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

Recommendations on the use of Moderna Spikevax COVID-19 vaccine in children 6 months to 5 years of age

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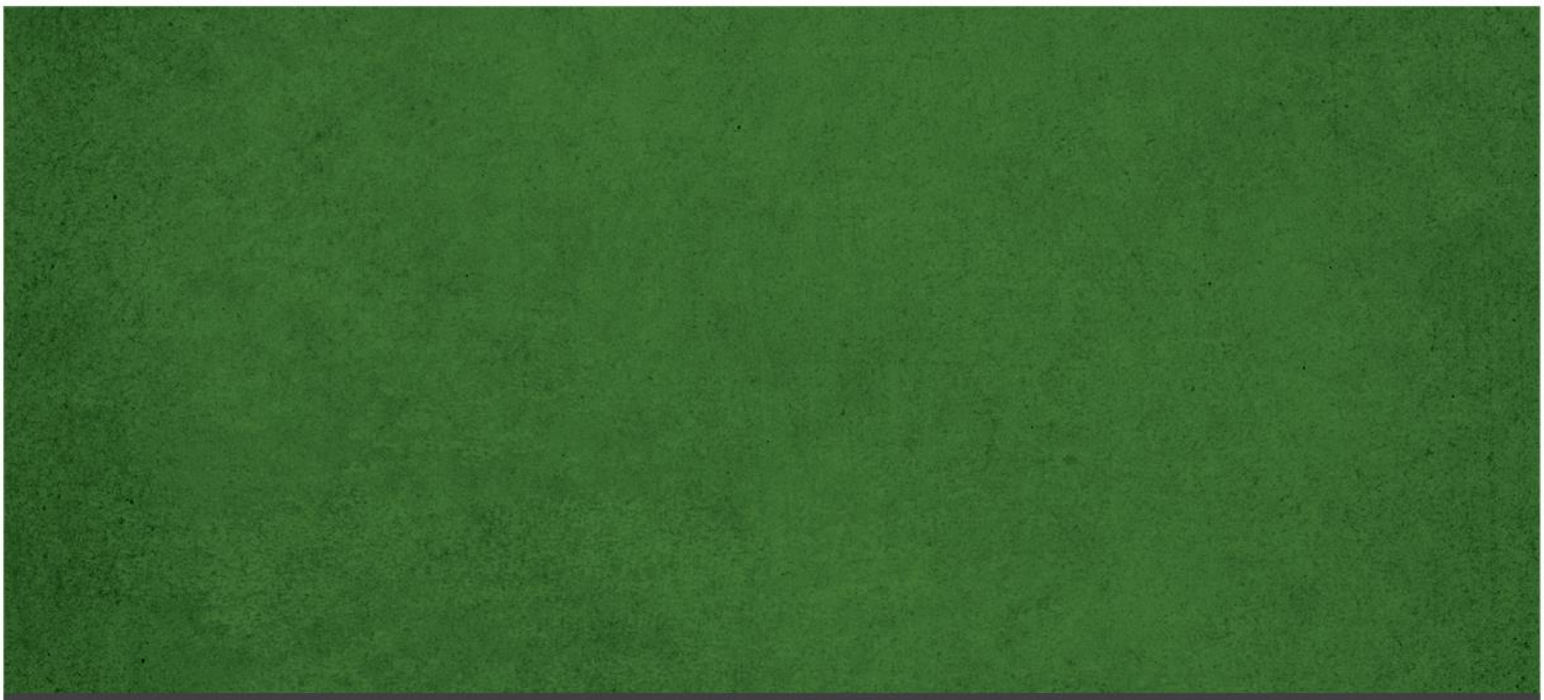

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Recommandations sur l'utilisation du vaccin Spikevax de Moderna contre la COVID-19 chez les enfants de 6 mois à 5 ans

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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

The Moderna Spikevax (25 microgram [mcg] dose) mRNA COVID-19 vaccine is the first COVID-19 vaccine authorized in Canada for use in pediatric populations under the age of 5 years. Moderna Spikevax (25 mcg) was approved for children 6 months to 5 years of age on July 14, 2022. Prior to July 14, 2022, mRNA COVID-19 vaccines have been previously authorized by Health Canada in other pediatric populations (<12 years of age) as follows:

- Pfizer-BioNTech Comirnaty authorized on November 19, 2021 for individuals 5 to 11 years of age (2 dose primary series; 10 mcg per dose)
- Moderna Spikevax authorized on March 17, 2022 for individuals 6 to 11 years of age (2 dose primary series; 50 mcg per dose)

For further information on NACI's recommendations on the use of mRNA COVID-19 vaccines, please refer to the COVID-19 vaccine chapter in the Canadian Immunization Guide (CIG).

NACI's recommendations are aligned with the following 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 June 7, 2022 and June 21, 2022, NACI reviewed the available evidence on the use of Moderna Spikevax COVID-19 vaccine (25 mcg) in children 6 months to 5 years of age. The body of evidence included manufacturer's clinical data in the regulatory submission to Health Canada, burden of COVID-19 disease in this population, and post-market safety data for other formulations of mRNA vaccines in older age groups. Ethical considerations related to COVID-19 vaccination in pediatric populations aged ≤ 12 years were discussed with the Public Health Ethics Consultative Group (PHECG) on May 3, 2021, July 6, 2021, September 21, 2021, and May 12, 2022. The Canadian Immunization Committee (CIC) provided feedback on key policy questions to ensure alignment with provincial/territorial program needs on April 28, 2022. NACI approved their recommendations on the use of Moderna Spikevax in children 6 months to 5 years of age on July 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

The majority of children with COVID-19 have mild or asymptomatic disease; however, some children get severe disease and require hospitalization. Population level estimates of hospitalization and ICU admission in pediatric populations have increased since Omicron became the predominant variant. For children 6 months to 4 years of age (the age group previously ineligible for COVID-19 immunization), the average monthly rate of hospitalization due to COVID-19 increased from 1.4 to 15.9 per 100,000, comparing March 1, 2020 - December 31, 2021 to January 1, 2022 – March 31, 2022 [3]. This analysis includes data from 6 of Canada's 13 provinces and territories that provide surveillance data to PHAC that includes age in months for pediatric cases. Increased COVID-19 associated hospitalization rates across pediatric populations are consistent with increased seroprevalence rates across older age groups and the overall increase in reported cases across the population since Omicron became the predominant variant.

Canadian seroprevalence studies from Quebec (January 26, 2022 ─ February 17, 2022) and British Columbia (BC) from March 2022 estimate that 30% to 70% of children under the age of 5 years have been previously infected with SARS-CoV-2; most of these infections occurred since Omicron became the dominant variant [4-6]. These data may not be generalizable to other regions of Canada though, and national COVID-19 seroprevalence estimates are unknown in children 5 years of age or younger.

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

Children who have had 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. Out of 419 nationally reported cases of MIS-C in Canada, no deaths have been reported to date [7]. MIS-C associated deaths have been reported in the United States (US) [8]; however, the generalizability of this data to the Canadian healthcare system is unknown.

While evidence is limited in children 5 years of age and younger, SARS-CoV-2 infection may lead to post-COVID condition/post-acute COVID syndrome. This evidence is evolving for younger (<12 years) pediatric age groups.

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

A rapid review on the magnitude of association between risk factors and severe outcomes of COVID-19 in children 5 years of age and younger was conducted by COVID-END (last updated on March 7, 2022) [9]. Children ≤5 years of age with any comorbidity may have an increased risk for severe COVID-19 outcomes (n=6 studies; moderate certainty of evidence) [10-15]. The evidence suggesting that race and ethnicity and/or living with social and structural inequities are risk factors for severe COVID-19 outcomes (n= 2 studies) is limited (very low certainty of evidence) [11, 15]. Five studies assessed the relationship between specific comorbidities and severe outcomes in children aged 0 to 2 months and 3-5 months. A number of risk factors had statistically significant associations with severe COVID-19 outcomes, including cardiac and circulatory congenital anomalies; chronic lung conditions; and feeding tube dependence [11-14, 16]. For children <2 years, statistically significant associations for severe disease were reported for prematurity, cardiovascular condition, respiratory condition, abnormality of airways, neurologic disorder, feeding tube dependence and hypertension. For children 2 to 5 years, statistically significant associations with severe disease were reported for neurodevelopmental disorders, epilepsy and/or convulsions, obesity, chronic metabolic disease and immunosuppression [13, 16, 17]. However, the majority of studies conducted to inform on the risk factors of severe outcomes of COVID-19 in pediatric populations occurred pre-Omicron and may not be generalizable to the current epidemiologic situation across Canada [9].

The severity of disease for future SARS-CoV-2 variants in children or any other population is unknown.

Clinical trial data on Moderna Spikevax (25 mcg) in children 6 months to 5 years of age

The Moderna Spikevax COVID-19 vaccine was evaluated in pediatric participants aged 6 months to 5 years as part of an ongoing, Phase 2/3, randomized, observer-blind, placebo-controlled study. For all analyses, the participants were split into two age-based subgroups; ages 6 to 23 months and 2 to 5 years. Participants were recruited from the US and Canada beginning November 2021 and enrollment is ongoing. Participants were randomly assigned to receive either two doses of the vaccine (25 mcg mRNA) or two doses of a placebo, administered 28 days apart [18].

Across both age groups and between the vaccine and placebo groups, approximately 50% of participants were female. Among participants that received the Moderna Spikevax vaccine, the majority were between 1 and <5 years of age, whereas about 8% were aged 6 months to 11 months and about 2% were age 5 years to < 6 years [19].

At data cut-off (February 21, 2022), median follow up after the second dose was 68 days for participants aged 6 to 23 months and median follow up time was 72 days for participants aged 2 years to 5 years.

Efficacy

Vaccine efficacy was assessed among children aged 6 months to 5 years following one and two doses of Moderna Spikevax (25 mcg) mRNA COVID-19 vaccine during a time when Omicron was the predominant variant of SARS-CoV-2 in the US and Canada (data cut-off February 21, 2022) [18]. The per-protocol population (negative baseline SARS-CoV-2 status and received two doses of either vaccine or placebo) included 5,476 participants who received two doses of either vaccine or placebo (for participants 6 months through 23 months, 1,511 participants in the vaccine group, 513 in the placebo group; for participants 2 years through 5 years, 2,594 in the vaccine group, 858 in the placebo group) [20].

Efficacy estimates among participants without evidence of prior SARS-CoV-2 infection (per-protocol population)

Efficacy against confirmed symptomatic SARS-CoV-2 infection starting 14 days after dose 2 was estimated at 50.6% (95% confidence interval [CI]: 21.4 to 68.6%) among study participants aged 6 to 23 months and 36.8% (95% CI: 12.5 to 54.0%) among participants aged 2 to 5 years [18, 20].

Efficacy against asymptomatic SARS-CoV-2 infection starting 14 days after dose 2 was estimated at 3.8% among study participants aged 6 to 23 months and 22.9% among participants aged 2 to 5 years; however, in both age groups, the confidence interval around the point estimate was wide and included zero (95% CI: -111.5 to 52.8% and 19.5 to 49.3%, respectively) [18, 20].

The estimate of vaccine efficacy against asymptomatic infection after 2 doses should be interpreted with caution as cases were identified among participants that were seronegative at baseline prior to dose 1 and who later had a positive reverse transcription polymerase chain reaction (RT-PCR) test or serology result at varying time points starting 14 days after dose 2; however, there was a limited number of participants providing samples for serology at later time points. Therefore, this finding could reflect infection acquired at any time after dose 1 prior to the time of sample collection, and may be an underestimation of 2 dose efficacy.

Efficacy against confirmed symptomatic SARS-CoV-2 infection from 14 days after dose 1 until dose 2 was estimated at -11.4% among study participants aged 6 to 23 months and 17% among participants aged 2 to 5 years. However, estimates of 1-dose vaccine efficacy should be considered with caution, as few cases were reported during this two-week time frame, and accordingly the confidence interval around the point estimate was wide and included zero (95% CI: -529.8 to 71.3% and -161.2 to 69.6%, respectively) [21, 22].

Efficacy estimates among participants with or without evidence of prior SARS-CoV-2 infection

Efficacy against confirmed symptomatic SARS-CoV-2 infection starting 14 days after dose 2 was also determined among participants regardless of evidence of prior to SARS-CoV-2 infection and was estimated at 50.6% (95% CI: 21.4 to 68.6%) among study participants aged 6 to 23 months and 36.5% (95% CI: 12.5 to 54.0%) among participants aged 2 to 5 years [23].

Efficacy estimates against severe outcomes of COVID-19

There were no deaths or cases of severe COVID-19 or MIS-C among trial participants that received the vaccine; however, one case of MIS-C was reported after the February 21, 2022 data cut-off in a participant that received the placebo [18]. Therefore, efficacy against outcomes of severe COVID-19 or MIS-C was not evaluated.

Real world evidence suggests mRNA vaccines in older age groups have high vaccine effectiveness (VE) at preventing severe outcomes of COVID-19 including hospitalization and death. Additionally, mRNA vaccines have high VE against hospitalization due to MIS-C in adolescent populations [24]. Estimates of Moderna Spikevax vaccine efficacy against symptomatic disease during the Omicron wave in children aged 6 months to 5 years are consistent with VE reported for Pfizer-BioNTech Comirnaty (10 mcg) vaccine among children 5 to 11 years of age during the Omicron wave [25]. However, waning of immune responses over time are well documented in older age groups and may also contribute to lower VE estimates when calculating VE at longer intervals following vaccination or infection. VE against any future variants is unknown.

For further information on the VE of mRNA COVID-19 vaccines against severe outcomes of COVID-19 including hospitalization due to MIS-C, please refer to the COVID-19 vaccine chapter in the Canadian Immunization Guide (CIG).

Immunogenicity

Immunogenicity as per protocol among participants without evidence of prior SARS-CoV-2 infection

The humoral immune response to Moderna Spikevax (25 mcg) was non-inferior in children aged 6 months to 5 years compared to young adults, meeting pre-established non-inferiority criteria (lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67; point estimate ≥0.8). SARS-CoV-2 neutralizing antibody titers (ID50) were assayed 28 days following dose 2, and the GMR of neutralizing antibody titres in children 2 to 5 years of age (n=264) and 6 to 23 months of age (n=230) relative to young adults (18 to 25 years of age; n=291) was 1.01 (95% CI: 0.88 to 1.17%) and 1.280 (95% CI: 1.12 to 1.47%), respectively. The neutralizing seroresponse rates (SRR) among children 2 to 5 years and children 6 to 23 months old were 98.9% and 100% respectively, with differences compared to young adults of -0.4% (95% CI: -2.7 to 1.5%) and 0.7% (95% CI: -1.0 to 2.5%), respectively, meeting non-inferiority success criteria (lower bound of the 95% CI of the SRR difference > -10%) [20].

Immunogenicity in participants based on SARS-CoV-2 serology at baseline

Approximately 9% of participants 2 to 5 years of age and 6% of participants 6 to 23 months of age had serologic evidence of prior SARS-CoV-2 infection at the start of the study and were thus excluded from immunobridging analyses [18]. Neutralizing antibody titres increased in these participants 28 days after dose 2. In seropositive children 2 to 5 years of age, antibody titres increased by 37-fold compared to pre-vaccination titres. In seropositive children 6 to 23 months of age, antibody titres increased by 49-fold compared to pre-vaccination titres [26]. Antibody titres for seropositive children aged 2 to 5 years and 6 to 23 months were at least 4- or 6-fold higher 28 days after dose 2 compared to seronegative children.

In both seronegative and seropositive participants, antibody titres were generally higher in children 6 to 23 months of age compared to children 2 to 5 years of age.

As an immunological correlate of protection has not been determined for COVID-19 at this time, it is unknown how the immune response levels that have been reported in clinical trials are related to the prevention of SARS-COV-2 infection or disease or the ability to transmit to others.

Safety

The Moderna Spikevax COVID-19 vaccine (25 mcg) was well tolerated in children aged 6 months to 5 years. Safety data were collected in a still ongoing Phase 2/3 clinical trial that included children 6 months through 5 years of age. The safety data analyzed was based on a February 21, 2022 data cut-off. At the time of data cut-off, the safety analysis set included 375 subjects who were 6 months to < 1 year of age, 1,373 subjects who were 1 to < 2 years of age, and 3,007 subjects who were 2 to < 6 years of age [20]. No safety signals were identified after a median of 103 days after dose 1 and 71 days after dose 2 for ages 2 to 5 years, and 98 days after dose 1 and 68 days after dose 2 for children 6 months to < 2 years of age. Duration of participant follow-up ranged from 0 to 127 days after dose 1 and from 0 to 99 days after dose 2 as the study was still recruiting participants at time of data cut off [18].

Overall, the safety profile of Moderna Spikevax (25 mcg) vaccine was consistent with the known safety and reactogenicity profile of the 50 mcg and 100 mcg Spikevax formulations authorized for use in older age groups. Events reported in the vaccine group were consistent with events commonly reported for other pediatric vaccines authorized for use in children 6 months to 5 years of age.

Local and systemic adverse events

Data on solicited local and systemic adverse reactions included 4,792 participants 6 months to 5 years of age who received at least one dose of vaccine, and 1,596 participants who received at least one dose of placebo. Solicited local adverse reactions within 7 days, including grade 3 events, were reported at a higher frequency in the vaccine group than in the placebo group in both the 2 to 5 year and the 6 months to < 2 year age groups, particularly after the second dose.

Solicited systemic adverse reactions within 7 days reported after dose 1 were similar when compared to placebo in both age groups, but were reported at a higher frequency in the vaccine group than in the placebo group after the second dose, including grade 3 events. The majority of solicited local and systemic adverse reactions were grade 1 or 2 and occurred within the first 2 days after any dose of vaccine and persisted for a median of 2 to 3 days. The incidence of grade 3 solicited adverse reactions was infrequent in both vaccine and placebo groups in both age groups (< 5% after any dose) [20].

The most frequently reported solicited local and systemic adverse reactions were irritability/crying, pain, sleepiness, and loss of appetite. Fatigue (48.4%) was the most frequently reported systemic adverse reaction in the participants 37 months to 5 years of age [20].

See Table 1 of the Appendix for the frequency of solicited local adverse events (AEs) for the Moderna Spikevax COVID-19 vaccine among children 6 months to 5 years of age.

Any type of AE that occurred in at least 1% of study participants aged 6 months to <2 years of age who received vaccine and at a rate at least 1.5-fold higher than in the placebo group, included acute otitis media (1.4% versus 0.7%), injection site lymphadenopathy (1.4% versus 0.2%) and injection site erythema (1.1% versus 0.2%). In children 2 to 5 years of age, only injection site erythema occurred in ≥ 1% in the vaccine arm and at a rate at least 1.5-fold higher than placebo (1.3% versus 0.2%) [18].

Serious adverse events and other adverse events of interest

For participants 2 to 5 years of age: Serious adverse events (SAEs) up to and beyond 28 days since last dose were reported at a frequency of 0.3% (n=9) for the vaccine group and 0.2% (n=2) for the placebo group. None of the reported SAEs were considered related to the vaccine [20]. The incidence of medically attended events up to 28 days after any dose was similar in the vaccine group (662/3031; 21.8%) compared with the placebo group (221/1007; 21.9%). No participants in either group discontinued the study due to an adverse event [18].

For participants 6 months to <2 years of age: SAEs up to and beyond 28 days since last dose were reported at a frequency of 0.9% (n=15) for the vaccine group and 0.2% (n=1) for the placebo group. In the vaccine group, there was 1 participant with two SAEs considered related to the vaccine (a grade 3 fever that occurred 6 hours after dose 1, which was followed by a febrile convulsion). None of the other reported SAEs were considered related to the vaccine [20]. The incidence of medically attended events up to 28 days after any dose were also similar in the vaccine group (486/1761; 27.6%) compared with the placebo group (161/589; 27.3%). One participant in each group discontinued study vaccination [18].

There was 1 event of anaphylaxis attributed to a concurrent medication in the 2 to 5 year age group (32 days after vaccination), and 2 events of egg or food product related-anaphylaxis unrelated to the vaccine in the younger age group 6 months to < 2 years (15 and 18 days after vaccination) [18].

There were no deaths, no cases of MIS-C, and no cases of myocarditis and/or pericarditis reported in any participant during the study period [18]. Given the trial was limited to n=4,792 participants randomized to receive the Moderna Spikevax (25 mcg) vaccine, it is unlikely that any AE occurring at a frequency less often than 6 in 10,000 would be detected.

Canadian and international post-market safety surveillance data for other mRNA COVID-19 vaccines in older populations have reported the rare risk of myocarditis and/or pericarditis with mRNA vaccines, which varies by sex, age, interval between doses, vaccine dose, and vaccine product. Current data suggests the risk of myocarditis and/or pericarditis in younger children is lower than that of adolescents or young adults.

For further information on the risk of myocarditis and/or pericarditis following vaccination with an mRNA COVID-19 vaccine, please refer to the COVID-19 vaccine chapter in the Canadian Immunization Guide (CIG).

VACCINE

COVID-19 vaccine preparations authorized for use among pediatric populations 6 months to 5 years of age in Canada

Table 1. Use of COVID-19 vaccines for children 6 months to 5 years of age

	Moderna Spikevax
Age	6 months to 5 years
Dose	25 mcg (0.25 mL)
Presentation	0.10 mg/mL Royal blue vial cap
Diluent	None
Potential allergens	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 • 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 transported at +2°C to +8°C for up to 12 hours.

[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 [27]
[b]Regardless of storage condition, vaccines should not be used after date of expiry printed on the vial and cartons.
[c] Frozen is -25°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, 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 5 years of age.

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

Vaccine Product	Age	Dose	Immunization Schedule	Authorized Interval	NACI - Recommended Interval[1]
Moderna Spikevax (25 mcg)	6 months to 5 years	25 mcg (0.25 mL)	2-dose schedule	28 days	At least 8 weeks
Pfizer-BioNTech Comirnaty (10 mcg)	5 to 11 years	10 mcg (0.2mL)	2-dose schedule	21 days	At least 8 weeks

[1]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 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 5 years of age (which is the age group in which the Moderna Spikevax 25 mcg primary series vaccine is authorized):

1. **NACI recommends that a complete series with the Moderna Spikevax COVID-19 vaccine (25 mcg) may be offered to children 6 months to 5 years of age who do not have contraindications to the vaccine, with a dosing interval of at least 8 weeks between the first and second dose. (*Discretionary NACI Recommendation)***

2. **NACI recommends that children 6 months to 5 years of age who are moderately to severely immunocompromised may be immunized with a primary series of three doses of the Moderna Spikevax (25 mcg) vaccine, using an interval of 4 to 8 weeks between each dose. (*Discretionary NACI Recommendation)***

3. **NACI recommends at this time that the Moderna Spikevax (25 mcg) COVID-19 vaccine primary series for children 6 months to 5 years of age should not routinely be given concurrently (i.e., same day) with other vaccines (live or non-live). (*Strong NACI recommendation*)**

- As this is a newly authorized vaccine in this age group, evidence relating to any risk of rare or very rare AEs will be monitored. It is advised to wait 14 days between vaccine products when administering the Moderna Spikevax (25 mcg) COVID-19 vaccine and other vaccines. This could prevent erroneous attribution of an AE to one particular vaccine or the other.

- This suggested minimum waiting period between vaccines is precautionary at this time, and is consistent with the initial NACI guidance on concurrent administration of COVID-19 vaccines in children 5 to 11 years of age at the time of vaccine authorization, when the risk of rare or very rare adverse events following immunization were unknown given the clinical trial size.

- However, it is acknowledged that it may be challenging for both healthcare providers and parents if multiple visits to healthcare providers are required to administer all recommended immunizations. Concurrent administration or a shortened interval between the Moderna Spikevax (25 mcg) COVID-19 vaccine and other vaccines may be warranted on an individual basis in some circumstances at the clinical discretion of the healthcare provider.

4. **For children 5 years of age** (the age group in which both the Moderna Spikevax (25 mcg) and the Pfizer-BioNTech Comirnaty (10 mcg) COVID-19 vaccine primary series are authorized):

   4.1 Moderna Spikevax (25 mcg) may be offered to children 5 years of age as an alternative to Pfizer-BioNTech Comirnaty (10 mcg); however, the use of Pfizer-BioNTech Comirnaty (10 mcg) is preferred to Moderna Spikevax (25 mcg). (*Discretionary NACI Recommendation*)

   4.2 Children who have received Moderna Spikevax (25 mcg) for a previous dose and turn 6 prior to completing their primary series are recommended to receive Moderna Spikevax (50 mcg) to complete their primary series. If the primary series was completed with Moderna Spikevax (25 mcg) or with Pfizer-BioNTech Comirnaty (10 mcg), the dose should be considered valid and the series complete. (*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.

- However, in following the established guidance on interchangeability of mRNA COVID-19 vaccines, when the same mRNA vaccine product is not readily available, is unknown, or is no longer authorized for the age group (e.g., once a child has turned 6 years of age), another mRNA COVID-19 vaccine product recommended in that age group can be considered interchangeable.

- For further information regarding interchangeability of mRNA COVID-19 vaccines, please refer to the COVID-19 vaccine chapter in the Canadian Immunization Guide (CIG).

Considerations on when to offer the Moderna Spikevax (25 mcg) primary series to children 6 months to 5 years of age who have been previously infected with SARS-CoV-2:

- Based on data from older (e.g., ≥5 years of age) populations, the duration of protection against Omicron infection conferred from a primary series of a COVID-19 vaccine is greater than that conferred by infection alone; however, protection wanes after several months. The duration of protection from a COVID-19 vaccine primary series against severe infection is sustained for at least 6 months.
- Hybrid immunity (i.e., immunity induced by vaccination and infection) in adult populations is associated with greater breadth and duration of protection.
- Seroprevalence studies suggest that many children have been infected with the Omicron variant of SARS-CoV-2.
- NACI's suggested intervals between previous infection and COVID-19 vaccination also 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) [28].

Summary of evidence, rationale, and additional considerations

- The Moderna Spikevax COVID-19 vaccine is the only authorized vaccine 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 vaccine met non-inferiority criteria in children aged 6 months to 5 years compared to young adults. The vaccine was well tolerated with no safety signals reported. Reactogenicity was consistent with other recommended vaccines in this age group. As real-world evidence on the use of this vaccine is not available yet, and the clinical trial size was limited, the risk of any rare or very rare AE such as myocarditis and/or pericarditis is unknown at this time. However, post-market vaccine safety in pediatric populations is closely monitored and signals of AEs will be reviewed on an ongoing basis.
- Seroprevalence studies from BC 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 of Canada (e.g., the Maritime provinces) or sub-populations 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 (vaccinated + infected) appears to confer stronger immunity that is more durable and of greater breadth than either vaccination or previous infection alone.
- Most children ≤ 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 who are considered medically fragile or have an underlying condition are at higher risk of severe outcomes of COVID-19.
- 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 some indirect evidence that mRNA COVID-19 vaccines (e.g., Pfizer-BioNTech Comirnaty [30 mcg]) decreases this risk in adolescent populations.
- SARS-CoV-2 infection may lead to post-COVID condition (post-acute COVID syndrome); however, evidence 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) COVID-19 vaccine for children 6 months to 5 years of age with other vaccines is not routinely recommended at this time.
- Informed consent should include transparency about the known and unknown factors when describing the benefits and risks of the vaccine.

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. 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. This includes review of emerging clinical data on additional COVID-19 vaccine products for this age group including mRNA vaccines (i.e., the 3 mcg Pfizer-BioNTech Comirnaty COVID-19 vaccine currently under clinical evaluation as a 3-dose primary series for children 6 months to 4 years of age).
- NACI recommends vigilant vaccine safety reporting across Canadian jurisdictions for timely assessment of any potentially rare or very rare AEs in children following COVID-19 vaccination. 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
IM	Intramuscular
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
RT-PCR	Reverse Transcription Polymerase Chain Reaction
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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APPENDIX A: FREQUENCY OF SOLICITED ADVERSE EVENTS FOLLOWING IMMUNIZATION WITH MODERNA SPIKEVAX (25 MCG) IN CLINICAL TRIALS

Table 1. Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade – 6 Months to 23 Months of Age for the Moderna Spikevax (25 mcg) COVID-19 vaccine[a,b]

Adverse Reactions	Dose 1		Dose 2	
	Vaccine Group (N = 1746) n (%)	Placebo[a] (N = 582) n (%)	Vaccine Group (N = 1596) n (%)	Placebo[a] (N = 526) n (%)
Pain				
Any	652 (37.4)	175 (30.1)	738 (46.2)	135 (25.7)
Grade 3[b]	0 (0)	0 (0)	0 (0)	0 (0)
Erythema (redness)				
Any	150 (8.6)	24 (4.1)	215 (13.5)	20 (3.8)
Grade 3[c]	5 (0.3)	2 (0.3)	13 (0.8)	0 (0)
Swelling (hardness)				
Any	146 (8.4)	15 (2.6)	243 (15.2)	11 (2.1)
Grade 3[c]	5 (0.3)	0 (0)	14 (0.9)	0 (0)
Axillary (or groin) swelling or tenderness				

Any	102 (5.9)	26 (4.5)	148 (9.3)	28 (5.3)
Grade 3[b]	0 (0)	0 (0)	0 (0)	0 (0)

n= # of participants with specified reaction, percentages are based on n/N.

N= number of exposed subjects who submitted any data for the event.

a Placebo was a saline solution.

b Grade 3 pain and axillary swelling/tenderness: Defined as prevents daily activity.

c Grade 3 swelling and erythema: Defined as >50 mm / >5 cm

The information in this table is up to date as of July 14, 2022. For updated information, please consult the SPIKEVAX product monograph.

Table 2. – Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 2 to < 6 Years of Age

Adverse Reactions	Dose 1		Dose 2	
	Vaccine Group (N = 2957) n (%)	**Placebo[a] (N = 970) n (%)**	**Vaccine Group (N = 2938) n (%)**	**Placebo[a] (N = 959) n (%)**
Pain				
Any	1813 (61.4)	382 (39.4)	2099 (71.4)	395 (41.2)
Grade 3 [b]	4 (0.1)	0 (0)	11 (0.4)	0 (0)
Erythema (redness)				
Any	164 (5.5)	14 (1.4)	259 (8.8)	15 (1.6)
Grade 3[c]	12 (0.4)	3 (0.3)	12 (0.4)	0 (0)
Swelling (hardness)				

Any	134 (4.5)	17 (1.8)	240 (8.2)	11 (1.1)
Grade 3 [c]	10 (0.3)	2 (0.2)	13 (0.4)	0 (0)
Axillary (or groin) swelling or tenderness				
Any	205 (6.9)	56 (5.8)	267 (9.1)	31 (3.2)
Grade 3[b]	0 (0)	0 (0)	1 (< 0.1)	0 (0)
Use of antipyretic or analgesic medications[d]	498 (16.8)	121 (12.5)	800 (27.2)	105 (10.9)

n= # of participants with specified reaction, percentages are based on n/N.

N= number of exposed subjects who submitted any data for the event.

a Placebo was a saline solution.

b Grade 3 pain and axillary swelling/tenderness: Defined as prevents daily activity.

c Grade 3 swelling and erythema: Defined as >100 mm / >10 cm

The information in this table is up to date as of July 14, 2022. For updated information, please consult the SPIKEVAX product monograph.

Table 3. Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 6 Months to 23 Months of Age

	Dose 1		**Dose 2**	
Adverse Reactions	**Vaccine Group (N = 1746) n (%)**	**Placebo[a] (N = 582) n (%)**	**Vaccine Group (N = 1596) n (%)**	**Placebo[a] (N = 526) n (%)**
Fever				
Any	191 (11.0)	49 (8.4)	232 (14.6)	44 (8.4)

Grade 3 (≥39.6°C to ≤40°C)	11 (0.6)	3 (0.5)	7 (0.4)	6 (1.1)
Grade 4 (>40.0°C)	1 (<0.1)	1 (0.2)	3 (0.2)	0 (0)
Use of antipyretic or analgesic medications[c]	482 (27.6)	141 (24.2)	543 (34.0)	111 (21.1)
Irritability/crying				
Any	1175 (67.6)	361 (62.1)	1021 (64.3)	307 (58.5)
Grade 3[b]	24 (1.4)	6 (1.0)	25 (1.6)	5 (1.0)
Sleepiness				
Any	645 (37.1)	217 (37.3)	558 (35.1)	175 (33.3)
Grade 3[b]	4 (0.2)	1 (0.2)	1 (< 0.1)	1 (0.2)
Loss of appetite				
Any	524 (30.2)	152 (26.2)	510 (32.1)	132 (25.1)
Grade 3[b]	10 (0.6)	1 (0.2)	16 (1.0)	2 (0.4)

n= # of participants with specified reaction, percentages are based on n/N.

N= number of exposed subjects who submitted any data for the event.

a Placebo was a saline solution.

b Grade 3 irritability/crying, sleepiness and loss of appetite: Defined as prevents daily activity

The information in this table is up to date as of July 14, 2022. For updated information, please consult the SPIKEVAX product monograph.

Table 4. – Solicited systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 24 Months to ≤ 36 Months of Age

Adverse Reactions	Dose 1		Dose 2	
	Vaccine Group (N = 944) n (%)	Placebo[a] (N = 320) n (%)	Vaccine Group (N = 963) n (%)	Placebo[a] (N = 330) n (%)
Fever				
Any	106 (11.3)	25 (7.8)	182 (18.9)	35 (10.6)
Grade 3 (≥39.6°C to ≤40°C)	3 (0.3)	3 (0.3)	12 (1.2)	0 (0)
Grade 4 (>40.0°C)	3 (0.3)	1 (0.3)	3 (0.3)	0 (0)
Irritability/crying				
Any	513 (54.5)	163 (51.1)	523 (54.3)	148 (44.8)
Grade 3[b]	12 (1.3)	6 (1.9)	10 (1.0)	2 (0.6)
Sleepiness				
Any	285 (30.3)	92 (28.8)	347 (36.0)	89 (27.0)
Grade 3[b]	2 (0.2)	0 (0)	1 (0.1)	0 (0)
Loss of appetite				
Any	225 (23.9)	71 (22.3)	294 (30.5)	69 (20.9)
Grade 3[b]	7 (0.7)	1 (0.3)	8 (0.8)	0 (0)

n= # of participants with specified reaction, percentages are based on n/N.
N= number of exposed subjects who submitted any data for the event.
a Placebo was a saline solution.
b Grade 3 irritability/crying, sleepiness and loss of appetite: Defined as prevents daily activity.
The information in this table is up to date as of July 14, 2022. For updated information, please consult the SPIKEVAX product monograph.

Table 5. – Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 37 Months to < 6 Years of Age

Adverse Reactions	Dose 1		Dose 2	
	mRNA-1273 (N = 2013) n (%)	Placebo[a] (N = 650) n (%)	mRNA-1273 (N = 1975) n (%)	Placebo[a] (N = 629) n (%)
Fever				
Any	155 (7.7)	33 (5.1)	316 (16.0)	28 (4.5)
Grade 3 (≥39°C to ≤40°C)	23 (1.1)	4 (0.6)	58 (2.9)	2 (0.3)
Grade 4 (>40.0°C)	1 (<0.1)	1 (0.2)	4 (0.2)	0 (0)
Headache				
Any	232 (11.5)	78 (12.0)	310 (15.7)	51 (8.1)
Grade 3[b]	5 (0.2)	2 (0.3)	8 (0.4)	1 (0.2)
Fatigue				
Any	807 (40.1)	236 (36.3)	956 (48.4)	185 (29.4)
Grade 3[b]	21 (1.0)	11 (1.7)	45 (2.3)	8 (1.3)

Myalgia				
Any	200 (9.9)	60 (9.2)	310 (15.7)	47 (7.5)
Grade 3[b]	5 (0.2)	2 (0.3)	9 (0.5)	3 (0.5)
Arthralgia				
Any	124 (6.2)	32 (4.9)	168 (8.5)	28 (4.5)
Grade 3[b]	2 (< 0.1)	1 (0.2)	3 (0.2)	0 (0)
Nausea/vomiting				
Any	137 (6.8)	50 (7.7)	194 (9.8)	30 (4.8)
Grade 3[b]	7 (0.3)	2 (0.3)	6 (0.3)	0 (0)
Chills				
Any	129 (6.4)	40 (6.2)	245 (12.4)	31 (4.9)
Grade 3[b]	1 (< 0.1)	0 (0)	10 (1.0)	2 (0.6)

n= # of participants with specified reaction, percentages are based on n/N.
N= number of exposed subjects who submitted any data for the event.
a Placebo was a saline solution.
b Grade 3 headache, fatigue, myalgia, arthralgia, nausea/vomiting and chills: Defined as prevents daily activity
The information in this table is up to date as of July 14, 2022. For updated information, please consult the SPIKEVAX product monograph.

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