FOCUS ON
Myocarditis and Pericarditis after COVID-19 mRNA Vaccines
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Key Messages

- A number of cases of myocarditis/pericarditis following immunization with mRNA COVID-19 vaccines have been reported in Ontario, Canada, and internationally. Reported cases have occurred more frequently in males under the age of 30 years, commonly following their second dose, usually within one week of vaccination, and have been mild with a quick recovery.

- The observed number of cases of myocarditis/pericarditis following administration of a mRNA vaccine is higher than expected in some jurisdictions, including Ontario, Canada, and the United States (US). Preliminary post-marketing safety data reported in Canada and the US suggests higher rates of myocarditis/pericarditis reported after Moderna Spikevax® compared to Pfizer-BioNTech Comirnaty®.

- The National Advisory Committee on Immunization (NACI) recommends that individuals who experienced myocarditis/pericarditis after a first dose of an mRNA COVID-19 vaccine should wait to receive a second dose until more information is available.

- On September 29, 2021, out of an abundance of caution, Ontario issued a preferential recommendation for the use of Pfizer-BioNTech vaccine for individuals 18-24 years of age, and the continued use of Pfizer-BioNTech for individuals 12-17 years of age, based on an analysis of data from Ontario’s vaccine safety surveillance system.

- The benefits of vaccination continue to outweigh the risks of COVID-19 illness and vaccination is highly recommended for all eligible individuals, including youth.

Introduction

This document provides an overview of what is currently known about events of myocarditis and pericarditis following COVID-19 mRNA vaccines. This document will be updated as new information becomes available.

This document was informed by a review of current literature on myocarditis/pericarditis generally and following COVID-19 vaccination. It includes a jurisdictional scan of resources from countries such as the United States, the United Kingdom, and Israel, and organizations such as the Public Health Agency of Canada, the Centers for Disease Control and Prevention, and the World Health Organization; and a synthesis of hand-selected peer-reviewed literature.
Background

In May 2021, international reports of myocarditis/pericarditis following vaccination with COVID-19 mRNA vaccines emerged from the United States\textsuperscript{1,2} and Israel.\textsuperscript{3} Preliminary reports, which have been confirmed with additional investigation (outlined below) indicated that these cases occurred mainly in adolescents and young adults, more often in males than females, more commonly after the second dose, and typically within one week after vaccination.\textsuperscript{1,2,4} Most cases appeared to be mild and responded well to conservative treatment (e.g., non-steroidal anti-inflammatory drugs) and rest. No myocarditis/pericarditis events were initially observed with Pfizer-BioNTech\textsuperscript{5} including among 12 to 15 year old adolescents\textsuperscript{6}, and Moderna\textsuperscript{7} clinical trials. Since these original reports, multiple immunization advisory groups and vaccine regulatory committees have met to discuss this vaccine signal and to provide recommendations. To date, all countries offering COVID-19 vaccination in young adults and adolescents continue to recommend their use.

Overview of Myocarditis and Pericarditis

Myocarditis is inflammation of the heart muscle and pericarditis is inflammation of the lining outside the heart. Symptoms of both can include shortness of breath, chest pain, or the feeling of a rapid or abnormal heart rhythm.\textsuperscript{1,2,4} Other non-cardiac symptoms can include fatigue, gastrointestinal symptoms (nausea, vomiting, abdominal pain), dizziness or syncope, edema (swelling of the lower legs), or cough.\textsuperscript{4}

In Ontario, baseline data for the period of 2015-2020 from the Institute for Clinical Evaluative Sciences (ICES) was available using a broad definition of myocarditis and pericarditis from the 10\textsuperscript{th} revision of the International Classification of Diseases.\textsuperscript{8} The average annual incidence of myocarditis/pericarditis per 100,000 individuals for the following age groups was: 12-19 years (16.0, 95% confidence interval [CI]: 15.1-16.9), 20-29 years (27.3, 95% CI: 26.4-28.2), 30-39 years (27.7, 95% CI: 26.7, 28.7), and 40-49 years (28.6, 95% CI: 27.7-29.7). For Ontarians 80 years of age and older, the average annual incidence of myocarditis/pericarditis (broad definition) was 78.1 per 100,000 individuals (95% CI: 75.3-81.0). Incidence was consistently higher in males than females for each of the above age groups. (Kwong J, ICES, personal communication email, 2021 Aug 5).

The list of possible causes or triggers for myocarditis/pericarditis is broad and includes both infectious (i.e., recent viral, bacterial, fungal, tuberculosis, parasitic infection)\textsuperscript{9}, and non-infectious triggers (i.e., autoimmune, connective tissue disease, metabolic (e.g., renal), malignancy, trauma, toxins, drug-induced)\textsuperscript{4,10}. Smallpox vaccination is the only vaccine that has ever been conclusively linked to myocarditis based on a significantly higher relative risk.\textsuperscript{11}

Myocarditis\textsuperscript{12,13} and pericarditis\textsuperscript{14} have also been associated with recent COVID-19 infection. In two case studies and one cohort study, competitive athletes infected with SARS-CoV-2 had cardiac magnetic resonance (cMR) findings consistent with myocarditis (1.4\%, 2.3\%, 15\%, respectively).\textsuperscript{15-17} A large nationwide Israeli study demonstrated that SARS-CoV-2 infection was associated with a substantially increased risk of myocarditis (risk ratio, 18.28; 95\% CI, 3.95 to 25.12; risk difference, 11.0 events per 100,000 persons; 95\% CI, 5.6 to 15.8) and of additional serious adverse events, including pericarditis.\textsuperscript{18} Subsequent analysis demonstrated that the risk of myocarditis and pericarditis after SARS-CoV-2 infection increased in both males and females under and over the age of 40 years. Specifically, in young male adolescents and adults ages 16-39 years old, there was an excess of 11.54 events of myocarditis per 100,000 persons (95\% CI, 2.48 to 22.55).\textsuperscript{19}
Early Reports of Myocarditis and Pericarditis Following COVID-19 Vaccination

In April 2021, an Israeli news release reported 62 cases of myocarditis out of approximately five million doses of Pfizer-BioNTech vaccine administered. Of these cases, 56 occurred after dose 2, with most occurring in men younger than 30 years of age.

In April 2021, 23 cases of symptomatic acute myocarditis presented within four days following COVID-19 mRNA vaccination (seven with Pfizer-BioNTech, 16 with Moderna) were reported by the US Department of Defence in healthy military members; twenty of which occurred after the second dose.

Clinical Description of Events

Numerous published studies of myocarditis following COVID-19 mRNA vaccinations (Pfizer-BioNTech, Moderna) demonstrated that these events typically present as chest pain in adolescent and young adult males, within two to seven days after their second dose. Cases were typically mild with no reported deaths. However, the majority of hospitalizations had short durations in non-ICU settings. Generally, these individuals recovered quickly with resolution of their symptoms within a couple of weeks of discharge. Troponin levels were elevated with abnormal echocardiogram and/or cMR.

Epidemiology of Myocarditis/Pericarditis after COVID-19 Vaccination

Reporting Rate of Myocarditis/Pericarditis in the United States

- As of June 30, 2021, reporting rate of myocarditis overall among adults was 3.5 cases per million second doses of mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) administered based on data from the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system in the US. In a subgroup analyses by age and sex, the reporting rate was highest among males aged 18–29 years (24.3 cases per million mRNA COVID-19 vaccine second doses administered).

- The Vaccine Safety Datalink (VSD) is an active surveillance system in the US that uses a rapid cycle analysis (RCA), to examine the observed number of adverse events compared with the expected number of events.

  - Klein et al. assessed the safety of the mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) from one to twenty-one days after dose 1 or 2 over a six month period from December 2020 through June 2021. Among individuals aged 12 to 39 years, the incidence of myocarditis/pericarditis per 1,000,000 person-years and adjusted relative risk (aRR) during the risk versus comparison intervals was 321 versus 35 (aRR 9.83; 95%CI, 3.35-35.77) during days 0 to 7 after vaccination after either dose 1 or 2. This corresponded to a statistically additional 6.3 cases per million doses (p < 0.001, 95%CI, 4.9-6.8) after either dose 1 or dose 2. The aRR estimates were higher for both Pfizer-BioNTech and Moderna vaccines with significant clustering within the first five days of mRNA vaccination with the risk being highest after dose two, with an excess of 11.2 (p < 0.001, 95%CI, 8.9 to 12.1) cases per million doses in days 0 through 7 for individuals 12 to 39 years old.
Reporting Rate of Myocarditis/Pericarditis in Israel

- Analysis of observational data of adverse events following mRNA vaccination from the largest health care organization in Israel compared matched individuals forty-two days after being vaccinated with two doses of Pfizer-BioNTech to unvaccinated individuals. Vaccination was most strongly associated with an elevated risk of myocarditis (risk ratio, 3.24; 95% CI, 1.55 to 12.44; risk difference, 2.7 events per 100,000 persons; 95% CI, 1.0 to 4.6).\(^{18}\)

- The risk of myocarditis increased by a factor of three after vaccination, which translated to approximately 3 excess events per 100,000 persons (95% CI, 1 to 5 excess events per 100,000 persons).\(^{18}\) Among the persons with myocarditis in the vaccinated group, the median age was 25 years and 90.9% were male.

- Further analysis of adverse events following mRNA vaccination stratified by age and sex, found that among males between 16 and 39 years old, there was an excess of 8.62 events of myocarditis per 100,000 persons (95% CI, 2.82 to 14.35) with a risk ratio of 4.95 (95% CI, 1.61 to 16.57).\(^{19}\) In comparison, the excess risk for the same group following SARS CoV-2 infection was 11.54 events of myocarditis per 100,000 persons (95% CI, 2.48 to 22.55). Similarly, there was an increased risk of pericarditis following mRNA vaccines in young males aged 16-39 years (risk ratio, 2.67; 95% CI, 1.03 to 9.26; risk difference, 5.28 events per 100,000 persons; 95% CI, 0.17 to 10.33).

Reporting Rate of Myocarditis/Pericarditis in Canada

- Up to and including October 15, 2021, there were 956 reports of myocarditis/pericarditis to the Public Health Agency of Canada and Health Canada.\(^{31}\) Of these reported cases, 573 occurred following a Pfizer-BioNTech vaccine for a reporting rate of 1.44 events per 100,000 administered doses. There were 357 events following Moderna vaccination for a reporting rate of 2.55 per 100,000 administered doses.

- The number of reports of myocarditis/pericarditis following the Pfizer-BioNTech is higher than what would be expected in the general population of males and females less than 30 years old and primarily following the second dose.\(^{31}\)

- The number of reports of myocarditis/pericarditis following the Moderna is higher than what would be expected in the general population, particularly among males and females less than 40 years old and following the second dose.\(^{31}\)

Reporting Rate of Myocarditis/Pericarditis in Ontario

- Passively reported events of myocarditis/pericarditis following COVID-19 vaccine are higher than expected in the general population based on trends in background rates for these types of events.\(^{32}\) Additional information on these events and other COVID-19 AEFI reports can be found in Public Health Ontario’s weekly AEFI summary.

- As of October 10, 2021, there have been 438 reports of myocarditis/pericarditis following receipt of COVID-19 mRNA vaccines in Ontario for an overall crude reporting rate of 20.9 per million doses of mRNA vaccines administered. Of these, 122 (27.9%) were diagnosed with myocarditis and 197 (45.0%) were diagnosed with pericarditis.\(^{32}\)

- Of the 438 reports of myocarditis/pericarditis, 242 required hospitalization (55.3%), for a median length of stay of two days among the 210 reports for which there was an admission and discharge date.\(^{32}\)
The highest reporting rates were observed in younger age groups (12-17 and 18-24 years) and among males, particularly after dose 2. The highest reporting rate was observed for males aged 18-24 years of age following dose 2, at 173.3 events per million doses administered. 

Public Health Ontario’s Enhanced epidemiological summary of myocarditis/pericarditis following vaccination with COVID-19 mRNA vaccines in Ontario from December 13, 2020 to September 4, 2021 found that the highest reporting rate of myocarditis/pericarditis was observed in males aged 18-24 years following a second dose. For this age group, the reporting rate following Pfizer-BioNTech vaccine and Moderna as second dose was 43.4 per million doses and 283.4 per million respectively. The reporting rate of myocarditis/pericarditis was higher following the second dose of an mRNA vaccine than after the first dose, particularly for those receiving the Moderna vaccine as the second dose of the series, regardless of the product received for the first dose.

Summary of Immunization Advisory Group Recommendations on COVID-19 Vaccine Use

WHO Global Advisory Committee on Vaccine Safety (GACVS)

As of July 9, 2021, after reviewing published guidance from countries including the US (VAERS), GACVS concluded that current evidence suggests a likely causal association between myocarditis and the mRNA vaccines. However, GACVS deemed that the benefits of mRNA COVID-19 vaccines outweigh the risks in reducing hospitalizations and deaths due to COVID-19 infections.

An unpublished Nordic study found men under the age of 30 in Finland, Sweden, Norway and Denmark, who had received Moderna Spikevax©, had a slightly higher risk than others of developing myocarditis. Based on this data, as of October 7, 2021, Finland, Sweden and Denmark have paused the use of Moderna COVID-19 vaccine for younger males.

Centers for Disease Control and Prevention (CDC)

Following a benefit-risk assessment for myocarditis/pericarditis after vaccination with mRNA COVID-19 vaccines, the Advisory Committee on Immunization Practices (ACIP) determined that the benefits of using mRNA COVID-19 vaccines clearly outweigh the risks of myocarditis/pericarditis. For this reason, the CDC continues to recommend COVID-19 vaccination for everyone 12 years of age and older given the greater risk of other serious complications related to COVID-19, such as hospitalization, multisystem inflammatory syndrome in children (MIS-C), or death.

It is recommended that any individuals who develop myocarditis/pericarditis after a dose of an mRNA COVID-19 vaccine should defer receiving a subsequent dose until additional safety data are available.

The National Advisory Committee on Immunization (NACI)

Based on a review of the literature, NACI assessed that the benefits of immunization with an mRNA vaccine for protection against COVID-19 infection and its potential complications outweigh any potential risks. NACI strongly 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 with informed consent, including information about very rare reports of myocarditis/pericarditis that have been reported following administration of mRNA vaccines (Pfizer-BioNTech, Moderna).37,38

- NACI recommends that “As a precautionary measure, 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.”37,38 A referral to an infectious diseases specialist or through the Special Immunization Clinic (SIC) Network (where available) may be considered to inform the decision regarding a second dose of the vaccine.

- **Ontario Ministry of Health (MOH)**
  - As of September 29, 2021, out of an abundance of caution, based on the current available analysis from Ontario’s adverse events following immunization (AEFI) surveillance system, Ontario issued a preferential recommendation for the use of Pfizer-BioNTech vaccine for individuals aged 18-24 years old, with continued use of Pfizer-BioNTech vaccine for youth ages 12-17.39
  - The Ontario MOH’s preferential recommendation for the use of Pfizer-BioNTech COVID-19 vaccine for individuals aged 12-2440 stemmed from an observed increase in the number of reports in Ontario of pericarditis/myocarditis following vaccination with Moderna relative to Pfizer-BioNTech in the 18-24 year old age group, particularly among males.32,33

**Clinical Practice Guidance Recommendations**

- 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/pericarditis in the days following immunization, they are advised to seek medical attention.1,2,37

- All suspected cases of post-vaccine myocarditis/pericarditis should be evaluated by a physician including consultation with a cardiologist as indicated, who may consider doing an electrocardiogram (ECG), troponins, or an echocardiogram.1,4

- It is important to evaluate for other potential causes of myocarditis/pericarditis in consultation with speciality services (e.g., infectious disease, rheumatology, cardiology), to assist in this evaluation, particularly for acute COVID-19 infection (e.g., PCR testing), prior SARS-CoV-2 infection, and other viral etiologies (e.g., enterovirus PCR and comprehensive respiratory viral pathogen testing).1

- In Ontario, clinical guidance of the evaluation and management of events of myocarditis/pericarditis following mRNA vaccines has been developed by the Hospital for Sick Children.4

**Surveillance and Reporting Requirements**

- Health care professionals in Ontario should submit any reports of myocarditis/pericarditis following COVID-19 vaccines to their local public health unit41 using the Ontario AEFI reporting form42. The Brighton Collaboration has issued case definitions for myocarditis/pericarditis43,44,
which have been summarized in the Adverse Events of Special Interest (AESIs) for COVID-19 Vaccines Surveillance document\textsuperscript{45}.

- As part of ongoing COVID-19 vaccine safety surveillance, the Public Health Agency of Canada (PHAC) and Health Canada are closely monitoring myocarditis/pericarditis in passive and active Canadian vaccine safety surveillance systems, including the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)\textsuperscript{46}, the Canada Vigilance Program (CV)\textsuperscript{47}, the Canadian National Vaccine Safety Network (CANVAS)\textsuperscript{48} and the Canadian Immunization Monitoring Program ACTive (IMPACT)\textsuperscript{49}.

Conclusions and Implications for Practice

- NACI continues to strongly recommend that a complete series with an mRNA vaccine should be offered to all eligible individuals without contraindications, including those 12 years of age and older.

- The benefits of COVID-19 mRNA vaccines continue to outweigh the risks of COVID-19 illness in the authorized populations as mRNA vaccines are effective in reducing COVID-19 infections, hospitalizations, and deaths.

- The Ontario Ministry of Health preferentially recommends the use of Pfizer-BioNTech COVID-19 vaccine for individuals 18-24 years and the continued use of Pfizer-BioNTech for individuals 12-17 years of age.

- As a precautionary measure, NACI recommends that all individuals who have experienced myocarditis/pericarditis following vaccination with a first dose of an mRNA COVID-19 vaccine should defer the second dose in the vaccination series until more information is available.

- Clinicians and vaccine-recipients need to maintain ongoing vigilance for this clinical syndrome. All patients presenting symptoms concerning myocarditis/pericarditis in the following days after COVID19 mRNA vaccination should be rapidly assessed in-person by a physician.

- Public Health Ontario will continue to monitor for reported events of myocarditis/pericarditis following COVID-19 vaccination in partnership with the Ontario Ministry of Health and federal/provincial/territorial vaccine safety networks, and will provide timely updates as more information becomes available.
References


36. Lehto E. Finland joins Sweden and Denmark in limiting Moderna COVID-19 vaccine. Reuters [Internet], 2021 Oct 07 [cited 2021 Oct 21]; Europe. Available from:


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