data collection, analysis, interpretation and timely dissemination is fundamental to planning, implementation, evaluation, and evidence-informed decision-making. To support such efforts, NACI encourages surveillance improvements in the following areas:

1. Epidemiology

- Enhance social and socioeconomic data collected and made available to understand and address health inequities related to COVID-19
- Systematic examination of the Canadian burden and epidemiology of COVID-19 outbreaks by setting and severity, identifying high-risk activities, settings and populations
- Evaluation of the success of public health interventions to minimize or prevent COVID-19 outbreak events, especially in vulnerable or high-risk communities

2. Laboratory (e.g., strain characterization)

- Enhance laboratory surveillance in order to provide early warning of increasing or decreasing activity by age, sex, and presence of symptoms, and help interpret case data based on changes to testing algorithms
- Conduct genomic surveillance to identify international and inter-provincial transmission and new strains/variants with differing severity, transmissibility, or vaccine comparability
- Explore other SARS-CoV-2 detection kits at point of care with immediate results

3. Vaccine (coverage, effectiveness, safety)

- Reliably monitor coverage rates for each authorized COVID-19 vaccine in different key populations, ensuring data on series completion
- Ensure existing mechanisms for the evaluation of adverse events are positioned to generate data for each authorized COVID-19 vaccine

Table 4: Strength of NACI recommendations

Strength of NACI recommendation based on factors not isolated to strength of evidence (e.g., public health need)	**Strong**	**Discretionary**
Wording	"should/should not be offered"	"may/may not be offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), **or** Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, **or**uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may/may not be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

List of abbreviations

AE

Adverse event

AEFI

Adverse event following immunization

CI

Confidence interval

CIC

Canadian Immunization Committee

CIG

Canadian Immunization Guide

COVID-19

Coronavirus disease 2019

EEFA

Ethics, Equity, Feasibility, and Acceptability

GRADE

Grading of Recommendations, Assessment, Development and Evaluation

HBV

Hepatitis B virus

HCV

Hepatitis C virus

HIV

Human immunodeficiency virus

IM

Intramuscular

Ig

Immunoglobulin

mRNA

messenger ribonucleic acid

NACI

National Advisory Committee on Immunization

PHAC

Public Health Agency of Canada

SAE

Serious adverse events

SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2

WHO

World Health Organization

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Appendix A: Evidence summary for Pfizer-BioNTech COVID-19 vaccine

Study C4591001 is the pivotal Phase 1/2/3 trial for the Pfizer-BioNTech COVID-19 vaccine. Evidence on immunogenicity is available for adults 18 to 55 and 65 to 85 years of age. Evidence on the safety and efficacy of the vaccine is available for adults 16 years of age and older. Studies did not include participants from long term care facilities. The Phase 2/3 portion of the trial involved approximately 44,000 study participants randomized (1:1) to receive either the vaccine or placebo. The data presented below are for an interim analysis, therefore the time of follow-up is not consistent but was less than four months after the second dose (maximum of 14 weeks) for all participants.

Efficacy

Severe outcomes due to COVID-19

There are no efficacy data for hospitalizations and deaths specifically, however data exists for efficacy against severe COVID-19 outcomes, as defined in the trial protocol [7].

There may be a protective effect against severe COVID-19 outcomes when receiving at least one dose of vaccine (overall vaccine efficacy of 88.9%, 95% CI: 20.1 to 99.7%), based on one case identified in the vaccine group (N=21,669) and nine cases in the placebo group (N=21,686). Vaccine efficacy against severe COVID-19 disease was also examined after receipt of Dose 2 (from 7 days and 14 days after Dose 2), but there were an insufficient number of events reported (one severe outcome in the vaccine group and three in the placebo group for each outcome) to determine whether the vaccine was efficacious in reducing severe outcomes with any precision (i.e., the resulting point estimates had wide confidence intervals that included zero).

Symptomatic COVID-19 disease

The estimated vaccine efficacy at least 7 days after Dose 2 was 94.6% (95% CI: 89.9 to 97.3%), with 9 confirmed symptomatic COVID-19 cases, as defined in trial protocol [7] identified among vaccine recipients (N=19,965) compared to 169 cases among placebo recipients (N=20,172). The vaccine efficacy at least 14 days after Dose 2 in this population was comparable (94.4%, 95% CI: 89.1 to 97.3%). Results were similar when estimating the efficacy specifically in individuals without evidence of prior SARS-CoV-2 infection at 95.0% (95% CI: 90.3 to 97.6%) with 8 confirmed cases among vaccine recipients (N=18,198) compared to 162 cases among placebo recipients (N=18,325).

When study participants without evidence of prior SARS-CoV-2 infection were stratified by age, vaccine efficacy against COVID-19 from 7 days after Dose 2 was between 93.7% (>55 years) and 95.6% (16 to 55 years). In individuals ≥65 years of age, vaccine efficacy was 94.7% (95% CI: 66.7 to 99.9%), while in participants ≥75 years of age, the observed vaccine efficacy was 100% compared to placebo (0 vs 5 cases, 95% CI: -13.1 to 100.0%). The estimated vaccine efficacy against confirmed COVID-19 from 7 days after Dose 2 was greater than 91% (between 91.7% and 100.0%) in all subgroups stratified by "at risk" status (e.g., presence of a 1 or more comorbidities). The estimated vaccine efficacy against confirmed COVID-19 from 7 days after Dose 2 was greater than 89% for all races (89.3 to 100%) and 94% for all ethnicities included in the sub-analysis (94.4 to 95.4%).

Fifty COVID-19 cases were identified in the vaccine group after Dose 1 compared to 275 cases in the placebo group for an overall estimated vaccine efficacy after Dose 1 of 82.0% (95% CI: 75.6 to 86.9%).

There is no analysis provided for efficacy specifically in individuals with prior evidence of SARS-CoV-2 infection.

Asymptomatic infection and transmission

There are no efficacy data for these outcomes at this time.

Immunogenicity

Humoral immune responses

Both SARS-CoV-2 binding and neutralizing antibodies induced by this vaccine had similar trends across both age groups studied (N=195). Maximal immune responses were seen on day 28, 7 days after the second dose. Binding and neutralizing antibodies were both induced by one dose of vaccine and boosted by the second dose of vaccine. The immune response elicited by one dose accounted for 10-20% of the maximal immune response. Up to day 35, older adults (65-85 years of age) had a lower immune response compared to younger adults (18-55 years of age). After the peak on day 28, immune responses decreased until the final evaluation point on day 52, 30 days after dose 2 in younger adults, while no decrease was observed in older adults. At all time points and age groups, immune responses were higher than placebo.

Cellular immune responses

Both CD4+ and CD8+ T-cells specific to SARS-CoV-2 were induced by the vaccine, as demonstrated by the increase in these cell population percentages from day 1 to day 28. Increases were seen in both younger adults (18-55 years of age) and older adults (65-85 years of age). The characterization of these cells indicates a Th-1 biased cellular immune response. Intermediate time points were not reported.

Vaccine safety and adverse events following immunization

Safety evidence is based on interim analyses of 37,586 participants with a median of two months of follow-up (range: <2 weeks to <14 weeks) after Dose 2. About 19,000 participants had at least 2 months of follow-up, including about 9,500 who received the vaccine.

Local reactions

In vaccine recipients, frequency of local reactions was similar after Dose 1 and Dose 2. Pain at the injection site was very common (occurred in 66.1 to 83.1%, dependent on age and whether it was Dose 1 or Dose 2 administered). Most local reactions among vaccine recipients were mild or moderate in severity, with any severe reactions being reported by ≤0.6% of participants. No Grade 4 local reactions were reported. Across both age groups, local reactions after either dose had a median onset between zero and 2 days post-vaccination and a median duration of 1 to 2 days.

Systemic reactions

Systemic events were generally increased in frequency and severity in vaccine recipients compared to placebo recipients, and in the younger age group (16-55 years old) compared with the older age group (≥56 years old), with frequencies and severity increasing with the number of doses (Dose 1 compared to Dose 2). Fatigue (34.1 to 59.4%), headache (25.2 to 51.7%), and muscle pain (13.9 to 37.3%) were very common in all age groups and after Dose 1 and Dose 2, respectively. Fever was common after the first dose (3.7% of 16-55 year olds, 1.4% of >55 year olds) but was very common after the second dose (15.8% of 16-55 year olds, 10.9% of >55 year olds). Joint pain was very common or common in all age groups (11.0 to 21.9% of 16-55 year olds, 8.6 to 18.9% of >55 year olds). Diarrhea was uncommon in both age groups (10.0 to 11.0% of 16-55 year olds, 8.0% of >55 year olds), and did not appear to differ between Dose 1 and Dose 2.

Across age groups, the median onset day for most systemic events after either dose of vaccine was 1 to 2 days post-vaccination, with a median duration of 1 day. The majority of systemic events were mild or moderate in severity.

Overall, the frequency of any severe systemic event after Dose 1 was ≤0.9%. After Dose 2, severe systemic events had frequencies of <2% with the exception of fatigue (3.8%) and headache (2.0%). The proportion of participants that experience severe fever (>38.9°C to 40.0°C) increased between Dose 1 (0.2%) and Dose 2 (0.8%). Grade 4 fever (>40.0°C) was reported for 2 participants in each of the vaccine and placebo groups.

Severe or serious adverse events (SAEs)

In total, 1.1% and 0.1% of participants in the vaccine group experienced at least one severe AE and one life-threatening adverse events (AE), respectively, compared to 0.7% and 0.1% of participants in the placebo group. There were no

clinically meaningful differences in AEs by category observed by age, sex, or race/ethnicity.

The proportions of participants who reported at least 1 SAE was similar in the vaccine group (0.5%) and in the placebo group (0.4%). Three of the SAEs in the vaccine group and none in the placebo group were assessed by the investigator as related to study intervention: 1 SAE each of shoulder injury related to vaccine administration, ventricular arrhythmia, and lymphadenopathy. No clinically meaningful differences in SAEs were observed by age, sex, or race/ethnicity. After either vaccine dose, no participant reported an immediate allergic reaction to vaccine.

Other serious adverse events

Lymphadenopathy

Among participants (n=37,586) who were followed for <2 weeks to <14 weeks after Dose 2, AEs of lymphadenopathy were reported in 0.3% (n=64) participants (0.5% [n=54] in the younger age group and 0.1% [n=10] in the older age group) in the vaccine group and 6 participants (0.0%) in the placebo group. Among the AEs of lymphadenopathy in the vaccine group, the majority (47 of 64) were judged by the investigator as related to the vaccine. Most lymphadenopathy events were reported within 2 to 4 days after vaccination. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cut-off.

Appendicitis

Among participants who were followed <2 weeks to <14 weeks after Dose 2, there were a total of 12 participants with SAEs of appendicitis; 8 of which were in the vaccine group. Six of those 8 occurred in younger adults and 2 occurred in older adults. None of the cases were assessed as related to the vaccine by the investigators. The rate in either age group was not estimated to be greater than expected compared to baseline rates.

Death

There were 6 participants who died as of 14 November 2020, the data cut-off date for the interim analysis. This included 2 participants in the vaccine group and 4 participants in the placebo group. None of these deaths in the vaccinated group were assessed by the investigator as related to the vaccine.

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