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

Recommendations on the use of Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine in children 6 months to 4 years of age

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Recommandations sur l'utilisation du vaccin Comirnaty de Pfizer-BioNTech (3 mcg) contre la COVID-19 chez les enfants de 6 mois à 4 ans

To obtain additional information, please contact:

Public Health Agency of Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications-publications@hc-sc.gc.ca

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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

Two mRNA COVID-19 vaccines have been authorized for use in young children. Moderna Spikevax COVID-19 vaccine was authorized by Health Canada on July 14, 2022 for children 6 months to 5 years of age (2 dose primary series; 25 micrograms [mcg] per dose). The Pfizer-BioNTech Comirnaty (3 mcg per dose) mRNA COVID-19 vaccine was authorized for use in children 6 months to 4 years of age on September 9, 2022. Both Moderna Spikevax (25 mcg) and Pfizer-BioNTech Comirnaty (3 mcg) products contain mRNA encoding for the original SARS-CoV-2 virus.
For further information on NACI's recommendations on the use of mRNA 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).

NACI's recommendations are aligned with the goals of the Canadian COVID-19 Immunization Program, 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

METHODS

On August 23, 2022, the NACI COVID-19 Working Group (COVID-19 WG) was convened to discuss and review available evidence on the use of Pfizer-BioNTech Comirnaty COVID-19 vaccine (3 mcg) in children 6 months to 4 years of age. The body of evidence included the manufacturer's clinical data in the regulatory submission to Health Canada, the burden of COVID-19 disease in this population, and post-market safety data of pediatric mRNA COVID-19 vaccines. On September 12 and 13, 2022, NACI reviewed the available evidence on the use of Pfizer-BioNTech Comirnaty COVID-19 vaccine (3 mcg) in children 6 months to 4 years of age and the recommendations proposed by the COVID-19 WG. Ethical considerations related to COVID-19 vaccination in pediatric populations aged less than 5 years were discussed with the Public Health Ethics Consultative Group (PHECG) on May 12, 2022. The Canadian Immunization Committee (CIC) provided feedback on key policy questions to ensure alignment with provincial/territorial program needs on July 19, 2022. NACI approved the recommendations on the use of Pfizer-BioNTech Comirnaty (3 mcg) in children 6 months to 4 years of age on October 6, 2022.

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

SUMMARY OF EVIDENCE

COVID-19 burden of disease in children in Canada

The majority of children with COVID-19 have mild or asymptomatic disease; however, a small number do get severe disease and require hospitalization. Similar to other age groups, the emergence of the Omicron variant of concern (VOC) led to significant increases in COVID-19 cases in all children, including those younger than 5 years of age, as well as corresponding increases in the number of hospitalizations and ICU admissions [3-5]. Children younger than 5 years of age have higher COVID-19-associated hospitalization and intensive care unit (ICU) admission rates compared to older pediatric age groups [6]. In addition, since the emergence of the Omicron VOC, monthly hospitalization rates in children younger than 5 years of age have been higher than the average monthly hospitalization rate calculated in this age group compared to the pre-Omicron period, reflecting the highly transmissible nature of the Omicron VOC and its resulting impact on pediatric infections [6]. Severe outcomes associated with SARS-CoV-2 infection, including hospitalizations, are more common among children younger than 6 months of age compared to children 6 months to 4 years of age; and children 6 to 11 months of age have a higher rate of severe outcomes compared to children 1 to 4 years of age [6, 7].

Seroprevalence studies from Quebec (January-February 2022) and British Columbia (March 2022) estimate that a large proportion of children younger than 5 years of age have already been infected with SARS-CoV-2 (30-70%); with the majority of infections occurring since the Omicron VOC became dominant [3-5]. These reports are consistent with a more recent seroprevalence estimate from British Columbia, where 84% of children less than 5 years of age surveyed in July and August 2022 were seropositive for SARS-CoV-2 [8]. These data may not be generalizable to other regions of Canada, and COVID-19 seroprevalence may vary between Canadian jurisdictions.

Multisystem inflammatory syndrome in children and post-COVID-19 condition in children

Children who have COVID-19 are at risk of multisystem inflammatory syndrome in children (MIS-C), a rare but serious post-infection complication that generally requires acute care hospital admission [9]. While no MIS-C-related deaths have been reported to date in Canada, they have been reported in the United States (US). Available data suggests that the incidence of MIS-C was reduced during Omicron waves, compared to prior waves in the pandemic [10-12]. Additionally, recent studies suggest a decrease in the severity of observed MIS-C cases during Omicron waves [11].

SARS-CoV-2 infection may lead to post-COVID condition/post-acute COVID syndrome (PCC). While the evidence is limited for younger (less than 12 years) pediatric age groups, available evidence suggests that the incidence of PCC is lower in children less than 5 years of age compared to older pediatric age groups [13]. Data on PCC following Omicron infection remains limited.

For more information on MIS-C and other signs and symptoms of COVID-19 or post-infection complications, please refer to COVID-19 signs, symptoms and severity of disease: A clinician guide.

Risk factors most frequently associated with severe disease in children 5 years of age and younger

For further information on risk factors associated with severe disease in children, please refer to the NACI Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 months to 5 years of age.

Clinical trial data

Clinical trial data on the use of Pfizer-BioNTech Comirnaty (3 mcg) in children 6 months to 4 years of age are presented below. For details regarding clinical trial data on Moderna Spikevax (25 mcg), please refer to the NACI Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 months to 5 years of age.

Clinical trial data on Pfizer-BioNTech Comirnaty (3 mcg) in children 6 months to 4 years of age

Study design

The Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine was evaluated in pediatric participants aged 6 months to 4 years as part of an ongoing, Phase 2/3, randomized, placebo-controlled study. A total of 4,526 participants (1,776 aged 6 to 23 months and 2,750 aged 2 to 4 years) recruited from the US, Finland, Poland, Spain, and Brazil were randomized 2:1 to receive two doses of Pfizer-BioNTech Comirnaty (3 mcg) or placebo, 3 weeks apart. Based on data analyses after the second dose, the protocol was amended to add a third dose to the primary series (at least 8 weeks after the second dose). At data cut-off (April 29, 2022), about 33% of all participants had received a third dose and median follow-up after the third dose was approximately 2.1 months [14, 15]. The median interval between Dose 2 and Dose 3 was 10.7 weeks.

For the analyses, participants were split into two age-based groups (ages 6 to 23 months and 2 to 4 years). In both age groups, demographic characteristics were similarly distributed in the vaccine and placebo groups. Approximately 50% of participants were female, and the majority of children were white (78% to 80%) and recruited in the US (81% to 82%).

Efficacy

Vaccine efficacy was assessed among children 6 months to 4 years of age following two and three doses of Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine during a time when Omicron was the predominant circulating variant of SARS-CoV-2.

Efficacy estimates against confirmed COVID-19 at least 7 days post-Dose 3 among participants without prior infection (as of June 2022)

Efficacy estimates after Dose 3 are available for a longer period of follow-up (June 2022 data cut-off) compared to the period of follow-up for other clinical trial outcomes such as safety and immunogenicity (April 29, 2022 data cut-off) [16]. As of June 2022, efficacy against confirmed symptomatic SARS-CoV-2 infection starting 7 days after Dose 3 among children 6 months to 4 years of age without prior infection was estimated at 73.2% (95% confidence interval [CI]: 43.8 to 87.6%) based on 13 cases in the vaccine group (n=794) and 21 cases in the placebo group (n=351) [16].

Among children without prior infection, vaccine efficacy by age subset was estimated at 75.8% (95% CI: 9.7 to 94.7%) among children 6 to 23 months of age and 71.8% (95% CI: 28.6 to 89.4%) among children 2 through 4 years of age. All cases following Dose 3 occurred between March and June, 2022, and were confirmed to be due to the Omicron variant (primarily Omicron BA.2) [16]. The median follow-up time after the third dose was 1.9 months for participants 6 to 23 months of age and 2.4 months for participants 2 to 4 years of age.

Efficacy estimates against confirmed COVID-19 at least 7 days after Dose 2 to before Dose 3 among participants with or without evidence of prior SARS-CoV-2 (as of April 29, 2022)

Among children aged 6 to 23 months, the observed vaccine efficacy from at least 7 days after Dose 2 to before Dose 3 was estimated at 15.6% (95% CI: -24.2 to 42.1%) based on 76 cases in the vaccine group and 47 cases in the placebo group. The estimated vaccine efficacy was 82.6% (95% CI: 2.7 to 98.3%) and 5.7% (95% CI: -41.6 to 36.5%) against Delta and Omicron, respectively.

Among children aged 2 to 4 years, the observed vaccine efficacy from at least 7 days after Dose 2 to before Dose 3 was estimated at 34.3% (95% CI: 9.7 to 52.0%) based on 97 cases in the vaccine group and 73 cases in the placebo group [14]. The estimated vaccine efficacy was 56.0% (95% CI: -28.4 to 85.2%) and 31.2% (95% CI: 3.6 to 50.7%) against Delta and Omicron, respectively.

Similar vaccine efficacy estimates were observed when restricting analyses to participants without evidence of prior SARS-CoV-2 infection.

Efficacy estimates against severe outcomes of COVID-19 (as of April 29, 2022)

Efficacy against severe COVID-19 was not evaluated (severe COVID-19 was defined as a confirmed COVID-19 infection and presence of at least one criterion that triggered a potential COVID-19 illness visit; The criteria were as follows: clinical signs at rest indicative of severe systemic illness, respiratory failure, evidence of shock or cardiac failure, significant acute renal failure, significant gastrointestinal/hepatic failure, significant neurological dysfunction, admission to an ICU or death). Of the 8 cases with severe outcomes, two had evidence of co-infection with other viruses and six without evidence of co-infection were considered as not clinically significant by the investigator. There were no deaths or cases of MIS-C reported among trial participants.

For further information on the efficacy/effectiveness of mRNA COVID-19 vaccines against severe outcomes of COVID-19 including hospitalization due to MIS-C, please refer to the NACI: Statements and publications and the COVID-19 vaccine chapter in the Canadian Immunization Guide.

Immunogenicity

Immunogenicity analysis from the evaluable immunogenicity population (i.e., those without evidence of prior SARS-CoV-2 infection) included data from 82 children 6 to 23 months of age and 143 children 2 to 4 years of age (3 mcg dose), where immunobridging of humoral immune responses after Dose 2 and Dose 3 was assessed against humoral immune responses following Dose 2 in 170 individuals 16 to 25 years of age who participated in the Phase 2/3 clinical trial where vaccine efficacy was assessed (30 mcg dose). For all age groups, immunogenicity assessments included the measurement of geometric mean titres (GMTs) of neutralizing antibodies against ancestral SARS-CoV-2 (reference strain USA-WA1/2020) and seroresponse rates (SRRs) one month following Dose 2 and one month following Dose 3. Pre-established non-inferiority criteria for the geometric mean ratio (GMR) of antibody titres between comparator groups were a point estimate greater than 0.8 and lower bound of the two-sided 95% CI greater than 0.67. Provided that GMR non-inferiority criteria was met, immunobridging statistical success was declared if the lower limit of the 95% CI for the difference in SRRs was greater than -10%.

One month after Dose 2, non-inferiority criteria were met in children aged 6 to 23 months (GMR: 1.03 [95% CI: 0.9 to 1.19]). In children aged 2 to 4 years old, GMTs one month after Dose 2 were lower compared to adults 16 to 25 years of age (763.9 [95% CI: 688.5 to 847.5] vs. 1,255.4 [95% CI: 1,131.2 to 1,393.3], respectively) and the GMR did not meet pre-established non-inferiority criteria (GMR: 0.61 [95% CI: 0.53 to 0.70]). SRRs (defined as greater or equal to 4-fold baseline increase in antibody levels compared to before Dose 1) in both age groups one month following Dose 2 were also found to be non-inferior to that in adults 16 to 25 years old. The lower 95% CI limits of the SRR differences were -1.4 and -4.3 for the 6 to 23 month and 2 to 4-year-old age groups, respectively.

One month following the administration of an additional vaccine dose (Dose 3), non-inferiority immunobridging criteria were met for all primary end points in both age groups. In children aged 6 to 23 months and children 2 to 4 years old, neutralizing antibody GMRs were 1.19 (95% CI: 1

to 1.42) and 1.3 (95% CI: 1.13 to 1.5), respectively, and the differences in SRR ratios were 1.2 (95% CI: -3.4 to 4.2) and 1.2 (95% CI: -1.5 to 4.2), respectively.

Safety

The Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine was well tolerated in children aged 6 months to 4 years. As of April 29, 2022, the safety analysis set included 1,776 participants aged 6 to 23 months (1,178 in the vaccine group and 598 in the placebo group) and 2,750 participants aged 2 to 4 years (1,835 in the vaccine group and 915 in the placebo group). The median blinded follow up time from Dose 3 to data cut-off was 1.3 months among participants aged 6 to 23 months and 1.4 months among those aged 2 to 4 years. The main safety analyses were conducted on blinded follow-up time; additional analyses on the blinded plus open label follow-up time (median of 2.1 months) yielded similar results.

Overall, no safety signals were identified, and the safety profile of Pfizer-BioNTech Comirnaty (3 mcg) was consistent with the known safety and reactogenicity profile of the 10 mcg and 30 mcg Pfizer-BioNTech Comirnaty formulations authorized for use in older age groups. The types of events reported in the vaccine group were consistent with events commonly reported for other pediatric vaccines authorized for use in children 6 months to 4 years of age [17].

Local and systemic adverse events

Solicited local and systemic adverse events (AEs) within 7 days were reported at a similar or slightly higher frequency in the vaccine group than in the placebo group in both the 6 to 23 months and 2 to 4 years age groups. In both age groups, most local and systemic reactions were mild to moderate in severity, with a median onset of 1-2 days following vaccination, and resolution within 1-2 days after onset [14, 15, 18].

Among participants 6 to 23 months of age receiving Pfizer-BioNTech Comirnaty (3 mcg), the frequencies of local AEs were similar after Dose 1 and 2 but slightly lower after Dose 3, while the frequencies of solicited systemic AEs were generally similar after Dose 1, 2 or 3. Among participants 2 to 4 years of age receiving Pfizer-BioNTech Comirnaty (3 mcg), the frequencies of local and systemic AEs were generally similar after Dose 1, 2 or 3.

The frequencies of local AEs among participants 6 to 23 months or 2 to 4 years of age who received Pfizer-BioNTech Comirnaty (3 mcg) were lower compared to those 5 to 11 years of age who received Pfizer-BioNTech Comirnaty (10 mcg) [15]. Systemic AEs such as fatigue, headache, chills, and muscle pain were generally reported less frequently and were milder in severity in participants 2 to 4 years of age than in those 5 to 11 years of age. Overall, the frequency of fever was lower than 10% in all three age groups. Fever was reported a bit more frequently in participants 6 to 23 months (7.2 to 7.4% by dose) or 2 to 4 years of age (4.9 to 5.3% by dose) than in those 5 to 11 years of age (2.5 to 6.5% by dose). Six participants 6 to 23 months (n=3, ≤0,3%) and 2 to 4 years (n=3, ≤0,3%) of age who received Pfizer-BioNTech Comirnaty (3 mcg) reported a fever higher than 40.0°C [15]. In contrast, one (≤ 0.1%) participant 5 to 11 years of age

who received Pfizer-BioNTech Comirnaty (10 mcg) reported a fever >40.0°C during the pivotal clinical trial [15, 19].

See Tables 1 to 4 in Appendix A for the frequencies of solicited AEs following Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine among children 6 months to 4 years of age.

Serious adverse events and other adverse events of interest

The frequencies of any serious adverse event (SAE) were comparable in the vaccine and placebo groups among both the 6 to 23-month-old (1.4% and 2.3%, respectively) and 2 to 4-year-old (0.7% and 0.9%) participants [20]. Among 6 to 23-month-old children, none of the reported SAEs were considered related to the vaccine while two (0.1%) SAEs reported by the same participant were considered vaccine-related among the 2 to 4-year-old age group. The two SAEs (fever and pain in the extremity) occurred in a 4-year-old participant who received Pfizer-BioNTech Comirnaty (3 mcg). The participant fully recovered on Day 10. A final diagnosis was not made despite the investigations performed [15].

There were no deaths, cases of myocarditis and/or pericarditis, MIS-C, Bell's palsy or vaccine-related anaphylaxis reported during the study period. However, given that the trial was limited to 3,013 participants who were randomized to receive the vaccine, it is unlikely that rare or very rare AEs would be detected. NACI will monitor post-market safety surveillance data as it emerges and update its recommendations as needed.

For further information on the safety of mRNA COVID-19 vaccines, please refer to the NACI: Statements and publications and the COVID-19 vaccine chapter in the Canadian Immunization Guide.

Post-market safety data

Available post-market vaccine safety data from V-safe, VSD (Vaccine Safety Datalink) and VAERS (Vaccine Adverse Event Reporting System) in the US show that the Moderna Spikevax (25 mcg) and Pfizer-BioNTech Comirnaty (3 mcg) mRNA COVID-19 vaccines are well tolerated among children aged 6 months to 5 years. No safety signal (including myocarditis) has been identified after administration of about 1.5 million vaccine doses [17, 21].

As of August 21, 2022, 23,266 V-safe participants aged 6 months to 5 years received Moderna Spikevax (n=14,725) or Pfizer-BioNTech Comirnaty (n=8,541) with a total of 35,630 vaccine doses administered (Dose 1, n=23,266 and Dose 2, n=12,364) [17, 21]. Most children (97.6%) did not receive any other vaccine at the time of receipt of the first COVID-19 vaccine dose. Overall, the safety profiles of both vaccines were consistent with that observed in Phase 2/3 clinical trials. Systemic reactions following vaccination were more frequently reported among children aged 6 months to 2 years than among children aged 3 to 5 years. Among participants aged 6 months to 2 years, systemic and local reactions were comparable after Dose 1 and Dose 2 for both mRNA vaccine products [17]. Among participants aged 3 to 5 years, systemic and local reactions were

comparable after Dose 1 and Dose 2 of Pfizer-BioNTech Comirnaty (3 mcg). For Moderna Spikevax (25 mcg), local and systemic reactions were slightly higher after Dose 2 compared to Dose 1. Data following Dose 3 of Pfizer-BioNTech Comirnaty (3 mcg) are not yet available.

As of August 21, 2022, following 1,554,862 doses of COVID-19 mRNA vaccines administered to children 6 months to 5 years of age (664,484 doses of Moderna Spikevax and 890,378 doses of Pfizer-BioNTech Comirnaty); 1,017 adverse events following immunization were reported to VAERS, of which 98% (n=998) were non-serious. No cases of myocarditis were reported [17, 21].

VACCINE

COVID-19 vaccine preparations authorized for use among pediatric populations 6 months to 4 years of age in Canada

Table 1. Use of COVID-19 vaccines for children 6 months to 4 years of age

	Moderna Spikevax	Pfizer-BioNTech Comirnaty
Age	6 months to 5 years	6 months to 4 years
Dose	25 mcg (0.25 mL; original SARS-CoV-2)	3 mcg (0.2 mL; original SARS-CoV-2)
Presentation	0.10 mg/mL Royal blue vial cap Purple label border	0.015 mg/mL Maroon vial cap Maroon label border
Diluent	None	Sterile 0.9% Sodium Chloride Injection, USP
Potential allergens	Polyethylene glycol (PEG), Tromethamine (trometamol or Tris)[a]	Polyethylene glycol (PEG), Tromethamine (trometamol or Tris)[a]
Storage[b,c]	• Store at temperatures of -50°C to -15°C and protect from light in original packaging • Vials can be thawed and stored at +2°C to +8°C for up to 30 days, or at +8°C to +25°C for up to 24 hours if unpunctured • Post-puncture, vials may be stored at +2°C to +25°C and discarded after 24 hours post-first puncture • Do not refreeze once thawed	• Store at temperatures 90°C to 60°C for up to 12 months from the date of manufacture • Vials can be thawed and stored at +2°C to +8°C for up to 10 weeks, or at +8°C to +25°C for up to 12 hours if unpunctured • Post-dilution (i.e., first puncture), vials may be stored at +2°C to +25°C and discarded after 12 hours post-dilution (first puncture) • Do not refreeze once thawed
Transport[c]	If transport at -50° to -15°C is not feasible, thawed vials in a liquid state may be	If local transport of full cartons containing undiluted vials at -90°C to -60°C is not

	transported at +2°C to +8°C for up to 12 hours	feasible, full cartons or individual undiluted vials may be transported at +2°C to +8°C

[a]Tromethamine (Tris or trometamol) is used as a buffer in vaccines and medications, including those for use in children, to improve stability and prevent pH fluctuations in the solution. No safety concerns have been identified with tromethamine. While tromethamine has been identified as a potential allergen, a review of existing evidence did not identify any cases of allergic reactions to tromethamine in children [22]

[b]Regardless of storage condition, vaccines should not be used after date of expiry provided.

[c]Frozen is -50°C to -15°C; Refrigerated is +2°C to +8°C; Room temperature is +15°C to +25°C.

For complete prescribing information for the pediatric and adult formulations of Moderna Spikevax COVID-19 vaccine and Pfizer-BioNTech Comirnaty COVID-19 vaccine, please refer to the product leaflets or information contained within Health Canada's authorized product monographs available through the Drug Product Database.

SCHEDULE

Refer to Table 2 for a summary of immunization schedules for authorized COVID-19 vaccines among children 6 months to 4 years of age.

Table 2. Immunization schedule for primary series, by COVID-19 vaccine

Vaccine product	Age	Dose	Immunization schedule[1]	Authorized interval	NACI-Recommended interval[2]
Moderna Spikevax (25 mcg)	6 months to 5 years	25 mcg (0.25 mL)	2-dose schedule	28 days	At least 8 weeks between each dose
Pfizer-BioNTech Comirnaty (3 mcg)	6 months to 4 years	3 mcg (0.2 mL)	3-dose schedule	First 2 doses, 21 days apart 3rd dose at least 8 weeks after 2nd dose	At least 8 weeks between each dose

[1] It is recommended that for moderately to severely immunocompromised children, a primary series of 3 doses with Moderna Spikevax (25 mcg) or 4 doses of Pfizer-BioNTech Comirnaty (3 mcg), with a 4 to 8 interval between each dose may be offered. Refer to the Recommendations and Table 3 for additional information.

[2]There is emerging evidence that longer intervals between the first and second doses of COVID-19 vaccines result in more robust and durable immune response and higher vaccine effectiveness (VE). Data from older age groups also suggests an extended interval may be associated with a reduced risk of myocarditis/pericarditis following a second dose of an mRNA COVID-19 vaccine. NACI will continue to monitor the evidence and update this interval as needed.

RECOMMENDATIONS

For children 6 months to 4 years of age, the age group for which Pfizer-BioNTech Comirnaty (3 mcg) is authorized:

1. **NACI recommends that children 6 months to 4 years of age who are not moderately to severely immunocompromised and do not have contraindications to either vaccine may be immunized with a primary series of an mRNA COVID-19 vaccine, with a dosing interval of at least 8 weeks between doses.**

   1.1 Moderna Spikevax (25 mcg) may be offered with a primary series of two doses

   1.2 Pfizer-BioNTech Comirnaty (3 mcg) may be offered with a primary series of three doses

   (Discretionary NACI Recommendation)

   - **If readily available (i.e., easily available at the time of vaccination without delay or vaccine wastage), the same mRNA COVID-19 vaccine product should be offered for the subsequent dose in a vaccine series started with a specific mRNA COVID-19 vaccine.**

   - If two different products are administered (i.e. mixed schedule), please refer to PHAC's resource: Quick reference guide on the use of COVID-19 vaccines: Managing vaccine administration errors or deviations for guidance.

2. **NACI recommends that children 6 months to 4 years of age who are moderately to severely immunocompromised and do not have contraindications to the vaccine may be immunized with a primary series of an mRNA COVID-19 vaccine.**

   (Discretionary NACI Recommendation)

   With regard to the product offered,

   2.1 A primary series of three doses of the Moderna Spikevax (25 mcg) vaccine should be offered, using an interval of 4 to 8 weeks between each dose.

   (Strong NACI Recommendation)

   2.2 If the Moderna Spikevax (25 mcg) COVID-19 vaccine is not readily available, to ensure timely protection, Pfizer-BioNTech Comirnaty (3mcg) COVID-19 vaccine may be offered with a primary series of four doses, using an interval of 4 to 8 weeks between each dose.

   (Discretionary NACI Recommendation)

- Consistent with NACI's advice for other age groups, an extended primary series (i.e., one additional dose) is recommended for children 6 months to 4 years of age who are moderately to severely immunocompromised (i.e., a 3-dose primary series using Moderna Spikevax [25 mcg] or a 4-dose primary series using Pfizer-BioNTech Comirnaty [3 mcg]). As a 4-dose primary series may have feasibility challenges, children who are moderately to severely immunocompromised should preferentially be immunized with the Moderna Spikevax (25 mcg) vaccine using a 3-dose primary series.
- If two different products are administered (i.e., a mixed schedule), please refer to PHAC's resource: Quick reference guide on the use of COVID-19 vaccines: Managing vaccine administration errors or deviations for additional guidance.
- Vaccine providers should consider the epidemiological context when choosing the interval between doses for moderately to severely immunocompromised children. 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. However, a longer interval may also increase the chance of a period with waning (lower) protection while awaiting a next dose.

3. **Children who received one or two doses of Pfizer-BioNTech Comirnaty (3 mcg) and turn 5 prior to completing the primary series are recommended to receive the age-appropriate dose(s) of Pfizer-BioNTech Comirnaty (10 mcg) to complete the three dose primary series.**

   (Discretionary NACI Recommendation)

   - If a second or third dose of Pfizer-BioNTech Comirnaty (3 mcg) is administered after a child turns 5 or if the primary series was completed with one or two doses of Moderna Spikevax (25 mcg), please refer to PHAC's resource: Quick reference guide on the use of COVID-19 vaccines: Managing vaccine administration errors or deviations for additional guidance.

The following guidance from NACI's Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 months to 5 years of age also apply to children 6 months to 4 years of age who receive the Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine:

4. **NACI recommends at this time that mRNA COVID-19 vaccines should not *routinely* be given concurrently (i.e., same day) with other vaccines (live or non-live) among children 6 months to 5 years of age.**

   (Strong NACI recommendation)

   - For further details regarding NACI guidance on concurrent administration of pediatric mRNA COVID-19 vaccines with other authorized vaccines, please refer to the NACI Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 months to 5 years of age.

Considerations on when to offer a primary series of mRNA COVID-19 vaccine to children 6 months to 5 years of age who have been previously infected with SARS-CoV-2:

- NACI guidance on suggested intervals between previous infection and COVID-19 vaccination continues to apply to this age group. For children 6 months to 5 years of age previously infected with SARS-CoV-2, NACI suggests an 8-week interval between infection and initiation or completion of a COVID-19 primary series (i.e., 8 weeks after symptom onset or positive test if asymptomatic). This interval may be shortened for children considered moderately to severely immunocompromised (e.g., 4 to 8 weeks after symptom onset or positive test if asymptomatic) [23].
- For further details, please refer to the NACI Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 months to 5 years of age.

For further details regarding administration of Moderna Spikevax (25 mcg) among children 6 months to 5 years, please refer to the NACI Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 months to 5 years of age.

Summary of evidence, rationale, and additional considerations

- The Moderna Spikevax (25 mcg) and Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccines are the only authorized vaccines for children 6 months to 4 years of age at this time. Based on Phase 2/3 clinical trial data, the humoral immune responses generated by the primary series of these vaccines met non-inferiority criteria in children aged 6 months to 4 or 5 years compared to older age groups. Clinical trial and post-market safety data show that the first and second doses of both vaccines are well tolerated with no safety signals (including the risk of myocarditis) identified. Reactogenicity was similar to other recommended vaccines in this age group [17].
- Most children younger than 5 years of age infected with SARS-CoV-2 have mild disease severity and are infrequently hospitalized; however, some children experience severe disease, including previously healthy children. Children younger than 5 years of age have higher COVID-19-associated hospitalization and ICU admission rates compared to older pediatric age groups.
- Children who are considered medically fragile or have an underlying condition are at higher risk of severe outcomes of COVID-19.
- Seroprevalence studies from British Columbia and Quebec suggest a large proportion of children under the age of 5 years have already been infected with SARS-CoV-2 in the regions studied, with the majority of infections occurring since Omicron became the dominant variant; however, whether these data are generalizable to other parts or sub-populations of Canada is unknown.
- Indirect evidence from adult populations suggests immunity by previous infection alone is inferior to immunity conferred by vaccination with a primary series of a COVID-19 vaccine. Hybrid immunity (i.e., protection conferred from both vaccination and infection) appears to confer stronger immunity that is more durable and of greater breadth than either vaccination or previous infection alone.
- Children who have been infected with SARS-CoV-2 are at risk of MIS-C, a rare but serious post-infection complication that requires acute care, and there is evidence in older

populations (adolescents) that mRNA COVID-19 vaccines (e.g., Pfizer-BioNTech Comirnaty [30 mcg]) decrease this risk [24].

- SARS-CoV-2 infection may lead to PCC; however, evidence about the risk of PCC is limited in this pediatric population as well as for the Omicron variant.
- Many children in Canada may have fallen behind in routine vaccinations. It is important for children to receive all recommended pediatric vaccinations as per jurisdictional guidance. Out of precaution, concurrent administration of the Moderna Spikevax (25 mcg) to children 6 months to 5 years of age or Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine to children 6 months to 4 years of age with other vaccines is not routinely recommended at this time. However, this is not a contraindication.
- Informed consent should include transparency about what is known and what is presently unknown when describing the benefits and risks of the vaccine.

Please refer to Table 3 for options and considerations regarding which vaccine may be preferred in certain populations for a primary series.

Table 3. Options and considerations regarding which vaccine may be preferred in certain populations for a primary series

Population	If vaccinating an individual in this population, vaccine product and schedule that may be preferred	Rationale
Children 6 months to 4 years of age considered immunocompetent	• Moderna Spikevax (25 mcg, 2 doses at least 8 weeks apart) may be offered or • Pfizer-BioNTech Comirnaty (3 mcg, 3 doses, at least 8 weeks apart) may be offered	• Children in this population may be immunized with a primary series of mRNA COVID-19 vaccine. • Both vaccines are authorized by Health Canada as a primary series for children 6 months to 4 years of age. • A third dose is required to complete the primary series for Pfizer-BioNTech Comirnaty (3 mcg) compared to the 2-dose primary series for Moderna Spikevax (25 mcg), which may have a negative impact on likelihood of completion of the primary series. Vaccine providers should also consider the total length of time it will take to complete a 2-dose primary series or a 3-dose primary series at the recommended intervals (8 versus 16 weeks, respectively), and the risk associated with incomplete protection during this period. • Both vaccines were well tolerated during clinical trials, which is consistent with post-market safety data. No safety signals have been identified (including no identified cases

		of myocarditis) from clinical trials, nor from US post-market data. • Reactogenicity was similar for both vaccine products. • Humoral responses after the last dose in the primary series for each vaccine met pre-specified non-inferiority criteria when compared to humoral responses in older age groups.
Children 6 months to 4 years of age considered moderately to severely immunocompromised	• Moderna Spikevax (25 mcg, 3 doses, 4 to 8 weeks apart) should be offered. • If Moderna Spikevax (25 mcg) is not readily available, Pfizer-BioNTech (3 mcg, 4 doses 4 to 8 weeks apart) may be offered	• Children in this population may be immunized with a primary series of mRNA COVID-19 vaccine. • Consistent with NACI's advice for other age groups, an extended primary series (i.e., one additional dose) is recommended for children who are moderately to severely immunocompromised (i.e., 3 doses for Moderna Spikevax [25 mcg] or 4 doses for Pfizer-BioNTech [3 mcg]). • A 4-dose primary series may have feasibility challenges, including the need to schedule 4 separate appointments and space appointments appropriately relative to other childhood vaccination appointments. Vaccine providers should also consider the total length of time it will take to complete a 4-dose primary series at the recommended intervals (12 to 24 weeks) compared to a 3-dose primary series (8 to 16 weeks), and the risk associated with incomplete protection during this period. • Therefore, a 3-dose primary series of Moderna Spikevax (25 mcg) is preferred.

RESEARCH PRIORITIES

- NACI recommends continuous monitoring of data on the safety, efficacy, and effectiveness of pediatric mRNA COVID-19 vaccines through clinical trials and studies in real-world settings, including clinical trials among children considered immunocompromised and children with evidence of previous infection. This should include examining the clinical implications of previous SARS-CoV-2 infection or MIS-C on the safety, efficacy, and effectiveness of COVID-19 vaccines in pediatric populations.
- NACI recommends vigilant vaccine safety reporting internationally and across Canadian jurisdictions for timely assessment of any potentially rare or very rare AEs in children following administration of COVID-19 vaccines (alone or with other vaccines). In addition, efforts should be made to facilitate global collaboration to enable data sharing so decision makers around the world can weigh benefits and risks of COVID-19 vaccination for their own specific pediatric populations.

ABBREVIATIONS

Abbreviation	*Term*
AE	Adverse event
CI	Confidence Interval
CIC	Canadian Immunization Committee
CIG	Canadian Immunization Guide
COVID-19	Coronavirus disease 2019
GMR	Geometric mean ratio
ICU	Intensive Care Unit
MIS-C	Multisystem Inflammatory Syndrome in Children
mRNA	Messenger Ribonucleic Acid
NACI	National Advisory Committee on Immunization
PEG	Polyethylene glycol
PHAC	Public Health Agency of Canada
PHECG	Public Health Ethics Consultative Group
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SRR	Seroresponse rate
US	United States
VE	Vaccine effectiveness

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NACI members: S Deeks (Chair), R Harrison (Vice-Chair), M Andrew, J Bettinger, N Brousseau, H Decaluwe, P De Wals, E Dubé, V Dubey, K Hildebrand, K Klein, M O'Driscoll, J Papenburg, A Pham-Huy, B Sander, and S Wilson.

Liaison representatives: L Bill (Canadian Indigenous Nurses Association), LM Bucci (Canadian Public Health Association), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), J Comeau (Association of Medical Microbiology and Infectious Disease Control), L Dupuis (Canadian Nurses Association), E Adams (Indigenous Physicians Association of Canada), J Hu (College of Family Physicians of Canada), M Lavoie (Council of Chief Medical Officers of Health), D Moore (Canadian Paediatric Society), M Naus (Canadian Immunization Committee), and A Ung (Canadian Pharmacists Association).

Ex-officio representatives: V Beswick-Escanlar (National Defence and the Canadian Armed Forces), E Henry (Centre for Immunization and Respiratory Infectious Diseases (CIRID), PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), C Lourenco (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), D MacDonald (COVID-19 Epidemiology and Surveillance, PHAC), S Ogunnaike-Cooke (CIRID, PHAC), K Robinson (Marketed Health Products Directorate, HC), M Routledge (National Microbiology Laboratory, PHAC), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

NACI COVID-19 Vaccine Working Group

Members: S Wilson (Chair), M Adurogbangba, M Andrew, Y-G Bui, H Decaluwe, P De Wals, V Dubey, S Hosseini-Moghaddam, M Miller, D Moore, S Oliver, and E Twentyman.

PHAC Participants: NK Abraham, O Baclic, L Coward, F Crane, P Doyon-Plourde, N Forbes, M Hersi, N Islam, S Ismail, C Jensen, CY Jeong, F Khan, A Killikelly, R Krishnan, SH Lim, N Mohamed, J Montroy, S Pierre, R Pless, M Salvadori, A Stevens, E Tice, A Tuite, MC Tunis, E Wong, R Ximenes, MW Yeung, and J Zafack.

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APPENDIX A: SUPPLEMENTAL INFORMATION ON THE CLINICAL TRIAL ON PFIZER-BIONTECH COMIRNATY (3 MCG) AMONG CHILDREN 6 MONTHS TO 4 YEARS OF AGE

Frequency of solicited adverse events following immunization

Table 1. Frequency of solicited local reactions within 7 days after each dose – children 6 to 23 months of age – safety population*

Solicited local reaction	Dose 1		Dose 2		Dose 3	
	Vaccine† N[a]=1159 to 1173 n[b] (%)	Placebo N[a]=591 to 595 n[b] (%)	Vaccine† N[a]=1137 to 1147 n[b] (%)	Placebo N[a]=590 to 591 n[b] (%)	Vaccine† N[a]=362 to 365 n[b] (%)	Placebo N[a]=170 n[b] (%)
Redness						
Any (≥0.5 cm)	124 (10.6)	44 (7.4)	107 (9.3)	39 (6.6)	26 (7.1)	9 (5.3)
Severe[c]	0	0	0	0	1 (0.3)	0
Swelling						
Any (≥0.5 cm)	46 (3.9)	15 (2.5)	45 (3.9)	9 (1.5)	10 (2.7)	3 (1.8)
Severe[c]	0	0	0	0	0	0
Tenderness at the injection site						
Any	192 (16.6)	66 (11.2)	171 (15.0)	50 (8.5)	58 (16.0)	20 (11.8)
Severe[d]	0	0	1 (0.1)	0	0	0

* Randomized participants who received at least 1 dose of vaccine or placebo

† Pfizer-BioNTech Comirnaty (3 mcg)

Note: Reactions were collected in an electronic diary (e-diary) from Day 1 to Day 7 after vaccination

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose

b. n = Number of participants with the specified reaction

c. Severe: >7.0 cm

d. Severe: causes limitation of limb movement

The information in this table is up to date as of October 21, 2022. For updated information, please consult the Comirnaty product monograph.

Table 2. Frequency of solicited systemic reactions within 7 days after each dose –children 6 to 23 months age – safety population*

Solicited systemic reaction	Dose 1		Dose 2		Dose 3	
	Vaccine† N[a]=1159 to 1173 n[b] (%)	Placebo N[a]=591 to 595 n[b] (%)	Vaccine† N[a]=1137 to 1147 n[b] (%)	Placebo N[a]=590 to 591 n[b] (%)	Vaccine† N[a]=362 to 365 n[b] (%)	Placebo N[a]=170 n[b] (%)
Fever						
≥38.0°C	85 (7.2)	43 (7.2)	85 (7.4)	36 (6.1)	25 (6.8)	10 (5.9)
>38.9°C to 40.0°C	20 (1.7)	7 (1.2)	24 (2.1)	7 (1.2)	6 (1.6)	1 (0.6)
Decreased appetite						
Any (≥0.5 cm)	257 (22.2)	125 (21.2)	252 (22.2)	106 (18.0)	73 (20.2)	23 (13.5)
Severe[c]	3 (0.3)	1 (0.2)	4 (0.4)	1 (0.2)	4 (1.1)	0
Drowsiness						
Any	313 (27.0)	173 (29.3)	271 (23.8)	125 (21.2)	72 (19.9)	22 (12.9)
Severe[d]	2 (0.2)	2 (0.3)	4 (0.4)	1 (0.2)	1 (0.3)	1 (0.6)
Irritability						
Any	593 (51.2)	279 (47.2)	539 (47.4)	240 (40.7)	158 (43.6)	64 (37.6)
Severe[e]	7 (0.6)	0	7 (0.6)	5 (0.8)	1 (0.3)	0
Use of antipyretic or pain medication[f]	281 (24.0)	117 (19.7)	243 (21.2)	111 (18.8)	70 (19.2)	28 (16.5)

* Randomized participants who received at least 1 dose of vaccine or placebo

† Pfizer-BioNTech Comirnaty (3 mcg)

Note: Events and use of antipyretic or pain medication were collected in an electronic diary (e-diary) from Day 1 to Day 7 after each dose

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose
b. n = Number of participants with the specified reaction
c. Severe: refusal to feed
d. Severe: disabling; not interested in usual daily activity
e. Severe: inconsolable; crying cannot be comforted
f. Severity was not collected for use of antipyretic or pain medication

The information in this table is up to date as of October 21, 2022. For updated information, please consult the Comirnaty product monograph.

Table 3. Frequency of solicited local reactions within 7 days after each dose – children 2 to 4 years of age – safety population*

Solicited local reaction	Dose 1		Dose 2		Dose 3	
	Vaccine† Na=1814 to 1825 nb (%)	Placebo Na=905 to 909 nb (%)	Vaccine† Na=1772 to 1779 nb (%)	Placebo Na=877 to 878 nb (%)	Vaccine† Na=547 to 552 nb (%)	Placebo Na=262 nb (%)
Redness						
Any (≥0.5 cm)	160 (8.8)	77 (8.5)	202 (11.4)	50 (5.7)	60 (10.9)	9 (3.4)
Severe[c]	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0
Swelling						
Any (≥0.5 cm)	67 (3.7)	26 (2.9)	102 (5.7)	18 (2.1)	17 (3.1)	3 (1.1)
Severe[c]	0	0	0	0	0	0
Pain at the injection site						
Any	559 (30.8)	186 (20.6)	550 (31.0)	178 (20.3)	146 (26.7)	35 (13.4)
Severe[d]	0	1 (0.1)	0	1 (0.1)	0	0

* Randomized participants who received at least 1 dose of vaccine or placebo

† Pfizer-BioNTech Comirnaty (3 mcg)

Note: Reactions were collected in an electronic diary (e-diary) from Day 1 to Day 7 after vaccination

a. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose

b. n = Number of participants with the specified reaction

c. Severe: >7.0 cm

d. Severe: prevents daily activity

The information in this table is up to date as of October 21, 2022. For updated information, please consult the Comirnaty product monograph.

Table 4. Frequency of solicited systemic reactions within 7 days after each dose – children 2 to 4 years of age – safety population*

Solicited systemic reaction	Dose 1		Dose 2		Dose 3	
	Vaccine† N[a]=1813 to 1824 n[b] (%)	Placebo N[a]=905 to 909 n[b] (%)	Vaccine† N[a]=1772 to 1779 n[b] (%)	Placebo N[a]=877 to 878 n[b] (%)	Vaccine† N[a]=547 to 552 n[b] (%)	Placebo N[a]=262 n[b] (%)
Fever						
≥38.0°C	95 (5.2)	48 (5.3)	88 (4.9)	46 (5.2)	28 (5.1)	11 (4.2)
>38.9°C	14 (0.8)	8 (0.9)	21 (1.2)	8 (0.9)	4 (0.7)	3 (1.1)
Fatigue						
Any	539 (29.7)	277 (30.6)	456 (25.7)	201 (22.9)	134 (24.5)	57 (21.8)
Severe[c]	6 (0.3)	5 (0.6)	8 (0.5)	3 (0.3)	2 (0.4)	0
Headache						
Any	81 (4.5)	44 (4.9)	81 (4.6)	36 (4.1)	27 (4.9)	11 (4.2)
Severe[c]	0	1 (0.1)	0	1 (0.1)	0	0
Chills						
Any	41 (2.3)	22 (2.4)	53 (3.0)	23 (2.6)	18 (3.3)	7 (2.7)
Severe[c]	3 (0.2)	0	0	0	1 (0.2)	0
Vomiting						
Any	54 (3.0)	24 (2.7)	61 (3.4)	29 (3.3)	9 (1.6)	10 (3.8)
Severe[d]	0	0	0	0	0	0
Diarrhea						
Any	139 (7.7)	72 (8.0)	118 (6.7)	64 (7.3)	28 (5.1)	13 (5.0)
Severe[e]	0	0	1 (0.1)	0	0	0
New or worsened muscle pain						
Any	43 (2.4)	15 (1.7)	46 (2.6)	21 (2.4)	11 (2.0)	4 (1.5)
Severe[c]	1 (0.1)	0	0	0	0	0
New or worsened joint pain						
Any	14 (0.8)	18 (2.0)	24 (1.4)	9 (1.0)	7 (1.3)	2 (0.8)
Severe[c]	0	0	0	0	1 (0.2)	0
Use of antipyretic or pain medication[f]	197 (10.8)	83 (9.1)	177 (9.9)	74 (8.4)	47 (8.5)	18 (6.9)

* Randomized participants who received at least 1 dose of vaccine or placebo

† Pfizer-BioNTech Comirnaty (3 mcg)

Note: Events and use of antipyretic or pain medication were collected in an electronic diary (e-diary) from Day 1 to Day 7 after each dose

a. N = Number of participants reporting at least 1 yes or no response for the specified event after the specified dose

b. n = Number of participants with the specified reaction

c. Severe: prevents daily activity

d. Severe: requires intravenous hydration

e. Severe: 6 or more loose stools in 24 hours

f. Severity was not collected for use of antipyretic or pain medication

The information in this table is up to date as of October 21, 2022. For updated information, please consult the Comirnaty product monograph.