

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

NACI Rapid Response: Interchangeability of Authorized
COVID-19 Vaccines

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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. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines 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.

BACKGROUND

Similar vaccines from different manufacturers are routinely used interchangeably, particularly during transitions between public health programs over time and when vaccine supply changes. Examples include different vaccine products in a vaccine series for Hepatitis A, monovalent Hepatitis B, Influenza, Measles, Mumps, Rubella (MMR), Meningococcal conjugate vaccines and vaccines used for routine primary immunization series of diphtheria toxoid, tetanus toxoid, pertussis, poliomyelitis and Haemophilus influenzae type b (DTaP-IPV-Hib). General vaccine principles indicate that to be considered interchangeable, vaccines should be authorized with the same indications and with similar schedules, for the same population, contain or produce comparable type(s) of antigen, and be similar in terms of safety, reactogenicity, immunogenicity and efficacy ⁽¹⁾.

All currently authorized COVID-19 vaccines in Canada use the spike protein of the SARS-CoV-2 virus as the antigen. The spike protein produced by the mRNA (Pfizer-BioNTech, Moderna) and Janssen vaccines is stabilized in the prefusion conformation while the AstraZeneca vaccine produces a wild-type spike protein in various conformations, including prefusion.

Previously conducted animal studies of mixed two-dose primary series of adenoviral vector and mRNA COVID-19 vaccines have demonstrated robust immune responses following the second vaccine dose. Similar immune responses have also been reported in clinical studies that evaluated immunogenicity of mixed schedules with the adenovirus and Modified Vaccinia virus Ankara (MVA) Ebola vaccines ⁽²⁾⁽³⁾.

Following the emerging evidence on the risk of vaccine-induced immune thrombotic thrombocytopenia (VITT) that is associated with the use of viral vector vaccines, several European countries (Denmark, Finland, France, Germany, Sweden, Norway and Spain) issued guidance to complete the two-dose COVID-19 vaccine series initiated with an AstraZeneca vaccine with a dose of an mRNA vaccine rather than a second dose of the AstraZeneca vaccine. Other countries are also considering the option to implement a mixed schedule. The Public Health Agency of Canada (PHAC) asked NACI to provide advice on whether the use of a mixed two-dose primary series schedule for COVID-19 immunization in Canada is recommended.

While most national immunization technical advisory groups (NITAGs) provide off-label recommendations for vaccines ⁽⁴⁾, these are most often issued when driven by an equity or ethical principle necessitating their use outside of regulatory indications as per product monographs, such as burden of disease in subpopulations ⁽⁵⁾. In the case of COVID-19 vaccines, NACI considered the risk of VITT associated with the use of viral vector vaccines, the availability of alternative mRNA COVID-19 vaccines without this risk, general principles of vaccinology, as well as evidence on the safety and immunogenicity of a mixed COVID-19 vaccine schedule. NACI applied its Core Ethical Dimensions and Procedural Ethical Considerations Filters throughout recommendation development to ensure the principles of justice, trust, respect for persons and

communities, and minimizing risks vs harms were upheld. NACI will continue to monitor the evidence and update recommendations as needed.

For further information, please refer to NACI's [Recommendations on the use of COVID-19 vaccines](#).

Guidance objective

The objective of this guidance document is to provide advice on the interchangeability of authorized COVID-19 vaccines in a two-dose primary series schedule for COVID-19 immunization in Canada.

METHODS

NACI conducted a review of available direct and indirect evidence on the safety and immunogenicity of mixed schedules of mRNA and viral vector COVID-19 vaccines that was available up to May 26, 2021. NACI also reviewed available evidence on vaccine acceptability, ethics, equity and program feasibility. The Canadian Immunization Committee (CIC) provided feedback on key policy questions to ensure alignment with provincial and territorial program needs (including vaccine availability and uptake) on May 20, 2021. Following the comprehensive review of evidence, NACI approved the recommendation on May 30, 2021.

Details of NACI's evidence-informed recommendation development process can be found elsewhere ⁽⁶⁾⁽⁷⁾.

SUMMARY OF EVIDENCE

Safety

Direct evidence on the safety of mixed COVID-19 immunization schedules was available from three studies ⁽⁸⁾⁽⁹⁾⁽¹⁰⁾⁽¹¹⁾. The CoM-Cov randomised clinical trial from the United Kingdom (UK), compared four permutations of the AstraZeneca and Pfizer-BioNTech vaccines at 28-day intervals among 463 study participants 50 years and older (median age 57 years). Increased local and systemic reactogenicity was observed with the use of heterologous schedules. Fatigue was reported by 68% of participants who received Pfizer-BioNTech after AstraZeneca, and by 77% of participants who received AstraZeneca after Pfizer-BioNTech, compared to 55% when Pfizer-BioNTech was administered as both doses and 50% when AstraZeneca was administered as both doses. Similar trends were observed for pain at the injection site, chills, headache, muscle pain, joint pain, and malaise. Most symptoms occurred within 48 hours after immunization and were short lived. Haematology and biochemistry profiles were similar between heterologous and homologous vaccine schedules, with all laboratory adverse events of grade 2 severity or less

occurring in the heterologous vaccine schedule. Thrombocytopenia, hospitalization, or serious adverse events (SAEs) were not reported in any group within 7 days following administration of the second dose.

In the CombiVacS trial that was conducted in Spain, the study authors reported similar frequencies of systemic adverse events in approximately 450 individuals (median age 44 years, with 65% being less than 50 years of age) who received a mixed two-dose schedule, (AstraZeneca followed by Pfizer-BioNTech) at least 8 weeks apart. The most common systemic adverse events were headache (44%), myalgia (43%), malaise (43%), chills (25%), mild nausea (11%), mild cough (7%), and fever (2.5%). There were no hospitalizations or SAEs reported by the study authors.

In an observational study of 326 healthcare workers in Germany (median age 34 years), Hillus et al., compared the reactogenicity after the second dose of a mixed schedule (AstraZeneca followed by Pfizer-BioNTech after 12 weeks) to that of a two-dose Pfizer-BioNTech series, one dose of AstraZeneca and one dose of Pfizer-BioNTech. Overall, the incidence of any systemic reaction was less common after the mixed series with Pfizer-BioNTech as second dose (48%), compared to the second dose of a two-dose series of Pfizer-BioNTech (65%) and one dose of AstraZeneca (86%). A similar trend was observed for severe systemic reactions, including headache, fever, muscle pain, chills, and joint pain. Study authors did not report on serious adverse events or hospitalizations.

Immunogenicity

Direct evidence on immunogenicity of mixed COVID-19 immunization schedules was available from one study ⁽⁹⁾⁽¹⁰⁾. In the CombiVacS trial, humoral immune responses were increased after administration of Pfizer-BioNTech vaccine following AstraZeneca vaccine compared to a single dose of AstraZeneca vaccine. The Pfizer-BioNTech vaccine was administered at least 8 weeks after the AstraZeneca vaccine. Compared to the immune response at baseline (which represents the residual immune response from the first dose of AstraZeneca), anti-receptor binding domain antibody titres increased by approximately 80-fold, 14 days post-second dose, with increases observed as early as 7 days post-second dose. Anti-spike antibody levels also increased approximately 37-fold 14 days post-second dose. Neutralizing antibody titres also increased by approximately 45-fold following the Pfizer-BioNTech dose.

RECOMMENDATIONS

Interchangeability of authorized COVID-19 vaccines in a vaccines series when the first dose is:

mRNA COVID-19 vaccine

NACI recommends that, if readily available, the same mRNA COVID-19 vaccine product should be offered for the subsequent dose in a vaccine series started with an mRNA COVID-19 vaccine. However, when the same mRNA COVID-19 vaccine product is not readily available, or is unknown, another mRNA COVID-19 vaccine product recommended for use in that age group can be considered interchangeable and should be offered to complete the vaccine series. The previous dose should be counted, and the series need not be restarted.

(Strong NACI Recommendation)

AstraZeneca/COVISHIELD COVID-19 vaccine

NACI recommends that either AstraZeneca/COVISHIELD COVID-19 vaccine or an mRNA COVID-19 vaccine product may be offered for the subsequent dose in a vaccine series started with an AstraZeneca/COVISHIELD COVID-19 vaccine. The previous dose should be counted, and the series need not be restarted. The recommendation to offer mRNA as the second dose is based on expert opinion and on the following elements:

- The risk of VITT after the first and second doses of the AstraZeneca/COVISHIELD vaccine
- The possibility of increased short-term reactogenicity with a mixed schedule
- Emerging data on immunogenicity of a mixed schedule of the AstraZeneca followed by the Pfizer-BioNTech vaccine

(Discretionary NACI Recommendation)

Summary of Evidence and Rationale

- Recommendations for the interchangeability of COVID-19 vaccines are consistent with the current NACI guidance on interchangeability for vaccines that are used for the same indication and contain comparable antigens. In line with basic principles of vaccinology⁽¹²⁾, it is expected that combining different COVID-19 vaccines that induce an immune response against the SARS-CoV-2 spike protein will lead to a robust immune response.
- Canada is anticipating large supplies of mRNA vaccines in the summer months that will be sufficient to complete the second dose in all age groups for whom immunization is recommended.

- Due to the observed AstraZeneca safety profile and risk of VITT, offering an alternative product with a more acceptable safety profile and expected comparable immunogenicity profile, while enabling individuals to make an informed choice is ethically justifiable. This is expected to lead to increased accessibility and acceptability for those who were initially offered a first dose of the AstraZeneca vaccine, including those who are most at risk of COVID-19. As of May 12, 2021, PHAC has estimated the rate of VITT in Canada to be 1 in 83,000 doses administered (of the first dose of AstraZeneca/COVISHIELD vaccine). However, as investigations continue, the rate could be as high as 1 in 55,000. The rate of VITT in the UK, after the second dose of AstraZeneca vaccine, is estimated to be approximately 1 in 600,000 (17 cases out of 10.7 million second doses administered)⁽¹³⁾. It should be noted that with increased observation times, VITT rates have generally increased.
- 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.
- Recent Canadian surveys have found that respondents are more comfortable with mRNA vaccines compared to viral vector vaccines, but intention to vaccinate has been increasing despite differences in comfort levels between vaccines. A study in late April found that most participants were more comfortable with Pfizer (92%) and Moderna (90%) vaccines, and comfort levels for AstraZeneca have increased since early April from 41% to 52%. Of those who were uncomfortable with the viral vector vaccines, 37% reported they would accept a vaccine if offered, 34% would reject, and 29% were unsure⁽¹⁴⁾. The most recent Canadian studies report that intention to vaccinate is increasing and currently varies between 66-80% in the general public and 57-82% in healthcare workers across Canada⁽¹⁵⁾.
- While the majority of international jurisdictions currently do not actively recommend mixed COVID-19 vaccines schedules, all consider individuals who received two vaccine doses of vaccines authorized in Canada to be fully immunized.
- No data currently exist on the interchangeability of COVID-19 mRNA vaccines. However, the spike protein encoded by either of the authorized mRNA vaccines is stabilized in the same manner to remain in the prefusion conformation, though other vaccine components like the lipid nanoparticle and the mRNA sequence may be different. At this time, there is no reason to believe that mRNA vaccine series completion with a different authorized mRNA vaccine product would result in any additional safety issues or deficiency in protection.
- Studies involving mixed schedules with vaccines using different platforms are ongoing and real-world evidence will also be forthcoming. Emerging evidence indicates that mixed COVID-19 schedules have an acceptable safety profile, which has been demonstrated at multiple dosing intervals between 4 and 12 weeks. Emerging evidence also indicates that mixed COVID-19 schedules may be associated with short-term increased systemic reactogenicity, which is potentially increased with shorter intervals between vaccines. Limited evidence indicates that humoral immune responses after the first dose of the

AstraZeneca vaccine increase after the Pfizer-BioNTech vaccine is administered as the second dose. At this time, data regarding a direct comparison to immune responses after two doses of AstraZeneca vaccine have not been released. Active surveillance of effectiveness and safety of a mixed schedule are important, and accurate recording of vaccines received will be critical. NACI will continue to monitor the evidence and update its recommendations as needed.

- NACI will be consulting with the Committee to Advise on Tropical Medicine and Travel (CATMAT) to provide advice on how to complete a vaccine series for people arriving in Canada who received a partial or complete series of a vaccine abroad that is not authorised or available for use in Canada.

RESEARCH PRIORITIES

- NACI recommends continuous monitoring of data on the safety, efficacy, and effectiveness of mixed schedules through clinical trials and studies in real-world settings, including:
 - Studies on interchangeability with other vaccine platforms (e.g. protein subunit vaccines) that may become available in Canada following regulatory review
 - Studies on interchangeability of mRNA booster dose (third dose) for those who received a partial or complete series of AstraZeneca vaccine
- Additional research priorities are listed in NACI's statement on Recommendations for the use COVID-19 vaccines.

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ABBREVIATIONS

<i>Abbreviation</i>	<i>Term</i>
Ad26	Modified human adenovirus 26
CATMAT	Committee to Advise on Tropical Medicine and Travel
CIC	Canadian Immunization Committee
COVID-19	Coronavirus disease 2019
DTaP-IPV-Hib	Diphtheria toxoid, tetanus toxoid, pertussis, poliomyelitis and Haemophilus influenzae type b
NACI	National Advisory Committee on Immunization
NITAG	National Immunization Technical Advisory Group
MMR	measles-mumps-rubella
mRNA	messenger ribonucleic acid
MVA	Modified Vaccinia virus Ankara
PHAC	Public Health Agency of Canada
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VITT	Vaccine-induced Immune Thrombosis and Thrombocytopenia
UK	United Kingdom
US	United States

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