Canadian Cardiovascular Society

Title: MYocarditis and/or pericarditis following mRNA COVID-19 VACCination national surveillance study

MYCOVACC

Protocol

Contents

1. STUDY MANAGEMENT AND REGULATORY

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1.2 Co-investigators

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Dr. Susanna Ogunnaike-Cooke (Public Health Agency of Canada).
Dr. Alexander Singer (University of Manitoba).
Dr. Karina Top (Dalhousie University).
Dr. Sean Virani (University of British Columbia).
Dr. Meredith Wright (Canadian Cardiovascular Society).

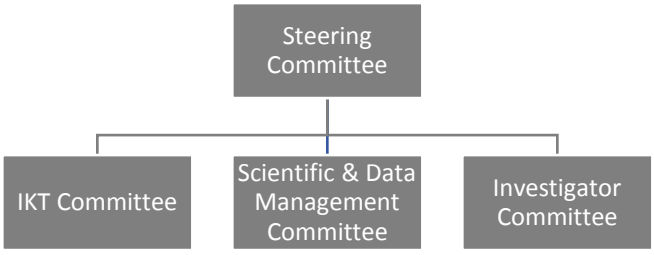
1.3 Steering Committee

The MYCOVACC Steering Committee (SC) provides direction, guidance and decision-making about study activities. Specifically, the SC guides implementation, operations and funding; and ensures key deliverables are achieved. The SC will ensure the study being conducted in accordance with the principles of Good Clinical Practice (GCP) and the relevant regulations. The membership of the Committee will include a chairperson, vice-chairperson, CCS Chief Executive Officer, representatives of the CCS Council/Board Executive, representatives of major partners, CCS members with expertise related to MYCOVACC, representatives of Public Health Agency of Canada, Immunization Senior Scientist. The SC will have its own charter outlining the role and responsibilities of its members. The SC may invite other attendees from the study team to present or participate in discussions on particular topics. These attendees will be non-voting members.

1.4 Governance structure

The study has 4 main governance structures.

1. Steering Committee.
2. Integrated Knowledge Translation Committee. Develops and implements the Integrated Knowledge Translation.
3. Scientific and Data Management Committee. Ensures high-quality data and ethical data collection, storage, and use; reviews and approves all protocols, publications, and reports
4. Investigator Committee. Provides a forum for collaborative engagement among site investigators; contributes to the design and direction of the project



1.5 Patient advisors

Patients or their carers who have experienced vaccine associated myocarditis/pericarditis will be invited to participate as study patient advisors and members of MYCOVACC committees. Advisors will help to refine study methods, communications and knowledge translation plans and activities.

1.6 Role of study funders and sponsors

1.6.1 Public Health Agency Canada (PHAC)

Public Health Agency Canada are funding this study. The funder will delegate specific roles to the Principal Investigators and other third parties. These arrangements will be clearly documented in agreements. The funder will have input into the study design, conduct, analysis, interpretation, and reporting. Final decision regarding all aspects of the study resides with the principal investigators and steering committee.

1.6.2 Canadian Cardiovascular Society

The Canadian Cardiovascular Society (CCS) is co-sponsoring this study. The sponsor will have input into the study design, conduct, analysis, interpretation, and reporting. Final decision regarding all aspects of the study resides with the principal investigators and steering committee.

CCS is the national professional home for Canada's cardiologists, cardiac surgeons, and scientists. Along with a mandate in clinical practice standards setting and education, CCS members, numbering more than 2,300, have a 75-year history of cardiovascular care leadership and research excellence in national and international arenas.

1.6.3 University of British Columbia coordinating centre

The study will be coordinated from a single coordinating centre located in British Columbia, the Centre for Cardiovascular Innovation (https://cci-cic.org/) which is an approved UBC Faculty of Medicine Centre.

1.7 Data ownership

UBC is the Data Controller of all the data generated from patients recruited to this study in Canada. The study data will be analysed and published by the clinical research team. The MYCOVACC data remains the proprietary of the PIs.

1.8 Confidentiality Statement

This protocol contains confidential information that must not be disclosed to anyone other than the sponsor, Canadian Cardiovascular Society, the Investigator Team, PHAC, regulatory authorities, and members of the Research Ethics Committee.

2. INTRODUCTION AND BACKGROUND

2.1 Vaccine associated myocarditis/pericarditis

Myocarditis is inflammation of the myocardium (heart muscle). Pericarditis is inflammation of the pericardium (lining surrounding the heart muscle). There are many different causes for myocarditis and pericarditis including viral infections and COVID-19 infection. Myocarditis is defined by the presence of 1) cardiac symptoms, 2) an elevated cTn, and 3) abnormal electrocardiographic, echocardiographic, cardiac magnetic resonance imaging, and/or histopathologic findings.

In rare instances myocarditis and pericarditis have occurred following mRNA COVID-19 vaccination. Canadian and international data indicate a higher rate of myocarditis and/or pericarditis following COVID-19 mRNA vaccination than would normally be expected in the general population.[1-7] Most reports suggest an incidence of up to 2 to 3 cases per 100,000 vaccinations. Male adolescents and male young adults are at the highest risk of myocarditis after mRNA vaccination for COVID-19,[8,9] with recent review indicating the incidence of myocarditis for might be as high as 140 cases per million for this cohort.[9] Although cases of myocarditis and/or pericarditis appear to be mild and self-limiting in the short-term follow-up, the long-term health and functional implications of the acute myocardial injury are currently unknown.[9,10]

2.2 MYCOVACC study overview

MYCOVACC is a multi-centre pan-Canadian surveillance study commissioned by The Public Health Agency of Canada to examine the outcomes of a cohort of adult and pediatric patients with post-mRNA myocarditis and/or pericarditis.

2.3 Public health imperative

The MYCOVACC surveillance study is commissioned by The Public Health Agency of Canada. Post-vaccination myocarditis/pericarditis was first identified in spring 2021. While still relatively rare, it has garnered significant public and media attention and has affected vaccine confidence in COVID-19 mRNA vaccines, particularly due to its higher risk among young people. The longer-term effects of myocarditis and/or pericarditis following mRNA COVID-19 vaccination remain unknown. These knowledge gaps negatively impact vaccine confidence, particularly in children and adolescents. In addition, as we face a seventh (and likely additional) wave of COVID-19 and possible repeated annual or bi-annual vaccine boosters, the need to establish an approach to monitor clinical and mental health outcomes is increasingly evident. mRNA platforms may carry inherent risk for myocarditis and/or pericarditis, and as such, understanding of long-term outcomes will likely impact confidence and use of future types of mRNA vaccines that may be approved for use in Canada.

The Public Health Agency of Canada has therefore identified that Canada needs a robust national surveillance study to answer emerging research and public health questions about this risk of mRNA COVID-19 vaccination. This is supported by the July 16, 2021 report of the Chief Science Advisor of Canada, which identified “active, coordinated and longer-term post-vaccine surveillance, including prospective cohort studies that monitor cardiac and immune parameters” as a priority for action.

Exploration conducted by the Centre for Immunization Surveillance of PHAC in summer and fall 2021 determined that there were no ongoing Canadian studies, national in scope, that could be promptly leveraged to address this gap. A comprehensive nation-wide approach for Canadian data is critical as the few international studies on long-term outcomes may not be representative of all people affected by this adverse event, and may not be readily applicable to Canada given population differences, health care system differences, and in the varying COVID-19 vaccination approaches used during the pandemic. In particular, there are no other countries with vaccine roll-out parameters similar to those implemented in Canada – two mRNA platforms, vaccine interchangeability, varying inter-dose intervals, booster intervals, and more recently, the introduction of two protein subunit vaccines.

The Public Health Agency of Canada therefore solicited a proposal from the Canadian Cardiovascular Society on the development of a national-in-scope surveillance study that would address the knowledge gap. The Canadian Cardiovascular Society is well placed for the project by virtue of their role as the national voice for cardiovascular clinicians and scientists, representing more than 2,300 cardiologists, cardiac surgeons and other heart health specialists and clinical investigators. To develop the proposal, the Canadian Cardiovascular Society formed a project team and approached Dr. Nathaniel Hawkins (Centre for Cardiovascular Innovation, University of British Columbia) to be the project’s scientific lead.

2.4 Case definition of vaccine associated myocarditis/pericarditis

There are two major case definition criteria currently in use for post-vaccine myocarditis. These are from the CDC and the Brighton Collaboration. They are very similar, but the Brighton Collaboration criteria have been updated and more widely used (Appendices 1 to 5). Similarities include some symptom combinations, troponin positivity, histopathologic confirmation, cardiac magnetic resonance imaging features of myocarditis and echocardiographic abnormalities. For the purposes of our study, we will primarily use Brighton Criteria case definitions for myocarditis and pericarditis because they are more inclusive. However, the CDC criteria will also be analysed to allow for international comparison.

This study will also include patients with COVID-19 myocarditis/pericarditis and MIS-C/A myocarditis. COVID-19 myocarditis/pericarditis will use the same case definitions as vaccine-myocarditis/pericarditis, but the precipitant is COVID-19 infection in the prior 42 days. MIS-C/A myocarditis uses the same case definition as Brighton criteria for vaccine myocarditis, but requires the criteria for MIS-C/A to be met (see Appendix 6).

2.5 COVID-19 myocarditis

Myocarditis has been recognized as an uncommon but serious complication of SARS-CoV-2 infection as well as COVID-19 mRNA vaccination. Prevalence rates widely varying depending upon the population studied. Several mechanisms may contribute including direct virus invasion, host inflammatory or immune responses, microvascular angiopathy, and maladaptive host immune response. Management of patients is primarily dictated by the clinical course and empirically based on treatment of other forms of myocarditis. Use of intravenous corticosteroids may be considered in those with hemodynamic compromise. Importantly, a very favorable benefit-to-risk ratio exists with the COVID-19 vaccine for all age and sex groups i.e. far more cases of COVID-19 associated myocarditis are avoided than vaccine associated myocarditis cases occur.

2.6 Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A) myocarditis

MIS-C is a rare but serious complication associated with SARS-CoV-2. MIS-C occurs in children, adolescents, and young adults and is characterized by inflammation across multiple body systems. MIS-C symptoms generally appear 2–6 weeks after infection. Children with MIS-C often had no or few symptoms of COVID-19. In addition to fever, children with MIS-C commonly present with abdominal pain, vomiting, diarrhea, rash, conjunctivitis, and hypotension. The pathogenesis is uncertain, possibly the SARS-CoV-2 spike protein acts as a superantigen to promote a cytokine storm. Patients with MIS-C will likely be hospitalized and may need treatment in intensive care including intravenous immunoglobulin, steroids, and immune modulators.

2.7 Novelty

Canada is uniquely placed to examine the longer-term outcomes in people with myocarditis and/or pericarditis following mRNA COVID-19 vaccination. In contrast to other countries, Canada has used mRNA vaccinations almost exclusively for second and booster doses. As well, Canada is one of the few countries to have implemented an extended interval vaccination schedule. Canada is seen as the right size for a cost-effective surveillance study.

This project shares the objectives of the “Myocarditis Outcomes after mRNA COVID-19 Vaccination Investigation” currently being conducted by the United States Centre for Disease Control (US-CDC), however, our Canadian study will allow for more in-depth analysis and has a number of advantages when compared to the US-CDC study.

1. The US-CDC study primarily employs a survey-based approach. This inherently is prone to survey bias and has already encountered a significant number of survey non-responders, particularly from the marginalized and ethnic/minority populations. Our approach is more comprehensive utilizing multiple sources of patient ascertainment, and engages healthcare providers across Canada including adult and pediatric cardiologists, infectious disease and public health specialists.
2. The CDC criteria for vaccine-myocarditis/pericarditis is distinct from international Brighton Criteria. MYCOVACC will use both CDC criteria and Brighton Criteria to allow for comparison with both US and International data sets.
3. The vaccines given in Canada are a different mix (AstraZeneca, Pfizer, Moderna, Johnson & Johnson, Medicago, Novavax) from the FDA approved vaccines (Pfizer, Moderna, Janssen) used in the US. Canada also allows mix and match vaccine combinations, hence our ability to assess the benefits and risks associated with these combinations. For example, Canada is the first country to identify that the combination of Pfizer primer and Moderna follow-up combination incurred a very significant increase in risk of myocarditis compared to other combinations.
4. Canada has the unique experience of varying vaccine time intervals such as the initial extended interval roll-out of 6 to 12 weeks. This allows assessment for whether risk is lower with delayed dosing, in contrast to a mostly fixed dose interval in the US.
5. Canada’s universal healthcare allows more patients (including marginalized and impoverished groups) to be identified with this condition, whereas care in the US is more limited to patients with health insurance. Our study will also endeavor to collect more data on marginalized groups and Indigenous communities.

2.8 Clinical management

The recent 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults highlighted the lack of evidence based management strategies for vaccine associated myocarditis/pericarditis.[11] The guidelines indicate nonsteroidal anti-inflammatory drugs, colchicine, and corticosteroids may be considered in those with ongoing symptoms. For those with those with rapidly improving symptoms, a normal or improving cTn level, and normal left ventricular ejection fraction, anti-inflammatory medications may not be needed.[11] However, these recommendations are all extrapolated from treatment of myocarditis/pericarditis of alternative etiologies. Whether similar strategies are effective for vaccine associated myocarditis/pericarditis is unknown.

2.9 Repeat vaccination

Limited data currently exist regarding the safety of COVID-19 vaccination for individuals with a history of myocarditis or pericarditis unrelated to COVID-19 mRNA vaccines. Centers for Disease Control and Prevention (CDC) guidelines currently recommend that such individuals be vaccinated against COVID-19 after their myocarditis/pericarditis episode has completely resolved. In contrast, the guidelines recommend that no further doses of any COVID-19 vaccine be given to those who developed myocarditis/pericarditis following COVID-19 mRNA vaccination. The guidelines acknowledge that this decision should be informed, however, by an individual's risk for severe COVID-19 illness. The Canadian National Advisory Committee on Immunization (NACI) currently advise against subsequent vaccination. Members of NACI have expressed a particular interest in the secondary endpoints of MYCOVACC assessing subsequent vaccination patterns and associated outcomes.[12]

2.10 Prognosis

Myocarditis and/or pericarditis are established adverse events following the administration of mRNA vaccines against COVID-19. However, the longer-term health and functional implications of the acute myocardial injury (especially when incurred at a young age) are currently unknown. In a recent prospectively enrolled cohort of 20 patients with acute myocarditis within 10 days of mRNA-based COVID-19 vaccination, convalescent cardiac magnetic resonance-based imaging at ≥3 months identified residual fibrosis in 90% of patients during follow up.[13] Fibrosis is a recognized risk marker of future cardiovascular outcomes in non-COVID community-acquired myocarditis and highlights the importance of future studies to evaluate long-term clinical outcomes in this patient population.

2.11 Impact and public health surveillance

Vaccines are a key component of efforts to control the COVID-19 pandemic. The Public Health Agency of Canada has identified documentation of longer-term outcomes as critically important to inform its decisions about risks and benefits of mRNA COVID-19 vaccination for boosters and new variants.

Assessment of the longer-term impact of adverse events following COVID-19 immunization is crucial for ongoing safety monitoring of vaccines, and informs best practices for clinicians, recommendations from national health advisory bodies, and expands public knowledge about vaccine safety. Public acceptance and trust in COVID-19 vaccine safety is necessary to support the long-term sustainable success of the ongoing vaccination campaign.

The MYCOVACC study will provide insights on the longer-term health and functional impacts of myocarditis and/or pericarditis following mRNA COVID-19 vaccination in addition to healthcare utilization and health outcomes. Data from this study will provide urgently needed data to support critical decision-making around the choice of COVID-19 vaccines for communities and individuals, particularly for boosters and new variants.

3. STUDY OBJECTIVES AND OUTCOMES

3.1 Primary objectives

1. Evaluate the incidence, type, and severity of major adverse cardiovascular events (MACE) in patients with vaccine associated myocarditis/pericarditis, COVID-19 myocarditis/pericarditis, and MIS-C/A myocarditis.

2. Assess cardiac function recovery in patients with vaccine associated myocarditis/pericarditis, COVID-19 myocarditis/pericarditis, and MIS-C/A myocarditis.
3. Evaluate functional outcomes including quality of life, depression, anxiety, and physical activity in patients with vaccine associated myocarditis/pericarditis, COVID-19 myocarditis/pericarditis, and MIS-C/A myocarditis.

3.2 Secondary objectives

• Describe the spectrum of presentation, severity, and predisposing factors of vaccine associated myocarditis/pericarditis, COVID-19 myocarditis/pericarditis, and MIS-C/A myocarditis.
• Describe the investigations and management of vaccine associated myocarditis/pericarditis in standard clinical practice, including care settings, diagnostic workup, imaging, and treatment.
• Compare the incidence, type, and severity of major adverse cardiovascular events in patients with vaccine associated myocarditis/pericarditis in patients treated/not treated with NSAIDs, colchicine and other contemporary treatments according to standard clinical practice.
• Develop a risk prediction score for MACE in patients with vaccine associated myocarditis/pericarditis.
• Evaluate subsequent vaccination patterns and risk of COVID-19 infection in patients with and without subsequent vaccination after vaccine associated myocarditis/pericarditis.

3.3 Primary endpoints

The primary endpoints for the three primary objectives are:

1. Composite MACE at 30 days post vaccination (preferred by cardiovascular community) and at 42 days post vaccination (preferred by vaccine monitoring investigators) including any of:
• Death from any cause.
• Ventricular arrhythmia (ventricular fibrillation or ventricular tachycardia).
• Heart block (type II or type III block).
• Heart failure (national guideline criteria).
• Left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] <55%).
• Cardiac tamponade.

2. Recovery of cardiac function in patients with previously documented abnormal cardiac function (LVEF<55% during anytime at baseline), with LVEF increase by 5% from worst baseline measurement.

3. Quality of life, depression, anxiety, and physical activity using validated instruments at baseline, 3 months,, 12 months, and annually.
3a. Quality of life: EQ-5D-5L questionnaire for adults or EQ-5D-Y questionnaire for children.[14,15]
3b. Depression and anxiety data: PHQ-9 and GAD-7.[16,17]
3c. Physical activity: International Activity Questionnaire.[18]

3.4 Secondary endpoints

• Individual components of primary composite endpoint at 30 days and 42 days post vaccination.
• Atrial arrhythmias.
• All-cause and cardiovascular mortality.
• All-cause and cardiovascular hospitalization.
• Recurrence of myocarditis/pericarditis.
• Constrictive pericarditis.

4. STUDY DESIGN

4.1 Study design

The surveillance study is a cohort study combining 1) passive surveillance by chart review, 2) active surveillance by prospective follow-up integrated with standard clinical care.

4.2 Study setting

The study is a multi-centre study conducted in secondary and tertiary care centres treating myocarditis and pericarditis in the inpatient or outpatient setting in all provinces and territories in Canada.

4.3 Study population

The study population will include any patient with:

1. Vaccine associated myocarditis/pericarditis.
2. COVID-19 myocarditis/pericarditis.
3. MIS-C/A myocarditis/pericarditis
4. Alternative etiology myocarditis.

Patients will be required to satisfy the inclusion and exclusion criteria. Eligibility waivers to the inclusion/exclusion criteria are not permitted.

4.4 Definitions

Patients will be diagnosed based on the Brighton Collaboration case definitions of the term “myocarditis” and “pericarditis”. This utilizes five degrees of certainty, of which three will be included: definitive case (level 1), probable case (level 2), and possible case (level 3). The Level 1 definition is highly specific for the identification of a case of myocarditis and pericarditis. Levels 2 and 3 offer a stepwise increase of sensitivity, with acceptable specificity. In this way it is hoped that all possible cases of myocarditis and pericarditis can be captured. Two additional levels (Levels 4 and 5) are helpful for real-world analysis. Level 4 cases are reported myocarditis or pericarditis with insufficient evidence to meet the case definition of vaccine-induced cardiac inflammation. These are anticipated from centres without easy access to cardiac investigations. Level 5 cases are defined as “Not a case of myocarditis or pericarditis”. These are anticipated to be cases of undifferentiated chest-pain without objective findings of myocarditis or pericarditis.

4.5 Inclusion criteria

4.5.1 Inclusion criteria for vaccine associated myocarditis/pericarditis.

1. COVID-19 vaccination within previous 42 days.

AND

2. At least one cardiac symptom of suspected myocarditis/pericarditis (Appendix 5).

OR

At least two non-specific symptoms (Appendix 5).

OR

In infants and young children, at least two non-specific pediatric symptoms (Appendix 5).

OR

No symptoms, but abnormal histopathology or a combination of abnormal cardiac biomarkers with abnormal cardiac imaging (echo or MRI).

AND

3. At least one of the following objective findings (Brighton Criteria case definitions, Appendices 1 to 5):

a. Histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) showed myocardial inflammation.
b. Elevated myocardial biomarker (Troponin T, Troponin I, or CK-MB).
c. Cardiac MRI abnormality.
d. Echocardiographic abnormality.
e. New or worsening arrhythmia on electrocardiogram, Holter monitor, or telemetry.
f. Elevated inflammation biomarkers: ESR, CRP, hs-CRP, or D-Dimer.
g. Physical examination pericardial friction rub or pulsus paradoxus.
h. Pericardial fluid or inflammation by imaging (echo, MRI, or CT).
i. Enlarged heart on chest radiograph.

AND

4. No alternative cause of presentation. e.g. infectious or autoimmune myocarditis.

4.5.2 Inclusion criteria for COVID-19 associated myocarditis/pericarditis

1. COVID-19 infection within the previous 42 days.

AND

2. Myocarditis/pericarditis as per Brighton Criteria for vaccine associated myocarditis/pericarditis.

AND

3. No alternative cause of presentation.

4.5.3 Inclusion criteria for MIS-C/A myocarditis/pericarditis

1. Brighton case definition for MIS-C/A (Level 1 to 3b).

AND

2. Myocarditis/pericarditis as per Brighton Criteria for vaccine associated myocarditis/pericarditis.

AND

3. No alternative cause of presentation.

4.5.4 Inclusion criteria alternative etiology myocarditis.

1. Myocarditis/pericarditis as per Brighton Criteria for vaccine associated myocarditis/pericarditis.
   AND
2. No alternative cause of presentation.

4.6 Exclusion criteria

• For prospective invitation and follow-up, inability to provide informed consent. Consent will be sought from patients or their authorised substitute decision maker.
• Patients not fulfilling Brighton Criteria levels 1-3 will be excluded if they are level 4 (insufficient evidence for myocarditis) or Level 5 (not myocarditis) or have an alternative diagnosis such as myocardial infarction.

4.7 Case identification

4.7.1 Provincial and territorial adverse event following immunization (AEFI) reporting.

The Public Health Agency of Canada will connect us with all provincial and territorial public health authorities to discuss collaboration. Public health partners will be invited to a priority-setting exercise (along with other key stakeholders) to refine the data collection protocol, outcomes and analyses, and identify priorities. Several public health units are already counting on this study to provide follow-up for these patients as the individual units do not have the capacity to do so.

4.7.2 Collaborating networks.

COVID-VIHPR. This is a CIHR funded study to elucidate the potential underlying mechanisms of the pathogenesis of mRNA vaccine myocarditis, and incorporates very detailed imaging, biospecimen and immunological analysis with controls also exposed to the vaccine. This study is not intended to be a broad comprehensive registry. However, the patients in COVID-VIHPR will contribute relevant data into the MYCOVACC surveillance study. Funding from MYCOVACC will support the longer term follow up of these patients.

POPCORN, IMPACT, and SIC. We have been coordinating closely with the pediatric teams led by Karina Top (POPCORN, IMPACT, and SIC). IMPACT is able to identify patients but they offer no follow-up of the patients identified. Thus, MYCOVACC is the only infrastructure able to follow the patients longitudinally.

4.7.3 Electronic health records

Patients will be identified by chart review of health records at participating sites by research teams led by site investigators according to their local guidelines and standard operating procedures. The study will be promoted through multiple communication channels of the Canadian Cardiovascular Society, including websites, emails, newsletters, and social media channels.

4.8 Cohort time period

The cohort entry start date is December 1, 2020. This date corresponds to the first authorization of mRNA vaccine in Canada by Health Canada (Pfizer BioNTech on December 9, 2020). The cohort entry end date will be determined by renewal of funding for the surveillance study by the Public Health Agency of Canada.

4.9 Ethical considerations

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions. Favourable ethical opinion will be sought from Research Ethics Committee (REC) in all jurisdictions where the study will be conducted. Patients will only be allowed to enter the prospective study once they have provided written informed consent. The PI will be responsible for updating the REC of any new information related to the study.

4.10 Retrospective chart review

The retrospective study will identify previous cases of vaccine associated myocarditis/pericarditis, COVID-19 associated myocarditis/pericarditis, MIS-C/A myocarditis/pericarditis, and alternative etiology myocarditis.

Recruiting clinicians will refer patients presenting with myocarditis/pericarditis since December 1, 2020 to research staff (i.e., the date Health Canada approved the first mRNA vaccine for COVID19). Initial chart review to determine eligibility for the study and subsequent chart review for initial presentation and follow-up time points will be completed. As vaccination for COVID-19 and COVID-19 infections are occurring continually, chart review of eligible patients will follow the same structure as patients identified from December 1, 2020.

The same clinical information as the prospective study will be collected, including presentation, clinical bloodwork, and cardiac imaging. No data will be collected for the purposes of this study that has not already been collected as part of routine follow-ups. Only available data will be extracted. Follow-up data will be extracted from charts using standardized chart extraction forms at 3 months,12 months, and annually for up to 3 years following the date of diagnosis of vaccine associated myocarditis/pericarditis, COVID-19 myocarditis/pericarditis or MIS C/A myocarditis/pericarditis.

4.11 Retrospective chart review waiver of consent

Waiver of consent is requested for retrospective chart review. Retrospective chart reviews are usually confined to a specific timeframe. However, this study has been commissioned by the Public Health Agency of Canada as a surveillance study for a new and unique disease entity for which our understanding is continually evolving and which has significant implications for vaccine confidence and public health. We therefore request permission to perform retrospective chart review of routine clinical care on an ongoing basis for the duration of the study.

4.12 Prospective follow-up invitation

The invitation to participate in prospective follow-up will follow local standard operating procedures as approved by the Research Ethics Committee in each participating centre, specific to the jurisdiction and patient circumstances. Invitation procedures may include:

1. For patients attending a care provider for standard clinical care, the care provider will provide information regarding the study and ask permission for the research team to contact the patient.
2. For patients who have previously provided general consent to contact for research of any form, which has been documented in the health record, the research team will contact the patient.
3. For patients not attending a care provider nor with previously documented consent to contact, an invitation letter to receive further information regarding the study will be sent by mail or email by the research coordinator with approval of the primary care provider.

4. The invitation letter will include a registration telephone number and be available in English and French languages. The invitation for contact will include an option for the potential participant to contact the participating site to opt out of the study. Otherwise, a research coordinator will follow-up by telephone to discuss the study within 2 weeks.

4.13 Consent process

The Principal Investigators will retain overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorized, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

The consenting process will be undertaken with one of two methods: Conventional 'in person' written consent and E-Consent. Assenting patients will be given the option of what form they would like to consent to the study. This is to ensure that patients unable or unwilling to complete an e-consenting process are not disadvantaged.

A copy of the consent form will be given to the patient, care giver, or parents. Copies will be filed in the study record and in the patient's primary healthcare record. e-consenting will also be used if deemed appropriate by study team. The original consent form or completed e-consent form will be filed in the study file and sites will be required to scan and upload the consent forms into a secure study database for each consented patient.

Where a participant is required to re-consent or new information is required to be provided to a participant, the PI will ensure this is done in a timely manner. The right of a participant to refuse participation without giving reasons will be respected. The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

4.13.1Conventional written consent

The process of conventional 'in-person' consent will involve:

• A discussion between the potential participant and an individual knowledgeable about the study about the nature and objectives of the study, and possible risks associated with their participation.
• The presentation of written material to read and digest (e.g., patient information sheet and consent document which must be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements).
• The opportunity for potential participants to ask questions.
• Potential participant will then be able to sign the consent form or decline to give their consent.

4.13.2Virtual electronic consent

• Following verbal consent and collection of electronic contact details, potential participants will be sent an electronic consent form (via REDcap) for their review.
• They will then review audio-visual and written information about the study – which will include information on the objectives of the study and outline any possible risks associated with taking part. This information (e.g., patient information sheet, electronic multimedia resources consent document which must be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements)
• Potential participants will be given the opportunity to ask any questions about the study either directly or at a later time.
• The e-consent form can then be signed and electronically returned to the study team or the participant can decline to give their consent.

4.13.3Mental Capacity

A person is assumed to have the mental capacity to make a decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain. Patients that are unable to provide informed consent will not be included in this study. Where a participant is able to consent but later becomes incapacitated, they will be withdrawn from the trial.

An assent form will be used for children up to but not limited to 13 years of age and for those 14 and older with limited mental capacity. Local REB guidelines and SOPs will be followed at participating sites.

4.13.4Withdrawal criteria

Participants may withdraw consent to the study at any time without giving reasons and without prejudicing any aspect of standard clinical care. When withdrawal is requested, the study team will clarify the level of withdrawal and offer a pre-determined tiered list of options to the patient:

- Complete withdrawal with no further in person visits, no virtual visits, no active data collection, and no outcome follow-up using administrative data.
- Withdrawal with no in person visits, no virtual visits, and no active data collection, but continued outcome follow-up using administrative data.
- Withdrawal with no in person and no virtual visits, but continued active data collection and outcome follow-up using administrative data.
- Withdrawal with no person visits, but continued virtual visits with active data collection and outcome follow-up using administrative data.

4.13.5Confidentiality

The signed version of the consent form will be stored in a separate file from de-identified, coded research records. A unique study ID code will be assigned to the subject. Study data will be entered in an electronic CRF which will identify the participant only by a unique study ID code. Consults and results collected from diagnostic tests will be de-identified by removing the patient name, date of birth, hospital ID number and any other identifying PHI. These will be replaced with the patient's unique study ID code. All hard copies of data will be stored in a locked filing cabinet, only accessible by the study investigator and his/her research team. Electronic data will be entered on a central database stored on a secure computer network that is password protected. The master file that links the subject to the unique study ID code will be stored electronically at each study site in a separate folder on a password protected computer on a secure institutional network. No personal identifiers will leave the study sites.

4.13.6Protocol amendments

Any protocol amendments will be communicated to the REB/IRB, co-investigators, and PIs at other study sites. Amendments will require ethics approval from coordinating and local site before implementation.

4.13.7Declaration of conflict of interest

All investigators declare no conflict of interest.

5. VISIT SCHEDULE AND PROCEDURES

Consenting patients will be followed up clinically by their regular physician (e.g. Cardiologist, Internist, other physician) in collaboration with their local site-PIs, in accordance with the 2022 ACC/AHA standard of care guidelines for the management of myocarditis.

Patients will be followed at 3 months and 12 months after diagnosis and annually thereafter for up to 3 years. To standardize follow-up timing the date of vaccination will be assigned as the baseline date. However, baseline visit data will be collected from initial presentation and medical contact which is usually the date of diagnosis. This distinction is made because there is a variation between cases in date of vaccination to date of diagnosis/initial presentation.

The case report form variable list (Appendix 7) outlines the essential elements to be collected including demographic data, vaccination status, presenting symptoms, physical examination findings, diagnostic testing (routine laboratory work, electrocardiogram, MRI), treatments, and patient outcomes. Quality of life, depression, anxiety, and physical activity will be measured at baseline, 3 months,, 12 months, and annually thereafter using validated instruments: quality of life EQ-5D-5L questionnaire for adults or EQ-5D-Y questionnaire for children;[14,15] depression PHQ-9 and anxiety GAD-7;[16,17] physical activity International Activity Questionnaire.[18] These will be conducted at clinical visits or by telephone if no concurrent clinical visit is scheduled.

Baseline data will be collected for all etiologies of myocarditis, but thereafter follow-up visits will only be undertaken for patients with vaccine associated myocarditis/pericarditis, COVID-19 myocarditis/pericarditis, and MIS-C/A myocarditis/pericarditis (i.e. not alternative etiology myocarditis).

5.1 Schedule for new cases

5.1.1 Baseline visit

Routine blood work, electrocardiogram, Holter monitor, echocardiogram, MRI. Appendix 8 outlines the schedule of assessments.

5.1.2 Follow-up visits

3-month,12-month and annual clinical visits with bloodwork to ensure normalization of CRP, troponin, CK. Consider repeat troponin even if previously normalized (to capture recurrence), and repeat electrocardiogram, Holter monitor, echocardiogram or MRI if the initial test was abnormal.

5.2 Schedule for remote (previous) cases

Cases of previous myocarditis and pericarditis will be identified from chart review using the same criteria as new cases. For example, if a patient case is out of the immediate post-diagnosis window or their experience of myocarditis/pericarditis occurrence more than 12 months ago, we will extract relevant information for Brighton diagnostic criteria from chart review. We will review relevant investigations that have already been completed previously rather than repeat delayed testing. These patients will be approached to participate in the surveillance study as outlined previously.

After consent, they will join the study schedule at the nearest scheduled study visit e.g. If diagnosis was 13 months ago, they will join the 12-month visit. Each visit will have a range e.g., 12-month visit range will be 12-15 months. This will allow for health outcomes to be retrieved retrospectively and also collected moving forward from the time of joining the study.

6. DATA MANAGEMENT, STATISTICAL ANALYSIS, KNOWLEDGE TRANSLATION

6.1 Data collection

A single electronic case report form will be used. Data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools, including electronic case report form (eCRF) (https://www.project-redcap.org/). REDCap is a secure, web-based application designed to support data capture, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. REDCap is the most widely used data solution in the world, compliant with all security and privacy measures in Canada.

6.2 Sample size estimation

We aim to enroll as many patients as possible. For our sample size calculation, we will use international comparison cohorts including from Israel as well as Canadian PHAC adverse events following immunization (AEFI) reports. For example, PHAC has 1,061 cases of myocarditis/pericarditis that meet Brighton Criteria levels 1 to 3. Mevorach et al. (2021) in Israel had 283 cases in 5.1 million fully vaccinated subjects (Pfizer only). If we scale this to Canada with a population of approximately 38 million people, the estimate is 2,094 cases in Canada (Mevorach et al., 2021). A second study from Israel reported 54 cases in 2.5 million vaccinated subjects (Pfizer only). If we also scale this to 38 million people in Canada, the estimate is 810 cases (Witberg et al., 2021). This provides us with a range of 810 to 2,094 cases. If we use a lower limit of capturing 60% of the 810 cases, accounting for loss to follow-up, our lower limit will be 486 cases. Our sample size will be between the lower and upper limits, and our goal will be to identify all 1,061 cases reported to PHAC as a starting point, while adding cases from our collaborators.

6.3 Statistical analysis

The study will have a comprehensive Statistical Analysis Plan authored by the study statistician and agreed by the Investigators before the final analysis. The Centre for Cardiovascular Innovation will manage and analyze study data.

6.4 Gender-based Analysis Plus

Analyses to date suggest that age and gender impact the risk of myocarditis and/or pericarditis following mRNA COVID-19 vaccination. Young men are more predisposed to myocarditis than other groups (e.g., Farahmand et al., 2020). To learn more about how myocarditis and/or pericarditis may impact different groups of people following mRNA COVID-19 vaccination, we plan to collect data about the patients' sex and age, as well as culture, race, ethnicity, occupation, ability, socioeconomics, and gender. We will strive to include patient representatives from diverse backgrounds in our stakeholder consultations and on our Steering Committee to understand their priorities and to refine our data collection, knowledge translation and dissemination strategies based on their experiences and needs. This will ensure sex, gender, and other intersecting identify factors, are integrated throughout the project lifecycle, and the Gender-based Analysis Plus framework is used to inform future vaccination programs.

6.5 Knowledge translation plan

Effective knowledge translation (KT) is foundational to this project. The Canadian Cardiovascular Society will use evidence-based models to develop a KT plan and resources to raise awareness and drive uptake over the duration of the funding period and beyond. To optimize collaboration and uptake, strategic activities and KT tools will be individualized for target stakeholder and community groups. The Canadian Cardiovascular Society will:

- Update KT tools (clinical considerations and non-traditional (social approach to Management) with latest evidence; individualize for audience needs: cardiologists and other healthcare professionals as appropriate.
- Disseminate KT tools in print and electronically to the Canadian Cardiovascular Society membership, national, provincial and territorial associations (as well as national, provincial and regional First Nations, Indigenous and Metis health organizations).
- Develop & launch companion patient tools regarding myocarditis/pericarditis following mRNA vaccine.
- Develop and host a series of webinars to raise awareness of the surveillance study, provide overviews of KT tools with tips for use in practice and provide live forums for discussion plus Q&A.

We will canvass decision-makers for communication preferences and tailor knowledge translation materials, such as webinars, social media strategies, policy briefs and infographics and presentations accordingly. Materials will be translated in English, French and possibly other languages. The Canadian Cardiovascular Society will engage with the Public Health Agency of Canada and provincial and territorial public health agencies over the course of the project. The connections established with provincial and national health partners will also support the availability of timely evidence from this project for decision-makers across the country.

A communications plan will support the above initiatives and include the best approach to informing all stakeholders with the right information, through the right channels at the right time. Channels of communication may include journal ads, the Canadian Cardiovascular Society membership news, Project e-newsletters, social media, web content. Key project information will be housed on the Canadian Cardiovascular Society website over the funding period and beyond and will be reviewed and updated as new evidence becomes available.

7. APPENDICES

7.1 Appendix 1. Brighton Collaboration myocarditis case definition and levels of diagnostic certainty

Level of certainty 1 (definitive case)

- Histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) showed myocardial inflammation
- OR
- Elevated myocardial biomarkers (at least one of the findings below)
  - Troponin T
  - Troponin I
- AND
- Abnormal imaging study
  - Abnormal cardiac magnetic resonance study (at least one of the findings below)
    - Edema on T2-weighted study, typically patchy in nature
    - Late gadolinium enhancement on T1-weighted study with an increased enhancement ratio between myocardial and skeletal muscle typically involving at least one non-ischemic regional distribution with recovery (myocyte injury).
  - OR
  - Abnormal echocardiogram (at least one of the findings below)
    - New focal or diffuse left or right ventricular function abnormalities (e.g., decreased ejection fraction)
    - Segmental wall motion abnormalities
    - Global systolic or diastolic function depression or abnormality
    - Ventricular dilation
    - Wall thickness change

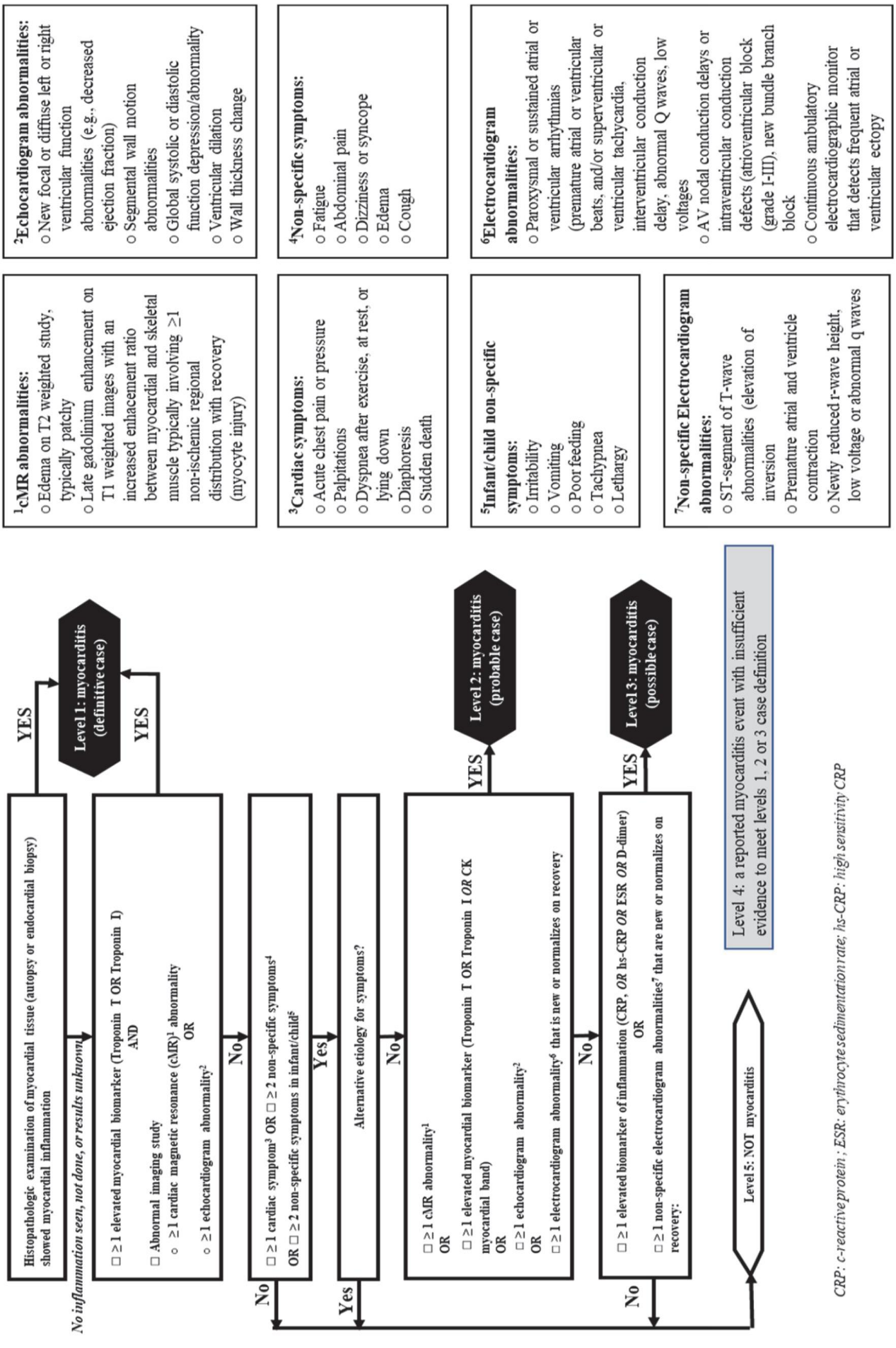
Level of certainty 2 (probable case)

- Clinical symptoms
  - Cardiac symptoms (at least one finding below)
    - Acute chest pain or pressure
    - Palpitations
    - Dyspnea after exercise, at rest, or lying down
    - Diaphoresis
    - Sudden death
  - OR
  - Non-specific symptoms (at least two findings below)
    - Fatigue
    - Abdominal pain
    - Dizziness or syncope
    - Edema
    - Cough
  - OR
  - Infants and young children (at least two findings below)
    - Irritability
    - Vomiting
    - Poor feeding
    - Tachypnea
    - Lethargy
- AND
- Testing supporting diagnosis (biomarkers, echocardiogram, and electrocardiogram)
  - Abnormal cardiac magnetic resonance study (see level 1 case definition)
  - OR
  - Elevated myocardial biomarkers (at least one of the findings below)
    - Troponin T
    - Troponin I
    - Creatine kinase-myocardial band
  - OR
  - Abnormal echocardiogram (See level 1 case definition)
  - OR
  - Electrocardiogram abnormalities that are new and/or normalize on recovery (at least 1 of the findings below)
    - Paroxysmal or sustained atrial or ventricular arrhythmias (premature atrial or ventricular beats, and/or supraventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages)
    - AV nodal conduction delays or intraventricular conduction defects (atrioventricular block (grade I-III), new bundle branch block)
    - Continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy
- AND
- No alternative diagnosis for symptoms

Level of certainty 3 (possible case)

- Clinical symptoms (see level 2 case definition)
- AND
- Testing supporting diagnosis (biomarkers and electrocardiogram)
  - Elevated biomarkers supporting evidence of inflammation (at least 1 of the findings below)
    - Elevated c-reactive protein or high-sensitivity c-reactive protein
    - Elevated erythrocyte sedimentation rate
    - Elevated D-dimer
  - OR
  - Electrocardiogram abnormalities that are new and/or normalize on recovery (at least 1 of the findings below)
    - ST-segment or T-wave abnormalities (elevation or inversion)
    - Newly reduced r-wave height, low voltage, or abnormal q waves
    - PACs and PVCs
- AND
- No alternative diagnosis for symptoms

7.2 Appendix 2. Brighton Collaboration myocarditis case definition flow chart



7.3 Appendix 3. Brighton Collaboration pericarditis case definition and levels of diagnostic certainty

Level of certainty 1 (definitive case)

- Histopathologic examination of myocardial tissue (autopsy or pericardial biopsy) showed pericardial inflammation
- OR
- Abnormal testing (at least two of the following three findings below):
- Evidence of abnormal fluid collection or pericardial inflammation by imaging (echocardiogram, magnetic resonance, cardiac magnetic resonance, computed tomography)
- OR
- Electrocardiogram abnormalities that are new or normalize on recovery (must have all findings below)
  - Diffuse concave-upward ST-segment elevation
  - ST-segment depression in augmented vector right
  - PR-depression throughout the leads without reciprocal ST-segment changes
- OR
- Physical examination finding (at least one finding below)
  - Pericardial friction rub
  - Distant heart sounds (infants and children)
  - Pulsus paradoxus

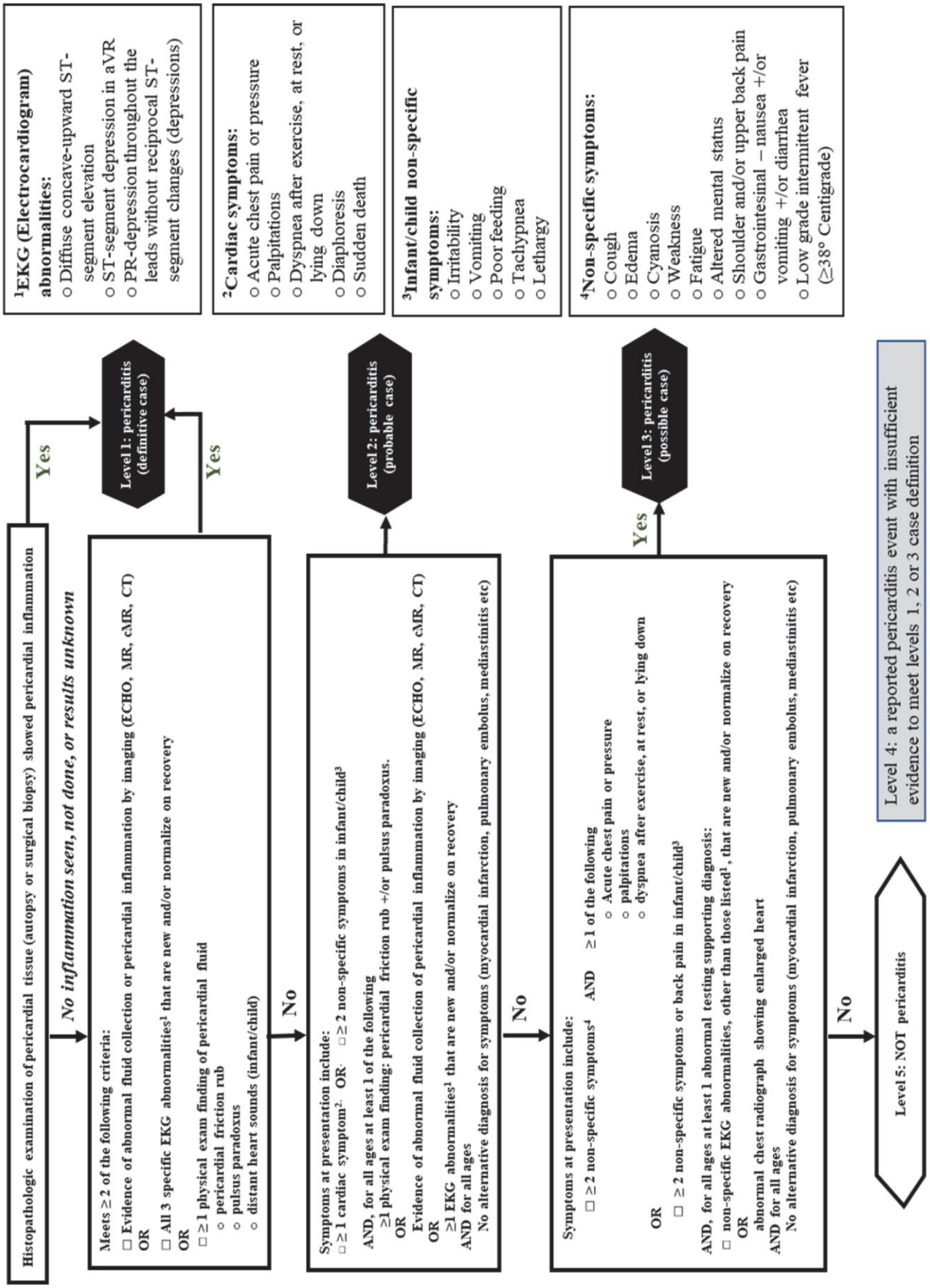
Level of certainty 2 (probable case)

- Clinical symptoms
  - Cardiac symptoms (at least one finding below)
    - Acute chest pain or pressure
    - Palpitations
    - Dyspnea after exercise, at rest, or lying down
    - Diaphoresis
    - Sudden death
  - OR
  - Infants and young children (at least two findings below)
    - Irritability
    - Vomiting
    - Poor feeding
    - Tachypnea
    - Lethargy
- AND
- Physical examination findings: (at least one finding below)
  - Pericardial friction rub
  - Pulsus paradoxus
- OR
- Evidence of abnormal fluid collection or pericardial inflammation by imaging (echocardiogram, magnetic resonance, cardiac magnetic resonance, computed tomography)
- OR
- Electrocardiogram abnormalities that are new and/or normalize on recovery (at least 1 finding below)
  - Diffuse concave-upward ST-segment elevation
  - ST-segment depression in augmented vector right
  - PR-depression throughout the leads without reciprocal ST-segment changes
- AND
- No alternative diagnosis for symptoms (myocardial infarction, pulmonary embolus, mediastinitis etc.)

Level of certainty 3 (possible case)

- Clinical symptoms
  - Cardiac symptoms (at least one finding below)
    - Acute chest pain or pressure
    - Palpitations
    - Dyspnea after exercise, at rest, or lying down
  - AND
  - Non-specific symptoms (at least two findings below)
    - Cough
    - Weakness
    - Gastrointestinal – nausea, vomiting, diarrhea
    - Shoulder/upper back pain
    - Cyanosis
    - Low grade intermittent fever
    - Altered mental status
    - Edema
    - Fatigue
  - OR
  - Infants and young children (at least two findings below)
    - Irritability
    - Vomiting
    - Poor feeding
    - Tachypnea
    - Lethargy
- AND
- Abnormal testing supporting diagnosis
  - Abnormal chest radiograph showing enlarged heart
  - OR
  - Nonspecific electrocardiogram abnormalities other than those listed in LOC 1 and LOC 2 that are new or normalize on recovery
- AND
- No alternative diagnosis for symptoms (myocardial infarction, pulmonary embolus, mediastinitis etc.)

7.4 Appendix 4. Brighton Collaboration pericarditis case definition flow chart



7.5 Appendix 5. Clinical symptoms associated with myocarditis and/or pericarditis.

	Myocarditis	Pericarditis
Cardiac symptoms		
Acute chest pain or pressure, positional changes	X	X
Palpitations	X	X
Dyspnea after exercise, at rest, or lying down	X	X
Diaphoresis	X	X
Sudden death	X	X
Non-specific symptoms		
Fatigue, malaise	X	X
Abdominal pain	X	
Dizziness or syncope	X	
Edema	X	X
Cough	X	X
Cyanosis		X
Weakness		X
Altered mental status		X
Shoulder and/or upper back pain		X
Gastrointestinal – nausea +/or vomiting +/or diarrhea		X
Low grade intermittent fever (≥38° Centigrade)		X
Infants and young children		
Irritability	X	X
Vomiting	X	X
Poor feeding	X	X
Lethargy	X	X
Tachypnea	X	X

7.6 Appendix 6. Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A) criteria

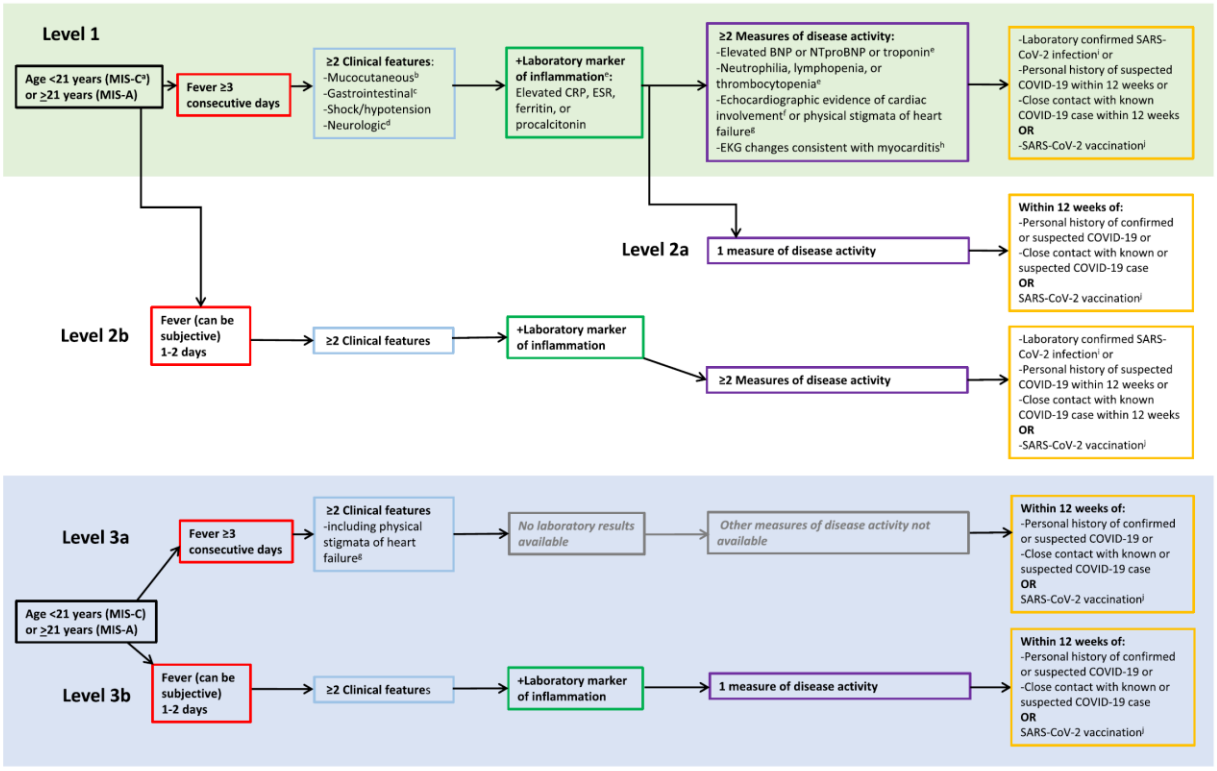


Fig. 3. Algorithm for utilization of the case definition for MIS-C/A.Note: Minimal to mild respiratory symptoms may be present and does not exclude a case of MIS-C/A, however a case must be excluded if there is concern for COVID-19-related pulmonary disease. One of the critical components of the case definition is that it is only applied when there is no clear alternative diagnosis for the reported event.Footnotes: [a] MIS-C=multisystem inflammatory syndrome in children, MIS-A=multisystem inflammatory syndrome in adults, CRP=C reactive protein (detected by any measure), ESR=erythrocyte sedimentation rate, BNP=brain natriuretic protein, NT-proBNP=N terminal pro-BNP, EKG=electrocardiogram, SARS-CoV-2=severe acute respiratory syndrome coronavirus-2, COVID-19=coronavirus disease 2019. [b] rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema or edema of the hands or feet. [c] abdominal pain, vomiting, diarrhea. [d] altered mental status, headache, weakness, paresthesias, lethargy. [e] laboratory values are defined as low or high based on local laboratory norms. [f] echocardiographic signs: dysfunction, wall motion abnormality, coronary abnormality (dilation, aneurysm, echobrightness, lack of distal tapering), valvular regurgitation, pericardial effusion, evidence of abnormal left ventricular strain. [g] physical stigmata of heart failure: gallop (IF diagnosed by expert) *or* rales, lower extremity edema, jugular venous distension, hepatosplenomegaly. [h] EKG changes consistent with myocarditis or myo-pericarditis: abnormal ST segments *and/or* arrhythmia *and/or* pathologic Q waves *and/or* AV conduction delay *and/or* PR segment depression *and/or* low voltage QRS. [i] laboratory evidence of SARS-CoV-2 infection: serologic evidence of SARS-CoV-2 infection OR SARS-CoV-2 antigen positivity OR SARS-CoV-2 nucleic acid amplification positivity. [j] if a known or suspected COVID-19 infection has not occurred within the preceding 12 weeks.

Table 4
Case definition of MIS-C/A: levels of diagnostic certainty.

Level 1 of Diagnostic Certainty – Definitive Case
Age < 21 years (MIS-C[a]) *OR* ≥ 21 years (MIS-A)
AND
Fever ≥ 3 consecutive days
AND
2 or more of the following clinical features:
-Mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema/edema of the hands and feet)
-Gastrointestinal (abdominal pain, vomiting, diarrhea)
-Shock/hypotension
-Neurologic (altered mental status, headache, weakness, paresthesias, lethargy)
AND
Laboratory evidence of inflammation including any of the following:
-Elevated CRP, ESR, ferritin, *or* procalcitonin[b]
AND
2 or more measures of disease activity:
-Elevated BNP *or* NT-proBNP *or* troponin[b]
-Neutrophilia, lymphopenia, *or* thrombocytopenia[b]
-Evidence of cardiac involvement by echocardiography[c] *or* physical stigmata of heart failure[d]
-EKG changes consistent with myocarditis or myo-pericarditis[e]
AND
Laboratory confirmed SARS-CoV-2 infection[f]

Table 4 (*continued*)

Level 1 of Diagnostic Certainty – Definitive Case
OR Personal history of confirmed COVID-19 within 12 weeks *OR* Close contact with known COVID-19 case within 12 weeks *OR* Following SARS-CoV-2 vaccination[g]. **Level 2 of Diagnostic Certainty – Probable Case** **Level 2a** Same criteria as Level 1 except: **1** measure of disease activity **AND** Within 12 weeks of a personal history of known or strongly suspected COVID-19 *OR* Within 12 weeks of close contact with a person with known or strongly suspected COVID-19 *OR* Following SARS-CoV-2 vaccination[g]. **Level 2b** Same criteria as Level 1 except: **Fever** lasting 1–2 days and can be subjective. **Level 3 of Diagnostic Certainty – Possible Case** **Level 3a** Age < 21 years (MIS-C) *OR* ≥ 21 years (MIS-A) **AND** Fever ≥ 3 consecutive days **AND** 2 or more of the following clinical features: - Mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema/edema of the hands and feet) - Gastrointestinal (abdominal pain, vomiting, diarrhea) - Shock/hypotension - Neurologic (altered mental status, headache, weakness, paresthesias, lethargy) **- Physical stigmata of heart failure: gallop (IF diagnosed by expert) *or* rales, lower extremity edema, jugular venous distension, hepatosplenomegaly** **AND** No laboratory markers of inflammation or measures of disease activity available **AND** Within 12 weeks of a personal history of known or strongly suspected COVID-19 *OR* Within 12 weeks of close contact with a person with known or strongly suspected COVID-19 *OR* Following SARS-CoV-2 vaccination[g]. **Level 3b:** Same criteria as Level 2a except: **Fever** lasting 1–2 days and can be subjective. **Level 4 of Diagnostic Certainty – Insufficient Evidence** Reported MIS-C/A with insufficient evidence to meet Level 1–3 in the case definition. Example: 2 clinical features and history of COVID-19 within 12 weeks, but laboratory results and measures of disease activity are not available, and the fever criteria is not met. **Level 5 of Diagnostic Certainty – Not a case of MIS-C/A** Sufficient clinical and laboratory evidence exists to ascertain that a case is **NOT** MIS-C/A. An alternative diagnosis has been ascertained.

Footnotes:

Note: At all levels of certainty, minimal to mild respiratory symptoms may be present and their presence does not exclude a case of MIS-C/A, however, a case must be excluded if there is concern for acute COVID-19-related pulmonary disease. Further, one of the critical components of the case definition is that it is only applied when there is no clear alternative diagnosis for the reported event.

[a] MIS-C = multisystem inflammatory syndrome in children, MIS-A = multisystem inflammatory syndrome in adults, CRP = C reactive protein (detected by any measure), ESR = erythrocyte sedimentation rate, BNP = brain natriuretic protein, NT-proBNP = N terminal pro-BNP, EKG = electrocardiogram, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2, COVID-19 = coronavirus disease 2019.

[b] Laboratory values are defined as low or high based on local laboratory normal ranges.

[c] Echocardiographic signs: dysfunction, wall motion abnormality, coronary abnormality (dilation, aneurysm, echobrightness, lack of distal tapering), valvular regurgitation, pericardial effusion, evidence of abnormal left ventricular strain.

[d] Physical stigmata of heart failure: gallop (IF diagnosed by expert) or rales, lower extremity edema, jugular venous distension, hepatosplenomegaly.

[e] EKG changes consistent with myocarditis or myo-pericarditis: abnormal ST segments and/or arrhythmia and/or pathologic Q waves and/or AV conduction delay and/or PR segment depression and/or low voltage QRS.

[f] Laboratory evidence of SARS-CoV-2 infection: serologic evidence of SARS-CoV-2 infection or SARS-CoV-2 nucleic acid amplification positivity or SARS-CoV-2 antigen positivity.

[g] If a known or suspected COVID-19 infection has not occurred within the preceding 12 weeks.

7.7 Appendix 7. Data collection variables

Eligibility	Study inclusion/exclusion criteria Brighton Collaboration case definition criteria
Diagnosis	Myocarditis etiology Brighton Collaboration case definition level
Demographics	Age, date of birth (Month/year), gender, ethnicity Occupation, education, urban/rural Province, city, postal code (3 digit)
Vaccine	Doses 1, 2, 3, 4, 5, additional doses Vaccine type and date
Covid-19 infection	Infections 1, 2, 3, 4, 5, additional infections Date symptom onset Date diagnosis Diagnostic test (PCR, rapid antigen, self-report, other) Symptoms Treatment
Medical history	Cardiovascular risk factors and disease Autoimmune condition Non-cardiovascular disease
Medications	NSAID, colchicine, steroid, PPI, other
Laboratory tests	CBC, renal function Cardiac biomarkers, inflammatory markers
Examination	Vital signs and clinical signs if recorded
Hospitalization	Date admission and discharge Diagnosis Presentation Management
Death	Date Location Cause
Echocardiography	Left and right ventricular function Pericardial
Cardiac MRI	Left and right ventricular function Late gadolinium enhancement
ECG and Holter	Date ECG abnormalities Holter abnormalities Arrhythmia classification
Outcomes	Primary and secondary endpoints

7.8 Appendix 8. Schedule of assessment

Tests/Procedures	Baseline	3 months (+/- 1 month)	12 months (+/- 1 month)	24 months (+/- 1 month)	36 months (+/- 1 month)
Eligibility	x				
Demographics	x				
Diagnosis	x				
Medical history	x				
Hospitalization	x				
COVID-19 infection	x				
Vaccination status	x				
Physical exam	x				
Vital signs	x	x	x		
Clinical symptoms	x				
Medications	x				
Bloodwork	SOC	x^	x^		
ECG, Holter, Echo, MRI	SOC	x^	x^	x^	x^
QOL, EQ-5D-5L	x	x	x	x	x
EQ-5D-Y	x*	x*	x*	x*	x*
PHQ-9	x	x	x	x	x
GAD-7	x	x	x	x	x
International Activity Questionnaire	x	x	x	x	x
Events, concomitant medication	x	x	x	x	x
Outcomes		x	x	x	x

* questionnaire for children only
^ repeat diagnostic tests if initial test was abnormal
Previous cases will join the study schedule at the nearest scheduled study visit

7.9 Appendix 9. Abbreviations

GCP – Good Clinical Practice
KT – knowledge translation
LVEF – Left Ventricular Ejection Fraction
MIS-C/A – Multisystem Inflammatory Syndrome Children/Adults
PI – Principal Investigator
SC – Steering Committee

7.10 Appendix 9. References

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