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COVID-19 VACCINE-ASSOCIATED MYOCARDITIS/PERICARDITIS

JULY 16, 2021

REPORT OF THE CHIEF SCIENCE ADVISOR OF CANADA

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EXECUTIVE SUMMARY

The timely development and deployment of COVID-19 vaccines are playing a key role in limiting disease severity and overcoming the pandemic. While these vaccines have proved safe and remarkably effective, mass vaccination has uncovered rare but potentially significant side effects such as heart inflammation consistent with myocarditis and pericarditis. The Chief Science Advisor convened a meeting with scientific experts on June 25, 2021, to discuss the reported incidence, presentation and possible causes of myocarditis and pericarditis associated with mRNA COVID-19 vaccines. This report builds on the expert discussion, summarizes scientific knowns and uncertainties, and suggests priority areas for consideration.

Scientific knowns: Inflammation of the muscle (myocardium) or outer layer (pericardium) of the heart can be caused by multiple agents and conditions. Viral infections, including with SARS-CoV-2, the virus responsible for the COVID-19 pandemic, are known inducers of myocarditis. Myocarditis is also a reported rare side effect of certain vaccines. In most cases, pericarditis and myocarditis resolve with no further heart damage but persistent heart inflammation can increase the risk of serious and irreversible organ damage. Cases of myocarditis and pericarditis are being reported in association with COVID-19 mRNA vaccination, mostly following the second vaccine dose. Symptoms generally manifested a few days post-vaccination and were reported in all age groups, but predominantly in male adolescents and young adults. Pericarditis was seen across the age spectrum. Most cases resolved quickly with supportive treatment only.

Scientific uncertainties: Data from COVID-19 mass vaccination are rapidly evolving with more countries stepping up vaccine rollouts among their populations. For now, most vaccine-associated myocarditis reports are derived from Israel and the USA, the first countries to use mRNA vaccines in their mass vaccination campaigns. Further post-vaccine surveillance data are required to determine the incidence frequency and distribution across age groups and gender. Additionally, because fewer young adults have been fully vaccinated with other types of COVID-19 vaccines, it is uncertain whether vaccine-associated cardiac inflammation is specific to the mRNA platform. The potential biological mechanisms underlying COVID-19 vaccine-associated myocarditis and pericarditis are currently unknown but hospitalized individuals have generally responded well to anti-inflammatory interventions. The mechanisms for these vaccine-associated heart conditions need to be uncovered in order to understand risk factors and develop prevention and treatment.

Priority considerations: The **benefits of vaccination**, including prevention of COVID-19 infection and transmission as well as post-COVID complications such as long-COVID and MIS-C, **outweigh the potential risk of vaccine-associated myocarditis and pericarditis** but **active monitoring and research are needed to understand and prevent vaccine-associated cardiac damage, now and in the future**. Timely efforts are required to address scientific gaps, engage with healthcare providers to raise awareness of the condition and standards of care, and build ongoing trusted communications with the public, including targeted approaches with younger adults. Suggested priorities include:

- Targeted biomedical and clinical research to better understand disease pathophysiology and develop preventive and therapeutic measures.
- Establishing whether vaccine platform affects the risk for vaccine-associated myocarditis and pericarditis.
- Active, coordinated and longer-term post-vaccine surveillance, including prospective cohort studies that monitor cardiac and immune parameters.
- Urgently developing and disseminating clinical guidance for healthcare professionals to effectively recognize and manage those affected and to counsel those potentially at higher risk.
- Providing balanced and transparent messaging to the general public and outreach to specific subgroups who may be at potential higher risk for cardiac adverse effects.

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ISSUE

This report summarizes the relevant scientific knowledge, uncertainties, and suggested priority actions regarding rare cases of heart inflammation consistent with myocarditis and pericarditis linked to mRNA COVID-19 vaccines. These rare cases have been reported mostly after the second dose of COVID-19 mRNA vaccination in all age groups and sex, but predominantly in male adolescents and young adults, few to several days after vaccination.

CONTEXT

The Chief Science Advisor convened a meeting with scientific experts on June 25, 2021, to discuss emerging reports of rare cases of heart inflammation consistent with myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining around the heart) following administration of mRNA-based COVID-19 vaccines. Most cases of myocarditis and pericarditis following COVID-19 vaccination have been reported from Israel and the USA, two countries that are well along in the administration of the second dose of mRNA vaccines. Cases have been predominantly reported in younger males (12-29 year age group mostly) shortly following the second dose of mRNA vaccine (typically within four days). Clinical outcome has been good.[1] Cases in older adults have also been reported and the outcome has varied depending on other pre-existing conditions.[2,3,4] The Israeli Ministry of Health reported 121 cases out of more than 5 million second doses within 30 days of vaccination. Early data from the Vaccine Safety Datalink in the USA reported 12.6 cases per million second dose of any mRNA vaccine within 21 days of vaccination. In Canada, as of July 9, 163 cases out of 41.5 million total vaccine doses have been reported to the Public Health Agency of Canada and Health Canada, with 67 reported following a first dose.

As a result of these growing reports, several regulatory agencies have added a warning about the risk of myocarditis and pericarditis for COVID-19 mRNA vaccines. They include the United States Food and Drug Administration (Moderna, Pfizer-BioNTech), Health Canada, and more recently the European Medicines Agency's Pharmacovigilance Assessment committee, EMA-PRAC, who recommended listing myocarditis and pericarditis as new side effects of these vaccines and including a warning to raise awareness among healthcare professionals and people taking these vaccines. It should be noted that a causal relationship between COVID-19 vaccination and heart inflammation has not been established and that the consensus view is that the benefits of vaccination continue to outweigh the risks. Nonetheless, understanding the mechanisms underlying vaccine-associated heart disease is essential for prevention and treatment.

SCIENTIFIC CONSIDERATIONS

Scientific and Clinical Knowledge

Myocarditis is clinically and pathologically defined as inflammation of the myocardium. The causes of the inflammation can be numerous and they influence treatment and prognosis.[5] They include infection, medications, cancer treatment and inflammatory diseases. Age, sex, and genetic and environmental

factors can influence disease severity. In children and adolescents, the most frequent cause of myocarditis is viral infection and most have a complete recovery with the right medical management. However, depending on damage to the myocardium, such as myocyte loss and remodelling, myocarditis could have long-term consequences on heart function and increase cardiac susceptibility to other agents and conditions. The frequency of myocarditis among the general population, including all causes, is estimated at approximately 2 per 100,000 people,[6] and is predominant in younger male individuals. The clinical course and outcomes vary but are typically longer and can be more severe than what is currently observed in cases associated with COVID-19 vaccines.

Infection-induced myocarditis: Myocarditis can be caused by viruses (including influenza, rubella, HIV, adenovirus, coxsackie, and SARS-CoV-2), bacteria, and toxins.[5,7] Cardiac involvement including myocarditis has been previously reported in individuals infected with SARS-CoV-2,[7,8] and as part of a more generalized hyperinflammatory response termed multi-system inflammatory syndrome in children (MIS-C) observed in children and young adults post-infection with SARS-CoV-2 (post-COVID condition).

Vaccine-associated myo/pericarditis: Previously, myocarditis has been reported as a rare event associated with some vaccination, notably smallpox vaccination.[9,10] The frequency of COVID-19 vaccine-associated myo/pericarditis is currently under investigation. Patients presenting with this complication typically have been healthy individuals; only some had previous SARS-CoV-2 infections, while most have not.[11] Past infection by other agents in reported cases was not examined.

An independent analysis (Liu, Peter et al., unpublished work) of inflammatory heart reactions post-COVID-19 mRNA vaccination that have been reported to the World Health Organization's VigiBase and the USA VAERS systems found the following case characteristics:

- Cases reported after mRNA vaccines did not exceed those reported following influenza vaccines except among those 17 to 28 years of age. Cases in females appeared to be more evenly distributed across age groups.
- The most common symptom is chest pain and the most common finding is elevated high sensitivity troponin levels.
- The cases that required hospitalization were characterized by short stays of about 2 to 3 days, and a good response to anti-inflammatory medications such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and other immunosuppressive agents.
- As noted above, myocarditis was predominantly observed in young males in the 18-29 age group, and was more common after a second dose of vaccine, with a typical symptom onset around day 3. Pericarditis cases were more often observed in individuals over 65 years of age.
- Fatal outcomes occurred in about 1% of cases reported to VigiBase and tended to be in older individuals with comorbidities.

Scientific Uncertainties

The heterogenicity of myocarditis triggers, clinical presentations and outcomes are accompanied by many knowledge gaps that make prevention, detection and treatment challenging. With respect to COVID-19 vaccine-associated myocarditis/pericarditis, important knowledge gaps need to be addressed such as who is at risk, what are the triggers and biological mechanisms, and what are the medium-term consequences on heart function.

Hypotheses regarding potential triggers and biological mechanisms

As stated above, a *causal* link has not yet been established between COVID-19 vaccination and myo/pericarditis, and the potential underlying biological mechanisms are not known. Possible pathways or factors that could play a role in triggering inflammation of the heart post-vaccination and in protecting against or worsening cardiac damage need to be investigated. These include the various components of the host immune response, the influence of vaccine dosage and interval as well as various vaccine components, the contribution of past or ongoing infections, and the regulatory role of sex hormones on cardiac manifestation.

Host immune response: A role for the vaccine-induced immune response is supported by a number of observations and circumstantial evidence suggesting that myocarditis occurring after vaccination may reflect a dysregulated immune response, perhaps as a consequence of RNA-recognition by pattern recognition receptors that lead to the production of type I interferons and other pro-inflammatory cytokines. The presence of fever, chills and myalgia occurring after receipt of mRNA vaccines are consistent with a heightened immune response. Of note, children and youth typically display a more robust immune response than adults which could explain the higher incidence of post-vaccination myocarditis in this age group. Interestingly, and unlike viral myocarditis, children with COVID-19 vaccine-associated myocarditis respond quickly to anti-inflammatory treatment, which further supports examining the immune response as a possible trigger. Other factors that could influence the host immune response and participate in COVID-19 associated myocarditis include past or lingering SARS-CoV-2 infection that may act as a priming event that leads to an exaggerated immune response to vaccination. Additionally, early reports of vaccine-associated myocarditis in members of the same family suggest that genetic predisposition may play a role in a hyperactivated immune response to the vaccine.

Dose concentration and dose interval: The vaccine dose concentration and the time interval between the first and second dose (dose interval) could be relevant factors.

- Dose concentration: As with other vaccines, adolescents are receiving the same dose of COVID-19 mRNA vaccines as adults. A direct relationship between mRNA-mediated immune response or resulting spike protein levels and adverse vaccine effects cannot be assumed, but is worth examining. Of note, Pfizer-BioNTech's clinical trial reported that adolescents 12 to 17 years of age mounted a stronger immune response compared to adults given the same dose of vaccine.[12] Pfizer-BioNTech is currently conducting clinical trials testing lower doses for children under 12 years of age. On the other hand, the Moderna COVID-19 vaccine, which has about three times the mRNA concentration of the Pfizer-BioNTech COVID-19 vaccine (100 vs. 30 micrograms), appears to be associated with higher incidence of myocarditis based on some analyses.
- Dose interval: The impact of the dose interval is presently unknown since the available data are from the two countries that used the 3-4 week interval recommended by the manufacturers. Depending on the immunobiology mechanisms at play, longer intervals may decrease or increase vaccine-associated myocarditis. Data from Canada and the UK, countries that have followed varying and longer dosing intervals than Israel and the US, may be informative. Different mechanisms of immune protection may be triggered after the first and second vaccine doses.[13]

Vaccine components: It is also possible that distinct components of mRNA vaccines (mRNA containing modified nucleosides, lipid nanoparticles, etc.) may contribute to vaccine adverse reactions including heart inflammation. Additionally, a possible role for the produced spike protein and/or its interaction with cardiac or vascular ACE2 (angiotensin-converting enzyme 2) receptors cannot be ruled out.

Sex differences: The prevalence of myocarditis in young males may reflect signal potentiation by male hormones, cardio protection by female hormones or other hormone independent differences. In the context of vaccine-associated myocarditis, a possible vascular or cardiac protective role for estrogen may explain the male prevalence. Interestingly, males affected by COVID-19 have a higher likelihood of severe disease than females. The role of sex hormones and sex chromosomes in cardiac inflammation and disease deserve further investigation.[14]

Key Knowledge Gaps

Further research and data gathering are needed to address important questions regarding the frequency, manifestation, cause and treatment of COVID-19 vaccine-associated heart disease. Priority questions include:

1. What is the accurate estimation of the number of cases of myocarditis and pericarditis associated with COVID-19 vaccination and what are their distribution patterns across age groups and sex? Do different vaccine platforms, dosages and dosing intervals affect myocarditis and pericarditis risk?

2. Are there groups or individuals that may be potentially at higher risk of vaccine-associated heart disease and how should they be managed? For example:
    i. Are young adults that were previously infected with COVID-19 at higher risk of myocarditis after receiving their first dose?
    ii. Are children with documented MIS-C at elevated risk of vaccine-associated myocarditis? Prospective cohort studies of this group before they get vaccinated are particularly important.

3. Are cardiac manifestations acute benign events or are there long-term impacts of vaccine-associated myocarditis, in certain age groups?

4. Why is heart inflammation more evident and are there subclinical injuries in other organs?

5. For patients who develop myo/pericarditis after a first dose of mRNA vaccines, what is the best recommendation for the second dose (both interval and types of vaccine)?

PRIORITY ACTIONS MOVING FORWARD

The emerging issue of vaccine-associated heart disease requires attention on two important levels: addressing data and knowledge gaps on the one hand, and promoting awareness and clinical care on the other.

Addressing Data and Knowledge Gaps

1. Enhance knowledge of the frequency, epidemiology and clinical picture of mRNA vaccine-associated myo/pericarditis. The following actions are suggested:

i. **Rapidly set up prospective cohort studies in pediatric and young adult populations to monitor cardiac and immune parameters in a longitudinal manner,** complementing existing passive post-vaccine surveillance efforts. Such studies would provide important health information for

Canada and the world. This is best achieved by partnering with and enabling already established networks and funded programs in vaccine surveillance such as existing rheumatology/cardiology networks and infectious disease clinical networks across the country. Central coordination for the collection of all clinical data (including cardiac imaging) and biobanking of peripheral blood mononuclear cells (PBMCs) and serum/plasma is required. Some of this will be captured through current initiatives such as CANVAS-COVID and the routine AEFI surveillance system, but passive reporting systems may not pick up all cases nor provide needed longitudinal monitoring. Similarly, the Special Immunization Clinic network and Canadian Pediatric Society IMPACT study for hospital-based surveillance will detect cases that come to medical attention in a hospital. The IMPACT network has started active surveillance with a rich clinical dataset for children admitted to 13 pediatric tertiary hospitals across Canada with AEFIs (adverse events following immunization), including myocarditis – but their data will be restricted to those who are admitted to hospital in the pediatric (<17 years) age group. Enabling expanded data capture together with standardized biospecimens at presentation of symptoms and serial protocolized follow-up study will provide important information. In addition, there is a need to prospectively capture and follow a subgroup of children pre-first-dose vaccine onwards in a uniform, serial and comprehensive manner. Additional research into familial adverse reactions could also help guide recommendations.

ii. **Introduce a single case identifier via a centralized universal case depository platform to enhance the ability to combine and match knowledge.** Special requests would be needed from provincial healthcare programs to avoid duplicates on one hand, and to match clinical, biological, biobank and genetic material on the other hand, as several research projects may emerge.

iii. **Using observational lab-based studies and animal models, explore both the trigger (which component of the vaccine) and the host response (immune and cardiac).** For now, the inflammatory complication appears to be more common with mRNA vaccines than viral vector vaccines. Among the mRNA vaccines, it is potentially more common with Moderna, which has a higher mRNA load. However, it should be noted that fewer COVID-19 vaccines have been administered to younger age groups to date. It is therefore important to determine for these age groups whether vaccine-associated myocarditis is a feature specific to mRNA vaccines or whether similar side effects may be seen with other COVID-19 vaccines developed using different platforms. In other words, is myocarditis due to RNA, lipid nanoparticles or the translated spike protein and/or its interaction with cardiac or vascular ACE2? Answers to these questions have significant implications for COVID-19 immunization and beyond. Experimental and clinical monitoring studies need to address the following issues, among others:

- Understand the **host immune response** (e.g. young male vs. female, and the immune response after first dose vs. second dose, considering the dose interval), and the immune imbalance inherent in the few individuals who develop the complications (e.g. innate immune genetic polymorphism). Information on immune response following the first dose in young males may be very helpful, as young male vaccinees may only need one dose.
- Determine whether the **inflammatory response is limited to the heart and pericardium** or whether **other organs are sub-clinically affected**, in which case, could this lead over time to other auto-inflammatory or auto-immune diseases such as diabetes, psoriasis atherosclerosis? In this respect, knowledge of the long-term impact of other vaccines associated myocarditis (e.g. smallpox) would be helpful. Severe cases with vaccine-

associated systemic inflammation similar to a MIS-C phenotype have been reported, with multi-organ involvement.

- Determine if the **damage to the heart** is only transient or if there will be long-term subclinical or progressive damage leading to susceptibility to other cardiac diseases, such as chronic cardiomyopathy, coronary artery disease or arrythmias.
- Understand the **immune basis underlying the myocarditis**. Is it auto-inflammatory or auto-immune? Innate or T-cell mediated? Does it involve triggering of type I interferon by RNA? Could it be prevented by prophylactic and systematic administration of anti-inflammatory drugs such as NSAIDs in susceptible age groups, without compromising immune protection?
- Conduct SARS-CoV-2 **infection studies using animal models** to determine the effects of the vaccines on expression of ACE2 in the heart and other relevant organs.
- Further dissect the **mechanisms and development of MIS-C** as it may represent the "tip of an iceberg" and lessons could be learned that inform vaccine-associated inflammatory organ responses.
- Develop a **long-term surveillance** cohort to determine whether individuals who become fully vaccinated would be at increased risk to develop myocarditis/pericarditis after exposure to classical causing agents (e.g. influenza, enteroviruses, coxsackie virus, etc.).

2. Standardize and collect clinical data on a research basis.

A cohort study of individuals who meet the criteria for vaccine associated myo/pericarditis needs to be set up along with standardized follow-up to determine the spectrum and relevance of this issue, as well as any non-cardiac morbidities. Additionally, standardized clinical research data should be collected as part of prospective cohorts of healthy adolescents/young adults and others with evidence of adverse response to previous SARS-CoV-2 infection (e.g. COVID-19 toes).

Extended clinical history and bloodwork to interrogate the immune response, exposure to the virus, and markers of myocardial damage would be important data to collect. Such information could be derived from plasma/serum measurements of certain cytokines and enzymes following the first and second vaccination. Additionally, standardized cardiac imaging studies are recommended. They can include echocardiograms to monitor cardiac effusion and global and regional wall motion abnormalities, as well as cardiac magnetic resonance imaging (MRI) (as per the updated Lake Louise Criteria[15]).

Prospective follow-ups of adverse events through app-based monitoring should be considered. Kits can be sent to individuals and returned by mail. With a single finger prick of blood, 10 proteins can be measured (e.g. troponin, antibody and inflammatory markers).

Promoting Awareness and Clinical Care

1. Identify groups at higher risk that could benefit from better follow-up or alternative approaches.

The data so far indicate that younger males may be at increased risk for the rare cardiac events. **Further research and longer-term data gathering are required to confirm who may be at higher risk of developing vaccine-associated myocarditis.** In the meantime, the following groups may benefit from closer follow ups:

- Those with a previous diagnosis of MIS-C or myo/pericarditis post-first-vaccine dose.
- Those with auto-immune myo-pericarditis (small but well-known population of patients followed by rheumatology/immunology), those with isolated single organ auto-immunity, as well as those

suffering from it due to an underlying auto-immune disease, e.g. systemic lupus erythematosus (SLE), vasculitis, arthritis, autoinflammatory disease, etc.
- Male adolescents who are immunocompromised and experiencing pro-inflammatory disease exacerbation, during a flare or acute phase.

The following actions may help **clarify who is most at risk**:
- Adopting a standard case definition (suggest using Brighton collaboration).
- Developing an agreed upon process for investigation and follow-up that is child-appropriate as well as adult-appropriate, and could be used in a variety of settings, including rural and remote locations.
- Coordinating with international monitoring efforts.

2. Provide targeted public communication and outreach to healthcare professionals.

Overall, myocarditis is a rare complication associated with COVID-19 mRNA vaccines. While the longer term consequences are not yet known, the consensus view of the experts, based on the rapid recovery of most individuals, is that the benefits of vaccination programs outweigh the risks at a population level, particularly as SARS-CoV-2 infection itself and associated MIS-C carry a much higher risk of myocardial injury[7] and long-term sequelae. Transparent **targeted communication and outreach** regarding evolving knowledge of myocarditis and pericarditis are important and should include:

- Transparent public communication to inform the **general public and potentially susceptible populations of the frequency, symptoms and management of vaccine-induced cardiac disease** without negatively impacting vaccine acceptance.

- Separate and appropriate **outreach, communications and guidance to healthcare providers** so that they are prepared to care for patients who present with vaccine-associated cardiac disease. Among others:
  - Health professionals should be alerted to the unique presentation, natural history, potential management strategies, and the risk of rare adverse outcomes of these inflammatory complications to further minimize downstream negative impact. This includes pediatricians and family and emergency physicians.
  - Canadian cardiology, rheumatology/immunology, and infectious disease societies could work together to develop common guidelines for investigation and care management, to be promoted as a best practice. Of note, a multidisciplinary group at the Hospital for Sick Children has developed a preliminary guidance document for healthcare professionals with plans in place for multi-pronged knowledge dissemination, including engaging the Canadian Pediatric Society. The document could be used as a basis, expanding guidance to adult populations.

CONCLUSION

Based on current scientific evidence, COVID-19 vaccines continue to be recommended for all eligible individuals, including youth. Population-wide vaccination is crucial to fighting the global pandemic and for protecting individual health. The benefits of vaccination are significant — the prevention of COVID-19 infection, transmission, hospitalizations and deaths, as well as post-infection complications such as long-COVID and MIS-C. At the same time, it is critical to gain better knowledge of the rare but potentially serious vaccine-associated adverse events, including heart inflammation. Canada has the

necessary expertise to contribute to global post-vaccine surveillance efforts and research that will advance science, improve care and enhance human health.

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**Denotes regular member of the Chief Science Advisor's COVID-19 Expert Panel*

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