Recommendation on the use of mRNA COVID-19 vaccines in adolescents 12 to 17 years of age

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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 Pfizer-BioNTech and Moderna COVID-19 vaccines are mRNA vaccines that were initially authorized by Health Canada for use in individuals 16 and 18 years of age and older, respectively, in December 2020. On May 5, 2021, Health Canada expanded the Interim Order authorization for the Pfizer-BioNTech COVID-19 vaccine to also include adolescents 12 to 15 years of age based on clinical trial results in this age group. On August 27, 2021, Health Canada expanded the Interim Order authorization for the Moderna COVID-19 vaccine to also include adolescents 12 to 17 years of age.

As per the Health Canada-approved product monograph, the Pfizer-BioNTech COVID-19 vaccine is to be administered via intramuscular (IM) injection, 2 doses, 30mcg mRNA per dose, 3 weeks apart, and the Moderna COVID-19 vaccine is to be administered via IM injection, 2 doses, 100mcg mRNA per dose, 4 weeks apart. Additional information on mRNA COVID-19 vaccines can be found here: Health Canada's Drug Product Database. The COVID-19 vaccine dosing intervals recommended by NACI for adults in Canada also apply to adolescents.

On May 18, 2021, following Health Canada authorization of the Pfizer-BioNTech COVID-19 vaccine for 12 to 15 years of age, NACI recommended the use of the vaccine in adolescents (Strong NACI Recommendation) based on a review of available evidence including additional clinical trial results in the adolescent population. Since then, NACI has reassessed its recommendations on the use of mRNA COVID-19 vaccines in adolescents, considering additional evidence including clinical data on the efficacy, safety, and immunogenicity of the Moderna COVID-19 vaccine in adolescents as well as post-market safety and effectiveness reports on both mRNA COVID-19 vaccines.

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

Methods

On May 9, 2021, NACI reviewed the available evidence on the use of the Pfizer-BioNTech COVID-19 vaccine in adolescents 12 to 15 years of age (manufacturer's clinical data in the regulatory submission to Health Canada). On June 15, 2021, NACI reviewed the available evidence on the use of Moderna COVID-19 vaccine in adolescents 12 to 17 years of age (manufacturer's clinical data in the regulatory submission to Health Canada). Additionally, NACI reviewed evidence of post-market safety and effectiveness of mRNA vaccines on January 19 and 28; April 1; June 2, 9, 15, 21, and 24; July 8 and 27; and August 3, 2021. Ethical considerations related to COVID-19 vaccination in adolescents were discussed with the Public Health Ethics Consultative Group (PHECG) on May 3 and July 6, 2021. The Canadian Immunization Committee (CIC) as well as Provincial and Territorial Chief Medical Officers of Health provided feedback on key policy questions to ensure alignment with program needs on May 6, 2021 and June 11, 2021, respectively. NACI approved the updated recommendation on the use of mRNA COVID-19 vaccines in adolescents on August 9, 2021.

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

Summary of evidence

COVID-19 burden of disease in adolescents

Since the beginning of the COVID-19 pandemic, the rate of COVID-19 in Canadian adolescents has been similar to that observed in young adults. Adolescents generally present with mild illness and report few severe outcomes of COVID-19 (i.e., COVID-19 associated hospitalizations, ICU admission, and deaths) compared to older age groups. Adolescents 12 to 17 years of age account for approximately 8% of the population [3], and this age group constitutes approximately 7% of COVID-19 cases reported nationally [4]. In contrast, adolescents 12 to 17 years of age account for approximately 0.6% of COVID-19 cases resulting in hospitalization, approximately 0.4% of COVID-19 cases admitted to ICU, and approximately 0.01% of cases resulting in death (January 1, 2020 to August 13, 2021) [4]. Since May 2021 (coinciding with both the increasing prominence of the B.1.617.2 Delta variant and decreasing number of adult hospitalization events), the relative burden of disease for adolescents 12 to 17 years of age shifted upwards to approximately 8% of COVID-19 cases, 1.2% of COVID-19 cases resulting in hospitalization, 0.8% of COVID-19 cases admitted to ICU and 0.08% of cases resulting in death [4]. These estimates are limited to the case reports provided by the provinces and territories and therefore do not account for all cases that have occurred in Canada [5]. As of August 13, 2021, over 70% of adolescents 12 to 17 years of age had received at least one dose of an mRNA COVID-19 vaccine [at the time when only the Pfizer-BioNTech vaccine was authorized] and more than 50% had received both doses [6].

Adolescents are at risk of multisystem inflammatory syndrome in children (MIS-C) following infection with SARS-CoV-2. This is a serious, though uncommon, condition associated with COVID-19 in children and adolescents [7]. The mechanisms of MIS-C are not well understood but include a dysregulated immune response to SARS-CoV-2 infection [8]. A 2020 study from the United States (US) found that MIS-C incidence was highest in children 5 years of age or less and between 6 to 10 years of age, with adjusted incidence estimated at 4.9 (95% CI: 3.7 to 6.6) and 6.3 (95% CI: 4.8 to 8.3) per 1,000,000 person-months, respectively. Incidence was lower for older children and adolescents aged 11 to 15 and 16 to 20 years old, with estimated adjusted incidence of 3.8 (95% CI: 2.8 to 5.3) and 2.4 (95% CI: 1.6 to 3.5) per 1,000,000 person-months respectively [9]. As of August 12, 2021, 135 laboratory-confirmed and/or epidemiologically linked cases of MIS-C were reported in Canada, with a median age of six years [4]. However, this count is likely an underestimate; 250 cases were reported that fulfilled WHO criteria for MIS-C but did not meet the criteria for laboratory-confirmed or probable SARS-CoV-2 infection. Of the 135 lab-confirmed cases, 27 cases occurred in adolescents 12 to 18 years old [4]. Emerging evidence available in preprint suggests approximately 1 out of 3 cases of MIS-C reported in Canada were admitted to ICU for treatment [10].

Adolescents are also at risk of indirect consequences of the COVID-19 pandemic. For example, national survey data [11] and cross-sectional studies [12] [13] suggest that children and adolescents in Canada have experienced deteriorations in mental health during the pandemic. Similar trends have been identified in other countries, with studies on mental health impacts reporting higher rates in adolescents of depression, anxiety, and stress, compared to before the pandemic [14] [15]. Significant increases in adolescent inpatient admissions for eating disorders have also been observed in Canada [16] and internationally [17]. School closures and social isolation from other public health measures have had disproportionate impacts on marginalized youth, such as racialized and Indigenous groups, persons with disabilities, refugees and other newcomers to Canada, persons living in low-income settings, and persons of diverse sexual orientations and gender identities [15] [18] [20].

The studies referenced above were identified by a non-systematic search of evidence, and therefore caution should be taken in the interpretation of the findings.

Risk factors most frequently associated with severe disease in adolescents

There is emerging evidence on risk factors for severe COVID-19 disease in adolescents and children. An updated rapid review of risk factors for severe COVID-19 conducted by the Alberta Research Centre for Health Evidence (ARCHE) was completed in May 2021 [21]. The review found a moderate certainty of evidence of ≥2-fold increase in COVID-19 associated hospitalizations in individuals 21 years of age and younger with 2 or more chronic conditions (versus no chronic conditions).

Several North American studies have highlighted the proportion of hospitalized pediatric/adolescent COVID-19 cases with underlying conditions and commonly reported underlying conditions. In a national prospective study led by the Canadian Paediatric Surveillance Program, a total of 264 children hospitalized with documented SARS-CoV-2 infection were reported between April 8 and December 31, 2020, through weekly surveys to a network of over 2,800 paediatricians [22]. At least one underlying comorbidity was reported in 39.3% of children admitted because of COVID-19, with the most common comorbidities reported as obesity, asthma, epilepsy, chronic encephalopathy with severe neurodisability, chronic lung disease, and neurodevelopmental disorders. In unadjusted analyses, hospitalized children with obesity, chronic neurological conditions, or non-asthma chronic lung diseases were associated with greater diseases severity [22]. A US cross-sectional study of 43,465 patients with COVID-19 aged 18 years and younger reported over 25% had one or more underlying condition, with the most common conditions reported including asthma, obesity, neurodevelopmental disorders, and certain mental health conditions [23]. Another US-based report based on surveillance data of 204 adolescents aged 12 to 17 years who were hospitalized for probable/confirmed COVID-19 from January 1 to March 31, 2021 found that approximately 70% had one or more underlying medical conditions, where the most common conditions reported were obesity, chronic lung disease (including asthma), and neurologic disorders [24].

Evolving evidence of indirect protection from COVID-19 vaccines in non-vaccinated populations

There has been increasing evidence of significant indirect protection of unimmunized individuals living in households (25-29) and communities [30] in which the majority of the population has been vaccinated with either one or two doses of an mRNA COVID-19 vaccine. The likelihood of household transmission among unvaccinated residents of households in which at least one member of the household was vaccinated has been reported to be reduced by up to 90% [28]. However, despite increasing vaccine coverage in adults, outbreaks in adolescents and children are occurring, including with the more transmissible Delta variant (31-33).

Direct protection of mRNA vaccines against SARS-CoV-2 Delta variant

Throughout June, the Delta variant was responsible for an increased proportion of confirmed COVID-19 cases and has now surpassed the Alpha variant as the most prevalent variant of concern (VOC) in circulation in Canada and internationally [34]. Emerging evidence suggests that while the Delta variant is more transmissible than previous VOCs [35], a complete 2-dose vaccination series with an mRNA COVID-19 vaccine remains effective against symptomatic infection as well as COVID-19 associated hospitalization, ICU admission, and death [36] [37]. However, breakthrough infections with the Delta variant are being reported at higher frequency than with the Alpha variant [36] [37].

Emerging real-world evidence reported in preprints noted somewhat higher effectiveness data against the Delta variant for one dose of the Moderna COVID-19 vaccine compared to one dose of the Pfizer-BioNTech COVID-19 vaccine [38] [39], which is consistent with reports of higher immunogenicity for Moderna compared to Pfizer-BioNTech [40].

Clinical trial data on mRNA COVID-19 vaccines in adolescent populations

The Pfizer-BioNTech COVID-19 vaccine was evaluated in 2,260 adolescent participants 12 to 15 years of age as an amendment to study C4591001, an ongoing randomized, observer-blind, placebo-controlled Phase 3 trial [41]. Participants were randomized to receive either two doses of the vaccine (30mcg mRNA each dose) (n=1,131) or

placebo (n=1,129), 21 days apart. All adolescent study participants were recruited from the United States between October 15, 2020 and January 21, 2021. Almost half (49.0%) of adolescent participants were female and the median age of adolescent participants at vaccination was 14.0 years (range: 12 to 15 years). After the second dose, 98.3% of all adolescent participants had ≥ 1 month of follow-up while 57.9% had ≥ 2 months of follow-up at time of reporting. Follow up will continue in trial participants for at least 2 years following the second dose for ongoing safety reporting to Health Canada.

The Moderna COVID-19 vaccine was evaluated in 3,732 adolescent participants aged 12 to 17 years as part of an ongoing, Phase 2/3, randomized, observer-blind, placebo-controlled study [42]. Participants were recruited between December 9, 2020 and February 28, 2021, and were randomized 2:1 to receive either two doses of the vaccine (100mcg mRNA each dose) (n=2,489) or a placebo (n=1,243), 28 days apart. All adolescent study participants were recruited from the US. Almost half (48.6%) of adolescent participants were female, 2,767 (74.3%) were aged 12 to 15 years, and 959 (25.7%) were aged 16 to 17 years. After the second dose, 97.3% of all participants had ≥ 1 month of follow-up while 41.9% had ≥ 2 months of follow-up.

Efficacy

In adolescent study participants 12 to 15 years of age without prior evidence of SARS-CoV-2 infection, the estimate of vaccine efficacy of the Pfizer-BioNTech COVID-19 vaccine against the first occurrence of confirmed symptomatic COVID-19 disease from 7 days after dose 2 was 100% (95% CI: 75.3 to 100.0%; 16 cases in the placebo group, 0 cases in the vaccine group). The estimate of vaccine efficacy in all participants 12 to 15 years of age (including those with prior evidence of SARS-CoV-2 infection) was also 100% (95% CI: 78.1 to 100.0%; 18 cases in the placebo group, and 0 cases in the vaccine group).

After dose one, there were 3 cases of confirmed COVID-19 identified in the Pfizer-BioNTech vaccine group and 35 cases identified in the placebo. All cases in the vaccine group occurred less than 11 days after dose 1, before a response to the vaccine would be expected (no cases were observed between 14 days after dose 1 and the time that dose 2 was administered).

For the Moderna COVID-19 vaccine (where the clinical trial had twice as many participants in the vaccine group than the placebo group), the estimate of efficacy against confirmed symptomatic COVID-19 disease starting 14 days after dose 2 in study participants 12 to 17 years of age without prior evidence of SARS-CoV-2 infection was 100% (95% CI: 29.0% to not evaluable; 4 cases in the placebo group, 0 cases in the vaccine group). The point estimate of efficacy against asymptomatic infection only (SARS-CoV-2 infection confirmed by either RT-PCR or serology) was 39.2%, starting 14 days after two doses of the vaccine, but the confidence interval around the point estimate was wide and included zero (95% CI: -24.7 to 69.7%; 16 cases out of 1,243 participants in the placebo group, 21 cases out of 2,489 participants in the vaccine group). The estimate of vaccine efficacy against asymptomatic infection should be interpreted with caution as cases identified due to a positive serology result are based on samples collected on Day 57 (i.e., 28 days after dose 2); therefore, this finding could reflect infection acquired at any time after dose 1 prior to the time of sample collection.

No estimate is available for the Moderna COVID-19 vaccine efficacy from 14 days after dose 1 until dose 2 was administered.

There were no cases of severe COVID-19, including deaths, reported in any of the adolescent study participants who received an mRNA vaccine (Pfizer-BioNTech or Moderna) or a placebo.

Immunogenicity

The humoral immune response following the second dose of a complete two-dose vaccination schedule with mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) was non-inferior in adolescents compared to young adults, exceeding the 1.5-fold pre-established non-inferiority criterion for both studies (lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67). For Pfizer-BioNTech, SARS-CoV-2 50% neutralizing

titers (NT-50) were assayed one month following dose 2, and the estimated ratio of antibody levels in adolescents (12 to 15 years of age; n=209) relative to young adults (16 to 25 years of age; n=186) was 1.76 (95% CI: 1.47 to 2.10). For Moderna, SARS-CoV-2 neutralizing titers (ID50) were assayed 28 days following dose 2, and the estimated ratio of antibody levels in adolescents (12 to 17 years of age; n=340) relative to young adults (18 to 25 years of age; n=305) was 1.077 (95% CI: 0.94 to 1.24). However, since no correlate of protection has 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 prevention of SARS-CoV-2 infection or disease or the ability to transmit to others. Immunogenicity in adolescents following dose 1 was not reported in clinical trials for either Pfizer-BioNTech or Moderna COVID-19 vaccines

Safety

Consistent with clinical trial findings in individuals 16 to 25 years of age [43], the Pfizer-BioNTech COVID-19 vaccine was well tolerated in adolescents 12 to 15 years of age. Local reactions were mostly mild to moderate in severity and occurred more frequently following the first dose. The median onset of solicited local reactions was within the first 2 days after any dose and reactions persisted for a median of 1-3 days. Systemic events were predominantly fatigue, headaches, chills, muscle pain, fever, and joint pain (in order of descending frequency) and occurred more frequently after the second dose. The median onset day for most solicited systemic events after either dose of vaccine was 1 to 3 days post-vaccination, with a median duration of 1 day, except for fatigue and chills, which had median durations of 1 to 2 days. Compared to individuals 18 to 55 years of age, adolescents 12 to 15 years of age demonstrated increased frequency of headache, chills, and fever. Following the second dose, up to 64.5% of adolescent participants had headaches, up to 41.5% had chills, and up to 19.6% had fever [44]. Vaccination-related lymphadenopathy in adolescents occurred in 0.6% of vaccine recipients (non-solicited adverse event), and no serious adverse events related to the vaccine, no cases of MIS-C, and no deaths were reported adolescents in the trial.

The Moderna COVID-19 vaccine was well tolerated in adolescents 12 to 17 years of age. Local reactions were mostly mild to moderate in severity and occurred similarly following the first and second doses. The majority of solicited local adverse reactions occurred within the first 1-2 days after each dose and persisted for a median of 3 days. In the vaccine group, axillary swelling or tenderness (a solicited adverse event) occurred in 23.3% of adolescents after dose 1 and 21.0% after dose 2. Systemic events were predominantly fatigue, headaches, muscle pain, chills, joint pain, nausea/vomiting, and fever (in order of descending frequency), and occurred more frequently after the second dose. The majority of solicited systemic adverse reactions occurred within the first 1-2 days after each dose and persisted for a median of 2 days. Solicited adverse reactions were generally similar between participants aged 12 to 15 years and participants aged 16 to 17 years and there were also no notable differences in the rates of reported unsolicited events between these age groups. Overall, in the vaccine groups, local reactogenicity was higher in adolescents compared with that observed in the adult Phase 3 study. In adolescents, there were no serious adverse events related to the vaccine, no cases of MIS-C, and no deaths reported in the trial.

Post-market safety data on myocarditis and pericarditis following vaccination with mRNA COVID-19 vaccines

Rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following vaccination with COVID-19 mRNA vaccines have been reported in Canada and internationally, including from Israel [33], the United States [45], Australia [46] and Europe [47]. Symptoms of myocarditis/pericarditis can include shortness of breath, chest pain, or the feeling of a rapid or abnormal heart rhythm. Symptoms can be accompanied by abnormal test results (e.g., electrocardiogram, serum troponins, echocardiogram).

International cases are consistently reported to have occurred:

- More often after the second dose
- Usually within a week after vaccination
- More often in adolescents and young adults (12 to 30 years of age)
- More often in males than females.

While follow-up is ongoing, available data indicate that the majority of individuals affected have responded well to conservative therapy, and tend to recover quickly.

As of August 6, 2021, active and passive surveillance data from Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) in combination with Canada Vigilance Database (CVD) indicates a higher number of myocarditis and/or pericarditis cases in younger age groups than would normally be expected [48]. Preliminary analyses suggest a higher unadjusted rate of myocarditis/pericarditis cases reported after vaccination with Moderna compared to Pfizer-BioNTech, however the analysis is ongoing.

Passive vaccine safety surveillance data alone from Ontario suggests a product-specific difference in the risk of myocarditis/pericarditis following mRNA vaccines, in particular following the second dose [49]. NACI reviewed an analysis restricted to medically reviewed AEFIs meeting levels 1-3 of the Brighton Collaboration case definitions [50] for myocarditis and pericarditis with data as of July 26, 2021, and the data were subsequently updated through to August 7th, 2021 (n=204, data as of August 7, 2021) and published [49]. The dose 2 reporting rates for all ages/genders combined were 28.2 and 8.7 per million doses administered for the Moderna vaccine and the Pfizer-BioNTech vaccine, respectively. Product-specific trends continued to be observed when the analysis was restricted only to those events where the vaccine series was initiated on or after June 1, 2021 (n=54) to account for the enhanced surveillance of myocarditis/pericarditis cases and the expanded Moderna vaccine supply that began in June. In this restricted analysis from June 1, 2021, the product-specific rate of myocarditis/pericarditis following the second dose was higher for Moderna than Pfizer-BioNTech among 18-24 year old males (198.6 per million doses of the Moderna vaccine compared to 35.5 per million doses of the Pfizer-BioNTech vaccine). Additional analyses are ongoing. Please see Public Health Ontario Enhanced Epidemiological Summary on Myocarditis and Pericarditis Following Vaccination with COVID-19 mRNA Vaccines in Ontario: December 13, 2020 to August 7, 2021, for detailed analysis.

Similarly, higher rates of cases of myocarditis and/or pericarditis have been reported after the Moderna vaccine compared to Pfizer-BioNTech in the US, although verification of this potential difference is ongoing [45]. An analysis of the US Vaccine Safety Datalink (VSD) data among individuals aged 12-39 years showed relatively higher frequencies observed after receipt of Moderna compared to Pfizer-BioNTech, however the reported rates were not statistically significantly different. Among individuals aged 12 to 39, VSD data showed more than double the rate of chart confirmed myocarditis and/or pericarditis following the second dose of the Moderna vaccine compared to the Pfizer-BioNTech vaccine (8 per 1,000,000 doses [95% CI: 3.2 to 16.5] vs. 19.8 per 1,000,000 doses [95% CI: 9.9 to 35.5]) [45].

Investigations into possible mechanisms of action that could explain the association between myocarditis and/or pericarditis and mRNA vaccines, identification of risk factors, including past history of myocarditis, and the potential impact of the interval between vaccine doses all continue in Canada and abroad [45] [47] [51] [52].

There are many potential causes for myocarditis and pericarditis, including both infectious and non-infectious causes, and disease severity can be variable. Myocarditis can also occur as a complication in people who are infected with SARS-CoV-2. A recent retrospective study from the US found myocarditis rates after confirmed COVID-19 infection to be as high as 450 cases per million infections in young males, aged 12-17 [53].

As part of ongoing COVID-19 vaccine safety efforts, the Public Health Agency of Canada (PHAC) and Health Canada are closely monitoring myocarditis and pericarditis through passive and active Canadian safety surveillance systems and collaboration with Canadian provincial and territorial health authorities, manufacturers and international regulators. Refer to the PHAC weekly AEFI report [48] for information on

numbers of cases reported in Canada. Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada [54] and to the recently developed Brighton Collaboration case definition of myocarditis/pericarditis [50] for additional information on the completion and submission of AEFI reports.

For further information, please refer to NACI's Recommendations on the use of COVID-19 vaccines; Vaccine safety and adverse events following immunization (AEFI).

Dose and route of administration

The dose and route of administration of the Pfizer-BioNTech and Moderna COVID-19 vaccines for adolescents (12 years of age and older) are identical to the respective dose and route in adults. For further information, please refer to NACI's Recommendations on the use of COVID-19 vaccines; Vaccine administration.

Recommendations

NACI recommends that a complete series with an mRNA COVID-19 vaccine should be offered to adolescents 12 to 17 years of age who do not have contraindications to the vaccine. (Strong NACI Recommendation)

Informed consent for all mRNA COVID-19 vaccines should include the following information:

- **Rare cases of myocarditis and/or pericarditis have been reported following administration of mRNA vaccines. Please see the section: Post-market safety data on myocarditis and pericarditis following vaccination with mRNA COVID-19 vaccines.**
- The benefits of immunization with an mRNA vaccine for protection against COVID-19 infection and its potential complications outweigh any potential risks, but as a precaution, all recipients are advised to seek medical attention if an individual develops symptoms including chest pain, shortness of breath, or palpitations following receipt of an mRNA vaccine, in light of the post-market safety surveillance reports of myocarditis and/or pericarditis in the days following immunization.
- Additionally, as a precautionary measure, NACI is advising that the second dose in the mRNA COVID-19 vaccination series should be deferred in individuals who experience myocarditis or pericarditis following the first dose of an mRNA COVID-19 vaccine until more information is available. Individuals who have a history of myocarditis unrelated to mRNA COVID-19 vaccination should consult their clinical team for individual considerations and recommendations. If the diagnosis is remote and they are no longer followed clinically for cardiac issues, they should receive the vaccine. NACI will continue to monitor the evidence and update recommendations as needed.

Additional considerations, summary of evidence, and rationale

- Some provinces/territories may decide to continue using only the Pfizer-BioNTech COVID-19 vaccine for adolescents 12 to 17 years of age, because there is more experience to date with Pfizer-BioNTech vaccine in this age group, and there is the possibility of a lower rate of myocarditis and/or pericarditis with this vaccine.
- Considering the ongoing risks of the COVID-19 pandemic, including increased risk of hospitalization and mortality from COVID-19, as well as emerging evidence on immune responses and effectiveness following the administration of the Pfizer-BioNTech and Moderna COVID-19 vaccines (including protection against VOCs), all authorized mRNA vaccines continue to be recommended for use in authorized age groups.
- Over 70% of Canadian adolescents aged 12 to 17 have already received one dose of an mRNA COVID-19 vaccine as part of the adolescent COVID-19 program, which began in May 2021 after Pfizer-BioNTech was authorized in this age group and over 50% have also received a full series [6].

- Adolescents 12 to 17 years of age represent approximately 8% of the Canadian population and constitute approximately 8% of COVID-19 cases reported in Canada since May 2021. COVID-19 disease severity in adolescents is generally mild, with infrequent incidence of severe outcomes including hospitalization, admittance to ICU, and death. There is limited evidence on risk factors for severe COVID-19 disease in adolescents, though having more than one underlying medical conditions is a risk factor.
- Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious complication of infection with SARS-CoV-2 in children and adolescents.
- While the adolescent trial sizes were small, both the Pfizer-BioNTech and Moderna COVID-19 vaccines met non-inferiority criteria for generating a humoral immune response to the vaccine in adolescents compared to young adults. Clinical findings in adolescents 12 years of age and older suggest that both authorized mRNA vaccines are efficacious at preventing symptomatic COVID-19, with a similar estimate of vaccine efficacy against symptomatic COVID-19 and with similar safety profiles as compared to that observed in clinical trials in adult populations.
- An increased frequency of myocarditis/pericarditis in adolescents and young adults in the days after mRNA COVID-19 immunization has been reported both in Canada and internationally. Cases frequently require hospitalization but are relatively mild in severity and individuals tend to recover quickly. Long-term follow-up is ongoing. Evidence to date suggests cases occur more often in those younger than 30 years of age, following a second dose of a COVID-19 mRNA vaccine, and more often in males as compared with females. Additional information can be found here.
- Post-market preliminary safety data reported by the US VSD as well as Canadian post-market passive and active surveillance data suggest relatively higher rates of myocarditis/ pericarditis reported after Moderna vaccination compared to Pfizer-BioNTech, although verification of this potential difference is ongoing.
- Evidence into the association between myocarditis/pericarditis and mRNA vaccines is evolving. Investigations into the mechanism of action and potential risk factors, including the impact of the interval between doses, are ongoing in Canada.
- Pfizer-BioNTech and Moderna vaccines are not authorized for use in children under 12 years of age at this time.

Research priorities

- NACI recommends continuous monitoring of data on the safety, efficacy and effectiveness of the Pfizer-BioNTech and Moderna COVID-19 vaccines in adolescents through clinical trials and studies in real-world settings, including clinical implications of previous SARS-CoV-2 infection, MIS-C, or myocarditis on the safety, efficacy, and effectiveness of COVID-19 vaccines in adolescent and pediatric populations.
- NACI recommends vigilant reporting across Canadian jurisdictions for timely assessment of myocarditis and pericarditis cases as well as other potential rare or very rare adverse events in adolescents 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 adolescent populations.
- NACI recommends further research on the use of mRNA vaccines with lower antigenic content and different schedules in children and adolescents.
- Additional research priorities are listed in NACI's statement on Recommendations for the use of COVID-19 vaccines.

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Abbreviations

Abbreviation Term

AEFI
Adverse event following immunization

ARCHE
Alberta Research Center for Health Evidence

CI
Confidence Interval

CIC
Canadian Immunization Committee

COVID-19
Coronavirus disease 2019

EMA
European Medicines Agency

GMR
Geometric mean ratio

ICU
Intensive Care Unit

IM
Intramuscular

MCG
microgram

MIS-C
Multisystem Inflammatory Syndrome in Children

mRNA
Messenger Ribonucleic Acid

NACI
National Advisory Committee on Immunization

PHAC
Public Health Agency of Canada

PHECG
Public Health Ethics Consultative Group

RT-PCR
Reverse Transcription Polymerase Chain Reaction

SARS-CoV-2
Severe Acute Respiratory Syndrome Coronavirus 2

US
United States

VOC
Variant of Concern

VSD
Vaccine Safety Datalink (United States)

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