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

Recommendations on the use of a first booster dose of Pfizer-BioNTech Comirnaty COVID-19 vaccine in children 5 to 11 years of age

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Recommandations sur l'utilisation d'une première dose de rappel du vaccin Comirnaty de Pfizer-BioNTech contre la COVID-19 chez les enfants de 5 à 11 ans

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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

NACI first published guidance on the use of COVID-19 vaccines in children 5 to 11 years of age on November 19, 2021 (Recommendation on the use of the Pfizer-BioNTech Comirnaty (10 microgram [mcg] dose) COVID-19 vaccine in children 5 to 11 years of age). The recommendations were updated on January 25, 2022 (Updated recommendations on the use of COVID-19 vaccines in children 5 to 11 years of age, and Amendment), and March 17, 2022 (Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 to 11 years of age). Since that time:

- NACI has provided recommendations on planning considerations for a fall 2022 COVID-19 vaccine booster program in Canada.
- NACI has also provided recommendations on the use of Moderna Spikevax (25 mcg) mRNA COVID-19 vaccine in children 6 months to 5 years of age.
- The Pfizer-BioNTech Comirnaty (10 mcg) mRNA COVID-19 vaccine was authorized on August 19, 2022, as a booster dose in children 5 to 11 years of age. This is the first COVID-19 vaccine authorized as a booster dose in this age group.
- A COVID-19 wave driven by the BA.5 and BA.4 Omicron sub-lineages is underway, with increasing rates of hospitalizations and deaths being observed since early summer [1].
- As of July 17, 2022, 42% of the population aged 5 to 11 years of age in Canada is vaccinated with a primary series. Hybrid immunity (i.e., protection due to a combination of both infection and appropriate vaccination) has increased as many Canadians, particularly young Canadians, have now been infected with SARS-CoV-2.
- Although to date Omicron variants have generally been associated with a less severe illness compared to previous strains, Omicron is partially evasive of immunity conferred by ancestral COVID-19 vaccines or a previous infection by pre-Omicron strains. Emerging data on BA.4 or BA.5 also suggests some degree of immune evasion against antibodies triggered by a previous Omicron BA.1 infection [2-4].
- Preliminary evidence in adults suggests infection- and/or vaccine-acquired immunity wanes over time, including protection against severe disease. This supports administration of subsequent vaccine doses (especially in groups at high risk of severe disease and/or waning) to improve protection in case of increases in COVID-19 indicators (e.g., case incidence, test positivity, outbreaks, wastewater signals).
- Manufacturers are working on new COVID-19 vaccines, including multivalent vaccines and vaccines specifically targeting VOCs, including Omicron variants. A bivalent vaccine, containing the ancestral strain and Omicron BA.1 strain, is anticipated to be available for use in adults in the coming months, and trials in the pediatric population are in progress.

NACI continues to recommend a primary series with an authorized mRNA vaccine in all age groups ≥5 years of age, and a booster dose for those who are eligible. Immunization of those who are eligible for vaccination but have not yet received a primary vaccine series continues to remain a top priority in Canada. For children 6 months to 5 years of age, NACI recommends that a complete series with the Moderna Spikevax (25 mcg) COVID-19 vaccine may be offered at this time.

NACI continues to monitor the rapidly evolving scientific data recognizing that the trajectory of the COVID-19 pandemic remains unclear. Updated recommendations will be made as needed.

NACI's recommendations remain aligned with the goals of the Canadian COVID-19 Pandemic Response that have been updated on February 14, 2022:

- To minimize serious illness and death while minimizing societal disruption as a result of the COVID-19 pandemic.
- To transition away from the crisis phase towards a more sustainable approach to long term management of COVID-19.

COVID-19 vaccines authorized for use in children 5 to 11 years of age

The Pfizer-BioNTech Comirnaty COVID-19 vaccine has been authorized by Health Canada for children 5 to 11 years of age, using a 10 mcg dose as a primary series (November 19, 2021) and booster dose (August 19, 2022). The Moderna Spikevax COVID-19 vaccine is authorized for use only as a primary series for children 6 to 11 years of age, using a 50 mcg dose (March 17, 2022), and for children 6 months to 5 years of age, using a 25 mcg dose (July 14, 2022). Booster doses of Moderna Spikevax (50 mcg) COVID-19 vaccine are authorized only for individuals 18 years of age and older.

In children who are moderately to severely immunocompromised, NACI recommends a primary series of 3 doses administered at least 4 to 8 weeks apart for both mRNA vaccines.

Methods

NACI's recommendations on booster doses are based on the decision-making framework outlined in the published statement entitled Interim guidance on booster COVID-19 vaccine doses in Canada. This framework has been updated with evolving evidence (e.g., including consideration of population level cumulative immunity and vaccine coverage) as outlined in Table 1. Recommendations are based on evidence of the need for (e.g., increased risk of severe illness from COVID-19 and/or increased risk of decreased protection, and waning protection due to increased time since last dose or infection) and benefit of (e.g., safety and effectiveness) booster doses in the Canadian context.

On June 21, 2022, NACI reviewed the available evidence on the burden of disease among the pediatric population, level and duration of protection conferred by vaccine-induced immunity, SARS-CoV-2 infection-induced immunity or hybrid immunity in children 5 to 11 years of age, and indirect evidence from other age groups. The body of evidence also included the Pfizer-BioNTech Comirnaty COVID-19 vaccine clinical data in the regulatory submission to Health Canada, and post-market safety surveillance data. Ethical considerations related to COVID-19 vaccination in younger pediatric populations were discussed with the Public Health Ethics Consultative Group (PHECG) on May 3, 2021, July 6, 2021, September 21, 2021, and May 12, 2022. NACI approved these recommendations on August 8, 2022.

For further information on NACI's recommendations on the use of COVID-19 vaccines, please refer to National Advisory Committee on Immunization (NACI): Statements and publications and the COVID-19 vaccine chapter in the Canadian Immunization Guide (CIG).

Further information on NACI's process and procedures is available elsewhere [5, 6].

Table 1. Factors* for consideration to determine the need for and benefit of a booster dose of COVID-19 vaccine in various populations

Factors* for consideration	Evidence reviewed to determine the need for and benefit of a booster dose of COVID-19 vaccine
Risk-benefit analysis	• Risk of severe illness and death • Risk of exposure (including access to Infection Prevention and Control [IPC] measures and healthcare) • Risk of transmission to vulnerable populations • Risk of societal disruption • Prevention of Multisystem Inflammatory Syndrome in Children (MIS-C) and post-COVID-19 condition
COVID-19 epidemic conditions	• Circulation of SARS-CoV-2, VoCs • Breakthrough cases, outbreaks • Case rates and implications for healthcare capacity
Population level cumulative immunity and vaccine coverage	• Previous vaccination (coverage, type, number of/interval between doses, time since last dose) • Previous SARS-CoV-2 infection
Vaccine types available and forecasted	• Number and type of available vaccines • Forecasted vaccines (e.g., multivalent vaccines)
Vaccine characteristics in different groups against wild-type and VOCs	• Duration of protection • Immunogenicity • Efficacy/effectiveness • Safety and reactogenicity of booster doses

* based on evolving evidence

Recommendations

Please see Table 2 for an explanation of strong versus discretionary NACI recommendations.

NACI reiterates previous evidence-informed recommendations for the primary series of COVID-19 vaccines:

1. **NACI recommends that a complete series with an mRNA COVID-19 vaccine should be offered to children 5 to 11 years of age who do not have contraindications to the vaccine, with a dosing interval of at least 8 weeks between first and second dose. (*Strong NACI Recommendation*)**

2. **NACI recommends that children 5 to 11 years of age who are moderately to severely immunocompromised* should be immunized with a primary series comprised of three doses of an mRNA vaccine, using an interval of 4 to 8 weeks between each dose. (*Strong NACI Recommendation*)**

*For the suggested list of conditions for children 5 to 11 years of age considered moderately to severely immunocompromised please see: Immunocompromised persons in the Canadian Immunization Guide (CIG).

For further information on these recommendations, please refer to the COVID-19 vaccine chapter in the Canadian Immunization Guide (CIG).

NACI makes the following recommendations on the use of a booster dose in children 5 to 11 years of age.

For children 5 to 11 years of age with an underlying medical condition that places them at high risk of severe illness due to COVID-19:

1. **NACI recommends that a booster dose of Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 vaccine should be offered ≥6 months after completion of a primary COVID-19 vaccine series to children 5 to 11 years of age with an underlying medical condition that places them at high risk of severe illness due to COVID-19* (including those who are immunocompromised** and who received a 3-dose primary series). (*Strong NACI recommendation*)**

*There is limited evidence on clinical risk factors for severe COVID-19 disease in pediatric populations. Children at increased risk for severe outcomes may include children: with obesity, who are medically fragile/have medical complexities, who have more than one comorbidity or neurological disorders, or who have Down syndrome or immunocompromising conditions.

**For children who are moderately to severely immunocompromised, the booster dose would be the fourth dose received.

For all other children 5 to 11 years of age:

2. **In the context of heightened epidemiological risk, NACI recommends that a booster dose of Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 vaccine may be offered ≥6 months after completion of a primary COVID-19 vaccine series to all children 5 to 11 years of age who do not have underlying medical conditions that could place them at higher risk of severe illness due to COVID-19.
(*Discretionary NACI recommendation*)**

Considerations on when to offer the first booster dose

- NACI recommends that a first booster dose be offered at an interval of at least 6 months since completion of the primary series or SARS-CoV-2 infection, as more time between exposures may result in a better immune response. A longer interval between doses may result in a better response after any subsequent dose, as this allows time for the immune response to mature in breadth and strength.
- In light of a fall 2022 COVID-19 vaccine booster program, a shorter interval of at least 3 months may be warranted. However, a longer interval between vaccine doses may increase immune memory response which may be an important consideration for long-term immunity in children.

- As protection against infection and severe disease is highest soon after vaccine administration, vaccination at a time of low disease incidence may have limited benefit particularly if there is an extended period of time before the next wave of SARS-CoV-2.
- A bivalent vaccine containing both the ancestral strain and an Omicron variant of SARS-CoV-2, is anticipated to be available for use in adults in the coming months; however, it is unclear if/when a pediatric bivalent vaccine would become available as trials are still underway. The potential benefits of a new vaccine formulation will need to be weighed against the risk of infection and severe disease while waiting for the vaccine to become available.
- There may be variability in how each province, territory and community assesses risk and responds to the needs of their respective jurisdictions, with a focus on protecting those at highest risk for serious outcomes from COVID-19 infection.

NACI continues to monitor and assess the evidence as it emerges and will update its recommendations as needed.

Summary of evidence

Epidemiology, vaccine coverage, and hybrid immunity

- The risk of severe outcomes, including hospitalization, intensive-care unit (ICU) admissions and deaths, is very low in children 5 to 11 years of age compared to other age groups, and lower in children who have a complete primary series than in children who are unvaccinated. These findings have also been observed during the recent Omicron waves. For the four-week period from March 28 to April 24, 2022, the hospitalization rate in children 5 to 11 years of age who received a complete primary series was 0.5/100,000, compared to 0.9/100,000 in unvaccinated children [7].
- Canadian seroprevalence studies from Quebec (January 26, 2022 to February 17, 2022) and British Columbia (March 2022) estimate that 45% to 70% of children 5 to 11 years of age have been previously infected with SARS-CoV-2; most of these infections occurred since Omicron became the dominant variant [8-10]. Preliminary unpublished data suggests that seroprevalence in individuals less than 17 years of age is higher compared to older age groups [8]. COVID-19 seroprevalence may vary between Canadian jurisdictions.
- As of July 17, 2022, 42% of children 5 to 11 years of age are vaccinated with a primary series [11]. Booster dose uptake in those ≥12 years of age has declined with decreasing age. The proportion of individuals who are vaccinated with a primary series and have received at least one additional dose falls from 90% in adults aged 80 years and older to 19% in adolescents 12-17 years of age.
- Hybrid immunity is protection due to a combination of both infection and appropriate vaccination, and has been shown to be more robust than immunity due to infection or vaccination alone. It is expected that children 5 to 11 years of age who have been infected with SARS-CoV-2 may optimize their benefit from future vaccine doses by timing them according to the interval since infection, using similar immunological principles to those informing intervals between vaccine doses.

Vaccine efficacy and vaccine effectiveness and duration of protection following the primary series against Omicron

- The currently available data on vaccine efficacy in the 5 to 11 age group suggest a vaccine efficacy against symptomatic Delta infection of 90.7% shortly after the completion of a 2-dose primary mRNA vaccination [12]. Protection is lower against Omicron at 51% ~2-3 weeks after vaccination [13, 14]. This reflects the reduced protection against Omicron compared to ancestral strain and previous VOCs that has been observed in adolescents and adults. Two additional studies looking at children 5 to 11 years of age fully vaccinated with Pfizer-BioNTech Comirnaty, estimated vaccine effectiveness (VE) of approximately 30% against Omicron infection or SARS-CoV-2 infection during an Omicron-predominant period [14, 15].
- Similar to data in adolescents and adults, studies looking at children 5 to 11 years of age are also showing that COVID-19 vaccines offer higher protection against hospitalization and severe disease than against infection. VE estimates against severe disease, including hospitalization due to Omicron infection or SARS-CoV-2 infection during an Omicron predominant period, ranged from 41 to 68% in this age group [15-17].
- In adults, VE against severe disease with Omicron infection is approximately 90% shortly after a first booster dose and remains above 75% in most studies up to 20 weeks from the first booster [18-21]. VE against Omicron infection and/or symptomatic disease from a first booster of mRNA vaccine is approximately 60% shortly after the dose and decreases over time since vaccination in most studies [18-20, 22, 23].
- In adolescents 12 to 17 years of age, VE against severe disease with Omicron infection is approximately 66-76% shortly after completion of the primary series and remains between 85-88% in several studies up to at least 25 weeks post-completion of the primary series [24, 25]. VE against Omicron infection and/or symptomatic disease after completion of a primary series is approximately 43-75% shortly after the dose and decreases over time since vaccination in most studies [16, 17, 24-27]. No data are available on VE against multisystem inflammatory syndrome in children (MIS-C) due to Omicron infection, however several studies in adolescents 12 to 17 years of age have shown high VE against MIS-C in the pre-Omicron era [28-30].

Clinical trial summary on Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 booster dose in children 5 to 11 years of age

Trial overview

- The Pfizer-BioNTech Comirnaty COVID-19 vaccine was evaluated in an ongoing, randomized, observer-blind, placebo-controlled Phase 1/2/3 clinical trial in healthy children from 6 months to 11 years of age (C4591007). This trial is described in NACI's statement: Recommendation on the use of the Pfizer-BioNTech COVID-19 vaccine (10 mcg) in children 5 to 11 years of age.
- A booster (third) dose of Pfizer-BioNTech Comirnaty (10 mcg) was administered at least 5 months after the primary series, in an open-label manner to Phase 2/3 participants between 5 to 11 years of age who previously received a 2-dose primary series with a 10 mcg dose.

Immunogenicity

- Immunogenicity was evaluated in a subset of 130 participants [31]. Participants received a booster (third) dose at least 175 days after a two-dose primary series and immune responses were measured 1 month following the booster dose (Dose 3 set). As a comparator, 70 participants were randomly selected from the set who received a two-dose primary series (Dose 2 set) in order to compare immune responses 1 month after Dose 2 to immune responses 1 month after dose 3 from the Dose 3 set. After exclusions (prior evidence of SARS-CoV-2 infection, lack of valid immunogenicity results), immunogenicity data for 67 participants in Dose 3 set and 67 participants in the Dose 2 set were analysed.
- In the Dose 3 set, neutralizing antibody geometric mean titres (GMTs) against the reference strain of SARS-CoV-2 (isolated in January 2020) increased by approximately 10-fold 1 month after a booster dose, compared to GMTs immediately prior to booster administration. The seroresponse rate increased from 77.6 % (95% confidence interval [CI]: 65.8 to 86.9%) immediately prior to booster administration to 98.5% (95% CI: 92 to 100%) 1 month after booster administration. The geometric mean ratio (GMR) of GMTs 1 month after a booster dose in the Dose 3 set compared to GMTs 1 month after a primary series (Dose 2 set) was 2.17 (95% CI: 1.76 to 2.68%).
- Neutralizing antibody titres against Omicron (B1.1.529) after a booster dose were available for 17 participants in the Dose 3 set without evidence of prior infection. Omicron-specific titres were approximately 22-fold higher 1 month after a booster dose compared to 1 month after a primary series. In this subset of participants, Omicron-specific titres 1 month after a booster dose were approximately 2.8-fold lower than reference strain-specific titres.

Safety

- The safety cohort included 401 children 5 to <12 years of age who received a booster (third) dose of Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 vaccine at least 5 months (range 5 to 9 months) after completing a two-dose primary series. The median follow-up time after dose 3 was of 1.3 months (range: 1.0 to 1.8 months). Almost half (47.6 %) of participants were female and the median age at vaccination was 8.0 years. A total of 5.5% of participants were baseline positive for evidence of prior SARS-CoV-2 infection. Safety data are reported for data available up to a cut-off date of March 22, 2022.
- The booster dose was well tolerated in children 5 to <12 years of age. Most local and systemic adverse events following immunization (AEFI) were mild or moderate in severity.
- The median onset of solicited adverse events was 1-2 days after dose 3 with a median duration of 1-2 days after onset.
- After dose 3, AEFIs in decreasing order of frequency were: pain at the injection site, fatigue, headache, muscle pain, swelling, redness, chills, joint pain, fever, diarrhea, and vomiting. No serious adverse events related to the vaccine, no case of MIS-C, myocarditis and/or pericarditis or death were reported. No immediate adverse events were reported within 30 minutes of receiving dose 3 of Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 vaccine.
- Local reactions were generally reported at similar frequencies after dose 3 compared with after dose 2 except lymphadenopathy which was reported in 2.5% of vaccinees after dose

3 compared to 0.9% after dose 2. The proportion of participants reporting use of antipyretic/pain medication was higher at dose 3 (30.7%) compared to dose 2 (21.8%).
- Systemic events were reported at similar or slightly higher frequencies after dose 3 compared with after Dose 2. The incidence of systemic events among children 5 to <12 years of age after Dose 3 of Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 vaccine was lower than previously observed in adults ≥18 years of age after dose 3 of Pfizer-BioNTech Comirnaty (30 mcg) COVID-19 vaccine.

Post-market safety surveillance on Pfizer-BioNTech Comirnaty (10 mcg) primary series

- Real-world post-market safety data show that the Pfizer-BioNTech Comirnaty primary series is well tolerated in children 5 to 11 years of age, where the majority of AEFIs reported are non-serious, and AEs are less frequently reported than in adolescents 12 to 15 years of age [32-35].
- Very rare cases of myocarditis and/or pericarditis have been reported following the Pfizer-BioNTech Comirnaty primary series in children 5 to 11 years of age. However, current data suggests the risk of myocarditis and/or pericarditis following mRNA COVID-19 vaccines is substantially lower in children 5 to 11 years of age compared to adolescents. In the United States, the risk of myocarditis and/or pericarditis within 7 days following dose 2 of Pfizer-BioNTech Comirnaty COVID-19 vaccine was 2.6 cases per million doses in males aged 5 to 11 years (10 mcg dose) compared to 46.4 and 75.9 cases per million doses among males 12 to 15 and 16 to 17 years of age (30 mcg dose), respectively [35].
- Very rare cases of MIS-C have been reported following administration of the Pfizer-BioNTech Comirnaty primary series among individuals aged 5 to 20 years [36-38]. The rate of MIS-C post vaccination is currently estimated at about 1.1 cases per 1 million doses administered. For some cases, the causal association between the vaccine and MIS-C was unclear as previous history of SARS-CoV-2 infection was also reported [36, 37]. While most reports for MIS-C cases were serious and required hospitalization, all described cases had been discharged home and there were no reported deaths.

Other considerations

- Manufacturers are working on new COVID-19 vaccines, including multivalent vaccines and vaccines specifically targeting VOCs, although their exact characteristics and timing of availability in Canada are not yet known. NACI will provide recommendations on the type of COVID-19 vaccine to be offered for this booster dose as evidence on multivalent vaccines in the pediatric population becomes available.
- Informed consent and transparency includes describing the known and unknown factors when discussing the benefits and risks of the booster dose in children 5 to 11 years of age.

RESEARCH PRIORITIES

- NACI recommends continuous monitoring of long-term consequences of SARS-CoV-2 infection in children 5 to 11 years of age.
- NACI recommends continuous monitoring of data on the safety, immunogenicity, efficacy/effectiveness (including against severe outcomes), and duration of protection of COVID-19 vaccines, including booster doses, through clinical trials and studies in real-world settings.
- NACI recommends study of the clinical implications of previous SARS-CoV-2 infection, MIS-C, or myocarditis and/or pericarditis on the safety, efficacy, and effectiveness of COVID-19 vaccines in pediatric populations.
- NACI recommends continuous monitoring of vaccine uptake, particularly according to the socioeconomic status of families with children 5 to 11 years of age, and for decision makers to consider measures to reduce the risk of socioeconomic disparities in vaccine confidence and uptake.
- NACI recommends vigilant vaccine safety reporting across Canadian jurisdictions for timely assessment of any potentially rare or very rare adverse events in children following COVID-19 vaccination.

Table 2. 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 be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

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